

博士論文

遷移金属触媒を用いる新規環化反応の開発と
天然物合成への応用

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略語表

本論文中に以下の略語を用いた。

| | |
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| Ac : acetyl | EI : electron ionization |
| AC : acetone cyanohydrin | elim. : elimination |
| AIBN: 2,2'-Azobis(isobutyronitrile) | eq. : equivalent |
| Ar : argon | ESI : electrospray ionization |
| Ar : aryl | Et : ethyl |
| Bn : benzyl | Fig. figure |
| Boc : <i>t</i> -butoxycarbonyl | g : gram(s) |
| br : broad | h : hour(s) |
| Bu : butyl | HMBC: heteronuclear multiple bond connectivity |
| Bz: benzoyl | HMPA: hexamethylphosphoric triamide |
| °C : degrees Celsius | HRMS : high-resolution mass spectrometry |
| Calcd : calculated | Hz : hertz |
| CAN: ceric ammonium nitrate | IC ₅₀ : 50% inhibitory concentration |
| cat.: catalyst | <i>i</i> Pr: isopropyl |
| CN: cyano | IR : infrared |
| cod : 1,5-cyclooctadiene | <i>J</i> : coupling constant |
| COSY: correlation spectroscopy | K : kiro |
| Cy : cyclohexyl | L : liter(s) |
| d : doublet | LDA: lithium diisopropylamide |
| DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene | LHMDS : lithium hexamethyldisilazide |
| DEAD : diethyl azodicarbodiimide | LUMO: lowest unoccupied molecular orbital |
| DIAD : diisopropyl azodicarboxylate | LRMS : low-resolution mass spectrometry |
| DIBALH : diisobutylaluminium hydride | M : molar (moles per liter) |
| DMAP : (N,N-dimethyl-4-aminopyridine | MCP : methylenecyclopropane |
| DMEAD:di-2-methoxyethyl azodicarboxylate | m : milli |
| Bis(2-methoxyethyl) Azodicarboxylate | m : multiplet (spectral) |
| DHP : 3,4-dihydropyran | <i>m</i> : meta |
| DMF : N,N-dimethylformamide | <i>m</i> CPBA : <i>m</i> -chloroperoxybenzoic acid |
| DMPU : N,N'-dimethylpropyleneurea | Me : methyl |
| DMSO : dimethylsulfoxide | MHz : mega-hertz |
| dppb :1,2-bis(diphenylphosphino)butane | min : minute(s) |
| dppe : 1,2-bis(diphenylphosphino)ethane | mol : mole(s) |
| dppp : 1,2-bis(diphenylphosphino)propane | mp : melting point |
| <i>E</i> : entgegen | |

Ms : methanesulfonyl
 MVK : methyl vinyl ketone
 m/z : mass-to-charge ratio
 n: nano
n: normal
 NBS: N-bromosuccinimide
 NMO : 4-methylmorpholine N-oxide
 NMR : nuclear magnetic resonance
 NOE : nuclear Overhauser effect
 NOESY : NOE correlated spectroscopy
o : ortho
p : para
 PCC: pyridinium chlorochromate
 PG: protecting group
 Ph : phenyl
 ppm : part(s) per million
 PPTS : pyridinium *p*-toluenesulfonate
 Py : pyridine
 q : quartet
 quant. : quantitative
r. e. : reductive elimination
 Red-Al : sodium bis(2-methoxyethoxy)
 aluminum hydride solution
 rt : room temperature
 s : single
s: secondary
 sat. : saturated
 solv. : solvent
 SOMO: singly occupied molecular orbital
 t : triplet
t: tertiary
 TBAI : tetrabutyl-ammonium iodide
 TBDPS: tert-butyl dimethylsilyl
 TBS: tert-butyl dimethylsilyl
 TDA-1:
 Tris[2-(2-methoxyethoxy)ethyl]amine
 temp. : temperature
 Tf : trifluoromethanesulfonyl
 TFA: trifluoroacetic acid
 THF : tetrahydrofuran
 TIPS: triisopropylsilyl
 TLC : thin-layer chromatography
 TMEDA: tetramethylethylenediamine
 TMS : trimethylsilyl
 TPAP:tetrapropylammonium perruthenate
 Ts : tosyl
 VCP : vinylcyclopropane
 xantphos:
 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Z: zusammen
 μ : micro

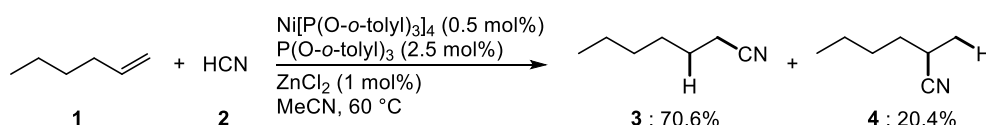
第一章 Ni 触媒を用いる新規ヒドロシアノ化反応の開発

序論

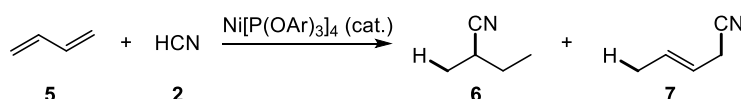
第一節 Ni 触媒による炭素-炭素多重結合のヒドロシアノ化反応

シアノ基は、カルボニル基やアミンに変換可能な汎用性の高い官能基であり、その導入法は活発に研究されてきた。中でも、活性化されていない炭素-炭素多重結合のシアノ化は、遷移金属触媒を用いる手法が主流であり¹、これまで Ni 触媒を用いる例が多数報告されている。1972 年の Taylor らによるアルケンのヒドロシアノ化反応^{1a}の開発を皮切りに、1974 年に Brown らが共役ジエン^{1b,o}、1982 年に Jackson らがアルキン^{1c,e}、1985 年には榊原らがアレン^{1f}を基質として用いるヒドロシアノ化反応をそれぞれ報告している (Scheme 1-4.)。しかし、これらの反応はいずれも単一異性体を得ることが困難であり、アレンのヒドロシアノ化反応に関しては、榊原ら以外には筆者らの研究グループしか報告例がない。そのため、基質適用範囲の詳細や環化反応への応用展開は研究例がほとんどなかった。

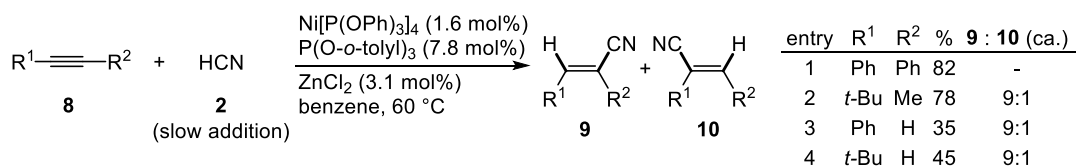
Scheme 1. Ni-catalyzed hydrocyanation of olefin



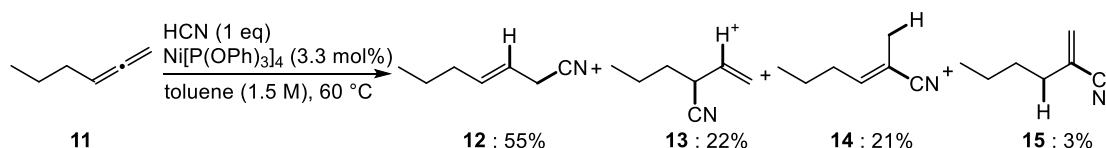
Scheme 2. Ni-catalyzed hydrocyanation of conjugated diene



Scheme 3. Ni-catalyzed hydrocyanation of alkyne

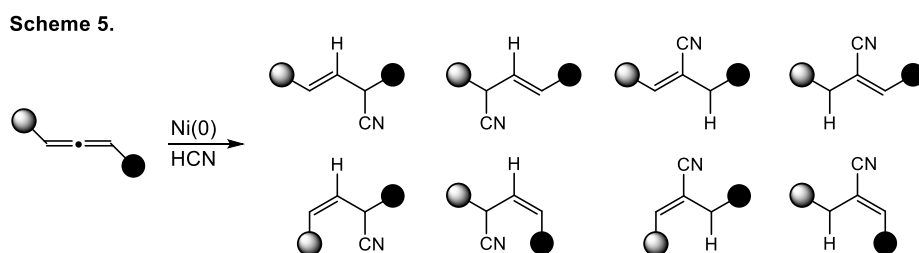


Scheme 4. Ni-catalyzed hydrocyanation of allene

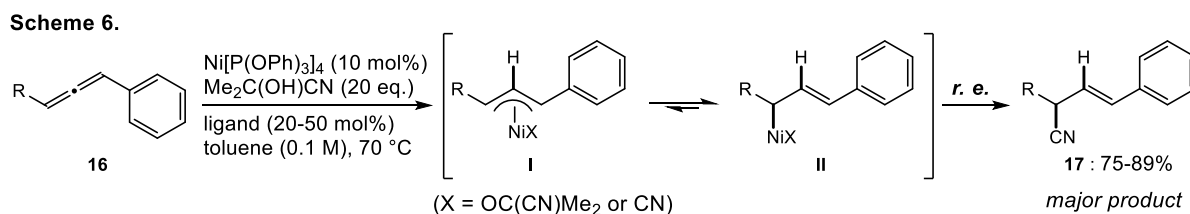


第二節 アレンのヒドロシアノ化反応

前述した Ni 触媒による炭素-炭素多重結合のヒドロシアノ化反応では、水素及びシアノ基導入における位置選択性の制御が困難であり、単一生成物は選択的に得られない。特に、非等価な炭素-炭素二重結合を持つアレンのヒドロシアノ化反応では位置選択性の制御が困難である (Scheme 4.)。そのため、アレンのヒドロシアノ化反応の選択性制御では、8 種の位置及び立体異性体の生成を厳密に制御する必要がある (Scheme 5.)。



この様に、アルケンやアルキンなどに比べてアレンのヒドロシアノ化反応では単一生成物を選択的に得ることは困難であり、これまでほとんど研究されていない。そうした背景を受け、当研究室では 1,3-二置換アレンを用いたヒドロシアノ化反応を詳細に検討し、一方に Ph 基を導入することで、高い位置選択性が発現することを見出した (Scheme 6.)²。



すなわち、アレン両端に置換基を有する場合、ヒドロニッケル化において水素がアレン中心炭素へ選択的に導入され、 π -アリル Ni 中間体 **I** が生じることが予想される。この際、二重結合が芳香環と共役し、尚且つより安定な *trans*-オレフィンが生成することにより平衡が中間体 **II** に傾き、還元的脱離が進行することで、**17** を主生成物として与えると考えられる。本系は、位置及び立体選択性が制御されたアレンのヒドロシアノ化反応としては初の成功例である。この際、芳香環の導入により中間体 **II** が位置及び立体選択的に生じることが見出されたため、本知見を基に新たな分子変換法を開発することにした。

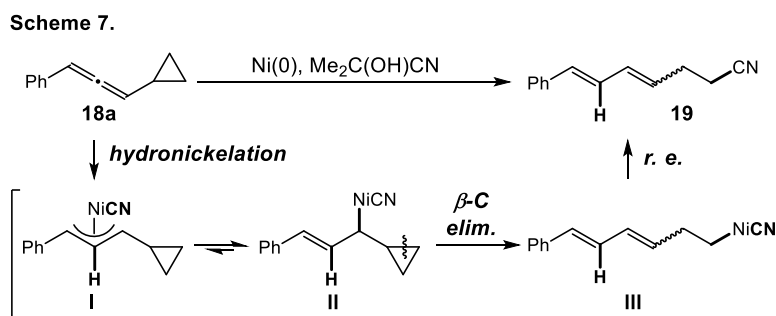
本論

第一節 アレニルシクロプロパンのヒドロシアノ化反応

はじめに、分子内に Ph 基とシクロプロパン環を持つ 1,3-二置換アレン **18a** を基質として設計し、新規環開裂反応への展開を試みた(Scheme 7)。

この場合、アレンへのヒドロニッケル化によってπ-アリル

Ni 中間体 **I** が生じた後、二重結合がベンゼン環と共役するように平衡が傾くことで中間体 **II** となり、続くβ-炭素脱離によるシクロプロパン環の開裂、還元的脱離を経てヒドロシアノ化体 **19** を与えると期待した。



第二節 反応条件の検討

実際にアレニルシクロプロパン **18a** を Ni 触媒存在下、HCN 等価体としてアセトンシアノヒドリン(AC)を加え、トルエン中で加熱したところ、当初予想した **19** は一切得られず、位置及び立体選択性が完全に制御されたヒドロシアノ化体 **20a** 及びトリエン **21a** を与えた(Table 1., entry 1)。なお、**20a** の構造は、二次元 NMR によって決定している。反応条件の検討では、温度の効果はわずかであったが(entry 2)、反応濃度の影響を大きく受ける事が分かった(entry 3, 4)。更に、配位子として P(OPh)₃ を添加することで **21a** の生成が抑制され、**20a** の収率が向上した(entry 5)。

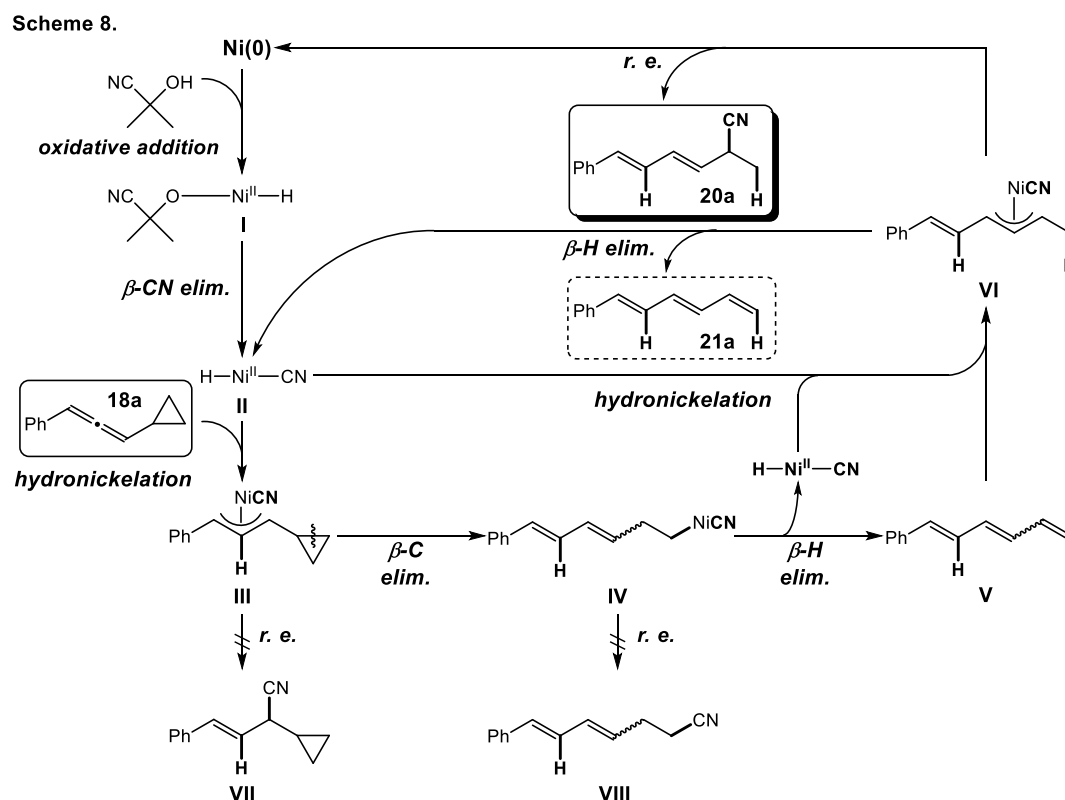
Table 1.

| entry | HCN source (eq.) | Ligand (mol%) | toluene (M) | temp. (°C) | time (h) | 20a (%) | 21a (%) |
|-------|-----------------------|---|-------------|------------|----------|---------|---------|
| 1 | AC (20) | - | 0.5 | 70 | 1 | 32 | 39 |
| 2 | AC (20) | - | 0.5 | 100 | 1 | 40 | 45 |
| 3 | AC (20) | - | 0.1 | 100 | 1 | 26 | 0 |
| 4 | AC (20) | - | 1.0 | 100 | 1 | 47 | 9 |
| 5 | AC (20) | P(OPh) ₃ (50) | 1.0 | 100 | 1 | 72 | 10 |
| 6 | AC (10) | P(OPh) ₃ (50) | 1.0 | 100 | 1 | 67 | 8 |
| 7 | TMSCN (10), MeOH (10) | P(OPh) ₃ (50) | 1.0 | 100 | 1 | 54 | 0 |
| 8 | AC (20) | PPh ₃ (50) | 1.0 | 100 | 1 | 40 | 39 |
| 9 | AC (20) | P(4-MeOPh) ₃ (50) | 1.0 | 100 | 1 | 15 | 60 |
| 10 | AC (20) | P(4-CF ₃ Ph) ₃ (50) | 1.0 | 100 | 1 | 40 | 0 |
| 11 | AC (20) | P(OMe) ₃ (50) | 1.0 | 100 | 1 | 59 | 0 |
| 12 | AC (20) | P(OEt) ₃ (50) | 1.0 | 100 | 1 | 13 | 51 |
| 13 | AC (10) | dppe (25) | 1.0 | 100 | 2 | 21 | 14 |
| 14 | AC (10) | dppp (25) | 1.0 | 100 | 2 | 42 | 18 |
| 15 | AC (10) | dppb (25) | 1.0 | 100 | 2 | 40 | 29 |
| 16 | AC (10) | xantphos (25) | 1.0 | 100 | 2 | 39 | 20 |

一方、アセトンシアノヒドリンの減量や、HCN源として MeOH 及び TMS-CN を用いた際には収率の低下が観測された(entry 6,7)。また、配位子としてアリールホスフィンやアルキルホスファイトを種々検討したが、いずれの場合も **20a** の収率は大幅に低下し(entry 8-12)、二座配位子として dppe, dppp, dppb, xantphos を用いた場合も収率は改善されなかった(entry 13-16)。

第三節 反応機構の考察

Table 1 の検討で得られた生成物の構造から、本系の触媒サイクルを次のように考察した (**Scheme 8**)。まず、アセトンシアノヒドリンの O—H 結合が Ni(0) に酸化的付加することで Ni(II) 錯体 **I** が生成し、続く β -CN 脱離を経て生じた **II** の **18a** へのヒドロニッケル化により、アレン中心炭素に水素が導入された π -アリル Ni 中間体 **III** が生成する。次に、**III** から β -炭素脱離が進行して *trans*-スチレンユニットを有する **IV** が生じ、続く β -水素脱離によってトリエン **V** が生成する。尚、**III**、**IV** からの還元的脱離によって生じるヒドロシアノ化体 **VII**、**VIII** は一切単離されていない。その後、生じた **V** の末端オレフィンへ位置選択的なヒドロニッケル化が起こることで π -アリル Ni 中間体 **VI** が生成し、位置選択的な還元的脱離によってシアノ基が導入されればヒドロシアノ化体 **20a** を、 β -水素脱離が進行すればトリエン **21a** を与える。



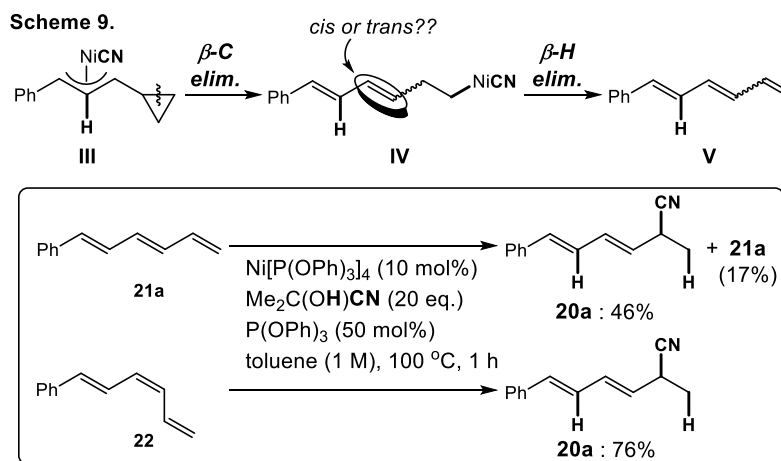
次に、生成物の構造から推定した反応機構を確認すべく、トリエン中間体**V**の反応性や生成経路の検証、及び重水素化実験を行った。

a) 共役トリエンの反応性の検証

まず、中間体として考えられる2種類の共役トリエン

21a, **22**を別途合成し、それぞれをヒドロシアノ化反応条件に付すことで、その反応性の違いを検証した(Scheme 9)。その結果、両者とも同一のヒドロシアノ化体**20a**を与えたものの、**21a**の場合は収率が低く、出発物質**21a**も17%回収されたのに対し、**22**の場合では**20a**のみを76%で与え、トリエンは回収されなかった。

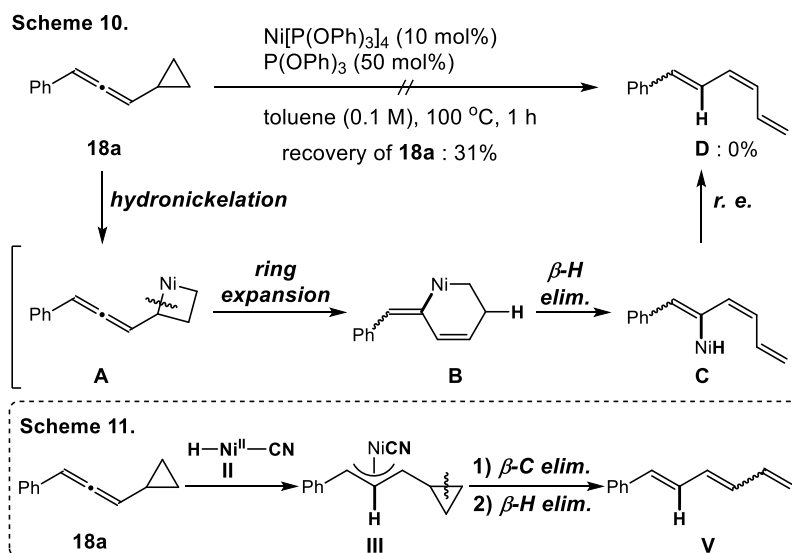
第二節の最適条件において72%の収率で**20a**が得られていることと本結果より、**III**からのβ-炭素脱離で生じる中間体**IV**は、*cis*体を主生成物として与えている事が示唆された。



b) トリエンの生成経路の検証

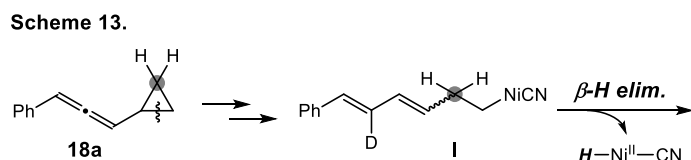
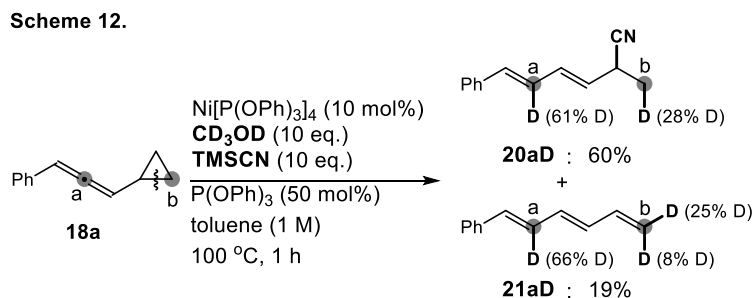
トリエンの生成経路としては、ヒドリド源が関与しない経路も想定される(Scheme 10)。すなわち、シクロプロパン環がNi(0)に酸化的付加して**A**が生じた後³、環拡大によってニッケラサイクル中間体**B**となれば、続くβ-水素脱離、還元的脱離を経てトリエン**D**が生成すると考えられる。本経路の可能性を検証するため、ヒドロシアノ化反応条件から、アセトンシアノヒ

ドリンを除いた条件に**18a**を付した。その結果、トリエン**D**は一切得られず、出発物質**18a**を31%回収するにとどまった。つまり本系では、トリエンの生成にはヒドリド源が必須であり、Ni(II)錯体のアレンへのヒドロニッケル化が引き金になっていることが示唆された(Scheme 11.)。



c) 重水素化実験によるヒドリド導入位置の確認

第三節で述べた推定反応機構が正しければ、ヒドリドは、アレン中心炭素 **a** 及びシクロプロパン環のメチレン炭素 **b** へ導入される。そこで、重水素化実験によりその確認を行った(**Scheme 12.**)。CD₃OD と TMSCN を用いて発生させた重シアン化水素⁴での反応を検討したところ、予想したニヶ所の炭素にのみ重水素が導入された付加体 **20aD** 及び **21aD** を与えた。



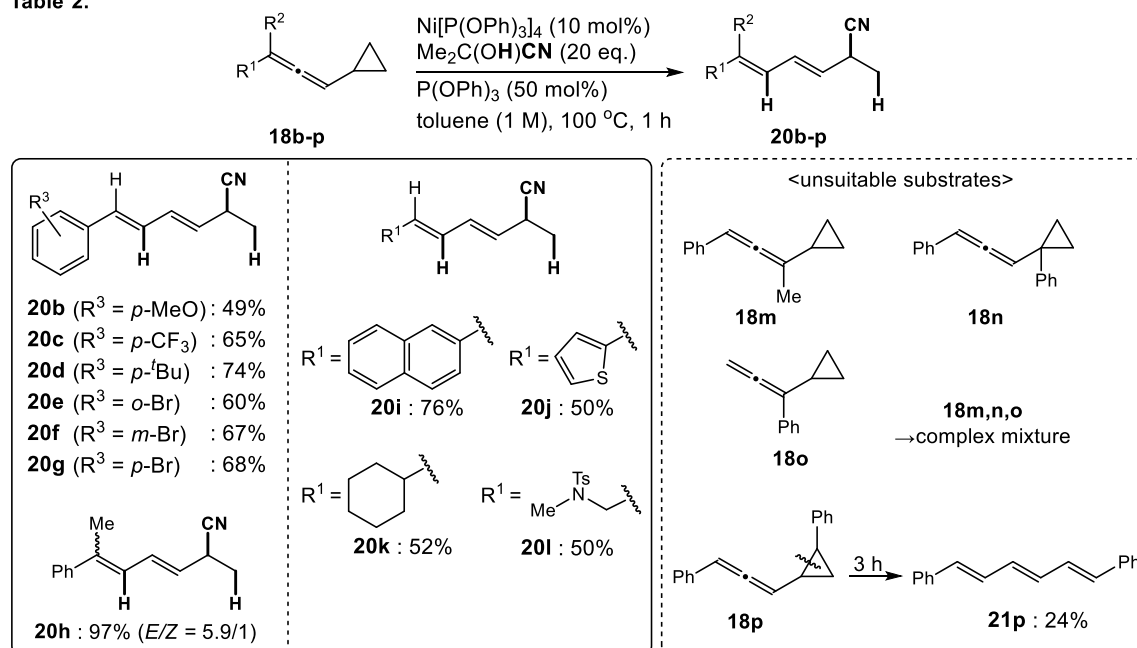
この際、重水素化率が低いのは、中間体 **I** からβ-水素脱離が起こる際に **18a** のメチレン水素由来の Ni-ヒドリド種が生じ、触媒反応に関与した為だと考えられる(**Scheme 13.**)。

これら **a)**—**c)**の結果により、前述した推定反応機構(**Scheme 8.**)に矛盾がないことを確認できた為、次に基質一般性を検討した。

第四節 基質一般性の検討

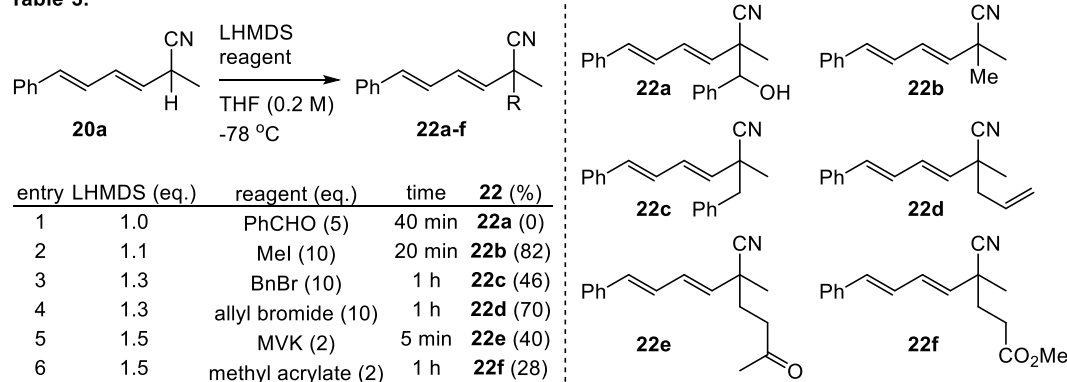
前述の最適条件(第二節、**Table 1.**, entry 5)を用いて、基質一般性の検討を行った(**Table 2.**)。まず、ベンゼン環 *p* 位の置換基効果を検討した(**18b-e**)。電子供与性基であるメトキシ基を導入した場合、収率が低下したものの、電子吸引性基である CF₃ 基や、アルキル基として *t*-Bu 基、ハロゲン原子としてブロモ基を導入した際には Ph 基の場合と同等の結果を与えた。この結果から、電子豊富な芳香環を用いた場合、反応性が低下すると考えられる。また、Br 基の導入位置による反応性の違いも検討した(**18e-g**)。その結果、ベンゼン環オルト位へ導入した際に若干の収率低下が見られたものの、大きな影響はなかった。また、シクロプロパン環が導入されていない炭素上に置換基を二つ導入した三置換アレン **18h** では、*E* 体及び *Z* 体の混合物 **20h** を 97% と高い収率で与えた。更に、芳香環として、ナフタレンやチオフェンを用いても反応は円滑に進行し(**18i, j**)、アルキル置換基であるシクロヘキシル基やトシルアミド誘導体でも同様の反応が進行することを見出した(**18k, l**)。一方、シクロプロパンが置換された炭素上にメチル基を導入した三置換アレン **18m** や、シクロプロパンのメチン炭素上に Ph 基を導入した基質 **18n**、及びシクロプロパン側に Ph 基を導入した **18o** を用いてヒドロシアン化反応を行うと、原料は消失するものの、複雑な混合物を与える結果に終わった。また、シクロプロパン環のメチレン炭素上に Ph 基を導入した基質 **18p** の場合、ヒドロシアン化体は一切得られず、Ph 基が導入された炭素とメチン炭素間の結合切断により生じるトリエン **21p** を収率 24% で与えた。トリエン **21p** は、両端に Ph 基が置換しており、立体的要因によって更なるヒドロシアン化反応を受けにくいと考えられる。

Table 2.



第五節 ヒドロシアノ化体の変換反応

Table 3.

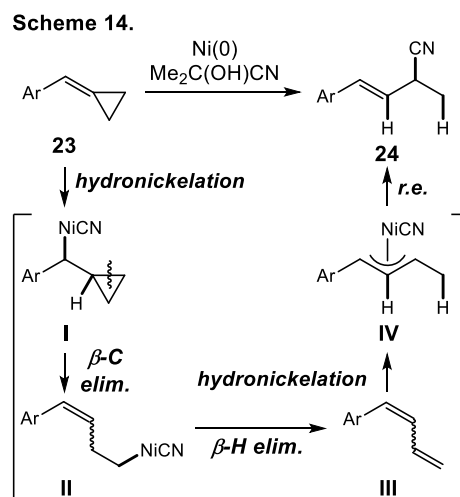
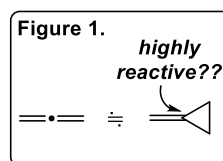


更に、得られたヒドロシアノ化体の合成化学的有用性を確認すべく、変換反応を検討した(**Table 3**)。そこで、LHMDSを用いてシアノ基 α 位の脱プロトン化を行った後、求電子剤やアルキルハライドを添加することで四級炭素の構築を図った。

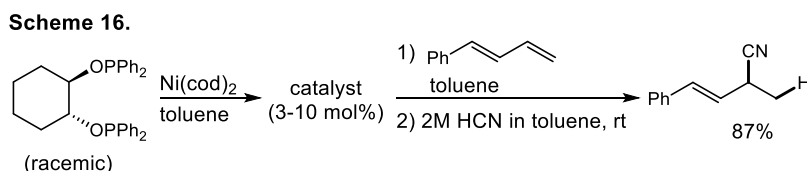
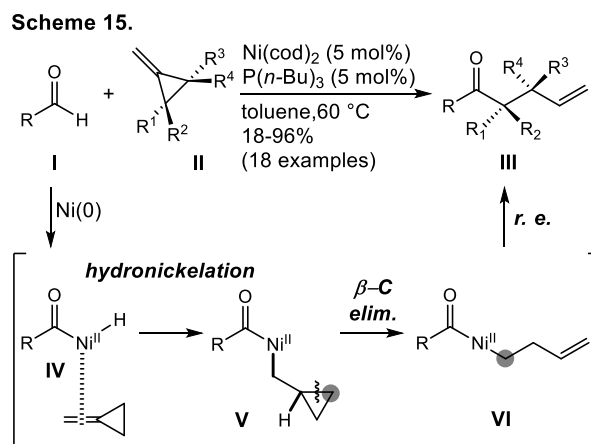
まず、PhCHOを検討したところ、反応は複雑化し、望みの付加体**22a**は得られなかった(entry 1)。一方、アルキル化剤として、ヨードメタン、ベンジルブロミド、アリルブロミドを検討したところ、望みのアルキル化体**22b,c,d**をそれぞれ収率82%、46%、70%で与えた(entry 2-4)。更に、求電子剤としてメチルビニルケトン(MVK)、アクリル酸メチルを用いた場合、低収率ながら1,4-付加体をそれぞれ40%、28%の収率で与えた(entry 5,6)。

第六節 メチレンシクロプロパンのヒドロシアノ化反応

ここまで述べてきたアレンシクロプロパンのヒドロシアノ化反応の検討過程で得た知見を基に、メチレンシクロプロパンを用いる環開裂反応の開発に着手した(**Figure 1.**)。メチレンシクロプロパンは、環内に sp^2 炭素を有するため、通常シクロプロパン環より歪んでおり、アレン等価体としてオレフィン内部炭素がアレン中心炭素と同様の高い反応性を示すと期待した。そこで、メチレンシクロプロパンをヒドロシアノ化反応条件に付した場合、次に示す環開裂反応が進行すると考えた(**Scheme 14.**)。すなわち、メチレンシクロプロパンが期待した反応性を有していれば、まず、シクロプロパン側の sp^2 炭素にヒドリド攻撃が起こり、中間体 **I** が生成した後、 β -炭素脱離によるシクロプロパン環開裂、続く β -水素脱離による共役ジエン中間体 **III** の生成が期待できる。その後、共役ジエンに対する位置選択的なヒドロニッケル化によって π -アリル Ni 中間体 **IV** が生成し、還元的脱離を経てシアノ基が導入されればヒドロシアノ化体 **24** に至ると予想した。



上述の Ni 触媒によるメチレンシクロプロパンの開裂反応は多数報告されている⁵。中でも、杉野目らが報告しているメチレンシクロプロパンのヒドロアルシル化反応では、**Scheme 14.** と類似した反応機構が提唱されている(**Scheme 15.**)^{5d}。すなわち、アルデヒド **I** が Ni(0) に酸化的付加することで **IV** が生じ、続くメチレンシクロプロパンへの位置選択的なヒドロニッケル化、 β -炭素脱離、還元的脱離を経て **III** を与える。



また、共役ジエンに対する位置選択的なヒドロシアノ化反応は RajanBabu らによって報告されており、**Scheme 14.**における **III** のヒドロシアノ化反応は位置選択的に進行することが期待できる(**Scheme 16.**)¹⁰。

実際に、Ph 基を有するメチレンシクロプロパン **23a** をヒドロシアノ化反応に付したところ、予想通りヒドロシアノ化体 **31a** を単一生成物として、63% の収率で与えた (**Table 4.**, entry 1)。ベンゼン環パラ位の置換基としては、電子吸引性基である CF₃ 基や、アルキル基として *t*-Bu 基、ハロゲン原子としてブromo基を導入しても円滑に反応は進行した (entry 2-4)。また、Br 基はメタ位に導入しても反応性に影響はなく (entry 5)、ナフタレンやチオフェンといった芳香環でもアレンと同様に高収率でヒドロシアノ化体を与えた (entry 6,7)。一方、置換基を二つ導入した基質 **23h,i** では反応が一切進行せず、原料回収にとどまった。これは、**23h,i** の様な四置換オレフィンに反応点が立体的に混みあっており、反応開始時のヒドロニッケル化が阻害された為だと考えられる。

Table 4.

| entry | 23 | Ar | 24 (%) |
|-------|------------|------------------------------|-----------------|
| 1 | 23a | Ph | 24a (63) |
| 2 | 23b | <i>p</i> -CF ₃ Ph | 24b (79) |
| 3 | 23c | <i>p</i> - ^t Bu | 24c (67) |
| 4 | 23d | <i>p</i> -BrPh | 24d (76) |
| 5 | 23e | <i>m</i> -BrPh | 24e (72) |
| 6 | 23f | 2-naphthyl | 24f (93) |
| 7 | 23g | 2-thiophene | 24g (75) |

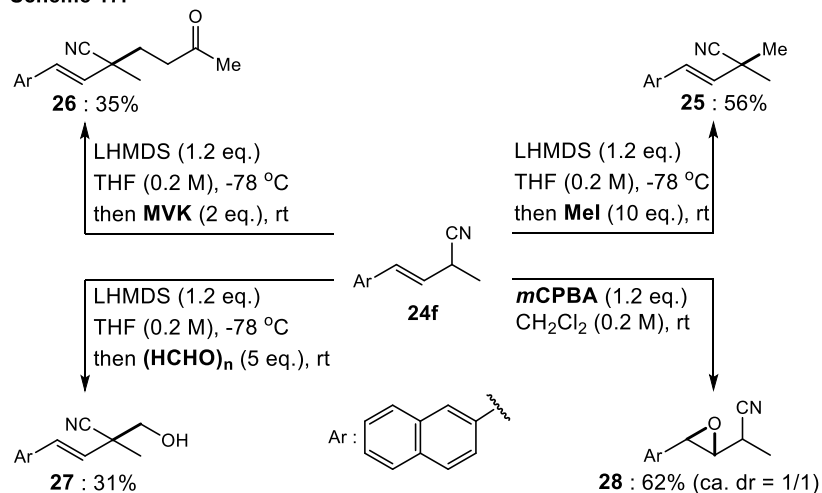
Reaction conditions:
 Ni[P(OPh)₃]₄ (10 mol%), Me₂C(OH)CN (20 eq.), P(OPh)₃ (50 mol%), toluene (1 M), 100 °C, 1 h

23a-i → **24a-i**

23h, i
 R = Me, Ph
 → No reaction

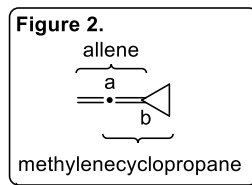
また、得られたヒドロシアノ化体 **24f** の変換反応も検討した (**Scheme 17.**)。まず、アレンシクロプロパンの場合と同様に、LHMDS を用いてシアノ基α位の水素を脱プロトン化した後、ヨードメタンを添加することでアルキル化体 **25** が収率 56% で得られた。また、メチルビニルケトン (MVK) を用いて、1,4-付加体 **26** を、パラホルムアルデヒドを加えることでアルコール体 **27** を得ることに成功した。更に、*m*CPBA によって *trans*-オレフィンのエポキシ化体 **28** が得られることも見出した。

Scheme 17.



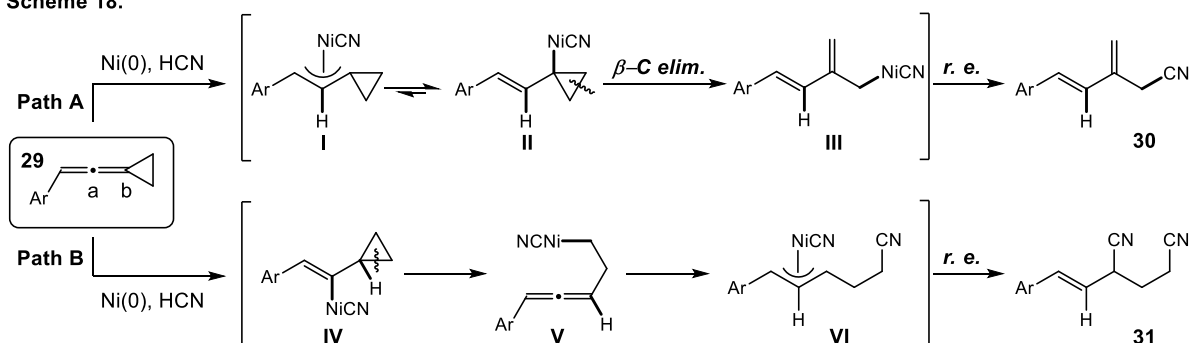
第七節 ビニリデンシクロプロパンのヒドロシアノ化反応

更なる検討として、ビニリデンシクロプロパンを出発物質に設定した (**Figure 2.**)。ビニリデンシクロプロパンは、アレン及びメチレンシクロプロパンユニットを有しており、ヒドロシアノ化反応における位置選択性の制御が課題となる。すなわち、ビニリデンシクロプロパンがアレンとして反応すれば、ヒドリド攻撃は炭素 **a** に起こり、メチレンシクロプロパンとしての性質を示せば、炭素 **b** へのヒドリド攻撃により反応が開始する。それぞれの場合において想定される反応機構を以下に示す。



ビニリデンシクロプロパン **29** がアレンとして反応した場合、まず、ヒドリド攻撃がアレン中心炭素 **a** に対して起こり、 π -アリル Ni 中間体 **I** が生じた後、 β -炭素脱離によるシクロプロパン環開裂、続く還元的脱離を経てヒドロシアノ化物 **30** を与える (**Scheme 18.**, Path A)。

Scheme 18.



一方、ビニリデンシクロプロパン **29** がメチレンシクロプロパンとしての性質を示した場合、ヒドリド攻撃は炭素 **b** に対して起こり、最初に中間体 **IV** が生じる。続く β -炭素脱離によってアレン中間体 **V** が生成し、還元的脱離によるシアノ基の導入とアレン部分へのヒドロニッケル化が進行すれば、 π -アリル Ni 中間体 **VI** を与え、続く位置選択的な還元的脱離を経てジシアノ体 **31** が生成すると考えられる (Path B)。

実際にビニリデンシクロプロパン **29a** をヒドロシアノ化条件に付したところ、**29a** はアレンとしての性質のみを示したものの、 β -炭素脱離による環開裂は一切進行せず、ヒドロシアノ化物 **32a** を単一生成物として収率 63% で与えた (**Scheme 19.**)。この際、シアノ基がベンジル位に導入された付加体 **33** は得られていない。想定した環開裂反応は進行しなかったものの、本反応は位置及び立体選択性が制御されたヒドロシアノ化反応であるため、次に基質検討を行うことにした。

Scheme 19.

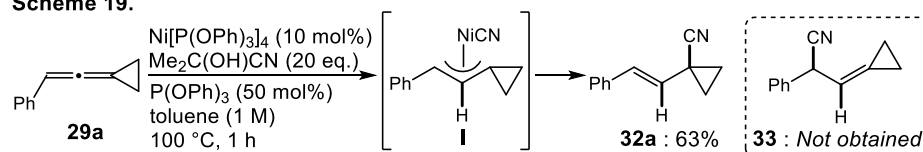
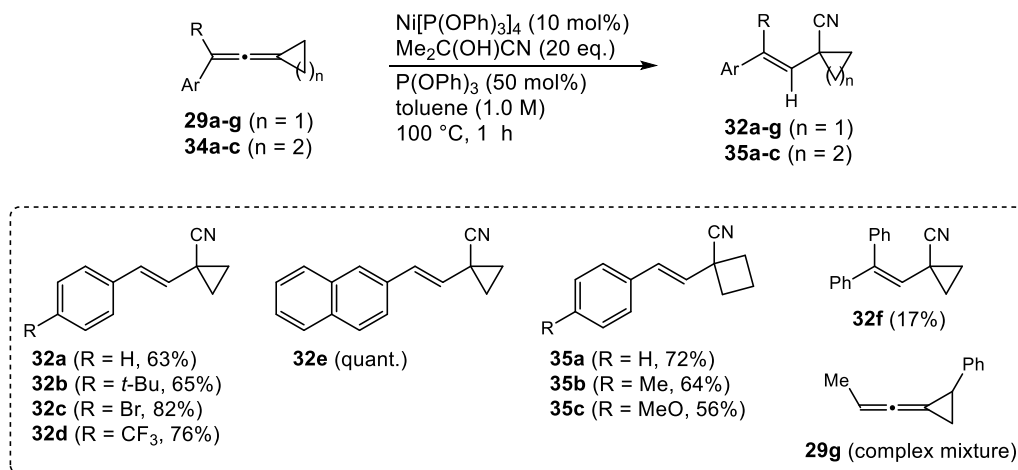


Table 5.



これまでの検討と同様に、ベンゼン環パラ位に *t*Bu 基、ブロモ基、CF₃ 基を導入しても反応は円滑に進行し、ヒドロシアノ化体 **32b-d** を与えた。また、ナフタレンを有する基質では定量的に **32e** が得られた。更に、シクロブタンをもつ基質 **34a-c** でも同様の反応が進行し、ベンゼン環パラ位にメチル基やメトキシ基を導入しても反応は円滑に進行した。

一方、Ar, R の両方に Ph 基を有する基質 **32f** では反応性が大幅に低下し、ヒドロシアノ化体の収率は 17%にとどまった。これは、**32f** は四置換アレンであるため、立体障害の影響により反応性が低下したためだと考えられる。また、アレン末端にメチル基及び、シクロプロパン環上に Ph 基を導入した基質 **29g** では反応が複雑化し、ヒドロシアノ化体 **32g** は一切得られなかった。この結果から、アレン上の芳香環は必須であり、シクロプロパン環上への置換基導入は反応の複雑化を招くことが示唆された。

本反応では、当初予想した環開裂反応は進行しなかったものの、得られる **32** や **35** はシクロプロパンやシクロブタン構造を有しており、ビルディングブロックとしての利用価値は高い。特にシクロプロパンは、遷移金属触媒を用いる反応系やラジカル反応条件において三炭素ユニットとして汎用される構造であるため、それらの検討に用いる基質を合成する上で **32** は有用な分子であると考えている。

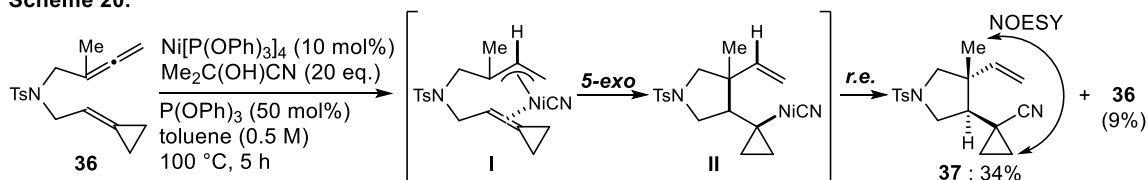
第八節 環化反応への展開

これまでの検討により、様々なヒドロシアノ化体を単一異性体として得ることに成功してきた。しかし、これらの反応で得られる生成物は鎖状化合物であったため、ビルディングブロックとしての利用価値がより高い環化体を与える反応の開発を次の研究課題に設定した。そこで、分子内に異なる二種類の炭素-炭素多重結合を持つ基質に対するヒドロシアノ化反応を検討することにした。なお本検討は、様々な炭素-炭素多重結合のヒドロシアノ化反応条件における反応性の違いの検証という側面も兼ね備えており、以下にその検討結果を示す。

a) アレン-メチレンシクロプロパン体の検討

第七節で述べた様に、ビニリデンシクロプロパンは、ヒドロシアノ化反応条件においてアレンとしての性質のみを示すことが示唆された。この結果から、アレンはメチレンシクロプロパンよりもヒドロニッケル化を受けやすいと考えられる。そこで、同一分子内にアレン、及びメチレンシクロプロパンを有する基質 **36** をヒドロシアノ化反応条件に付せば、アレンへのヒドロニッケル化を引き金とした環化反応の進行が期待できる。実際に基質 **36** を用いて検討したところ、予想通りアレンから反応が進行した環化体 **37** を単一成績体として得た (**Scheme 20.**)。なお環化体 **37** の立体化学は、メチル基とシクロプロピルメチレンとの NOESY 相関によって決定している。また、本反応において、メチレンシクロプロパンから反応が進行したヒドロシアノ化体や、シクロプロパン環が開裂した付加体は一切得られなかった。ビニリデンシクロプロパンのヒドロシアノ化反応の結果と併せて考えると、アレンはメチレンシクロプロパンよりもヒドロニッケル化に対する反応性が高いこと、及び Ni がシクロプロパンのメチン炭素上に生じた場合は (**Scheme 19.-I, Scheme 20.-II**)、 β -炭素脱離よりも還元的脱離が優先することが示唆された。

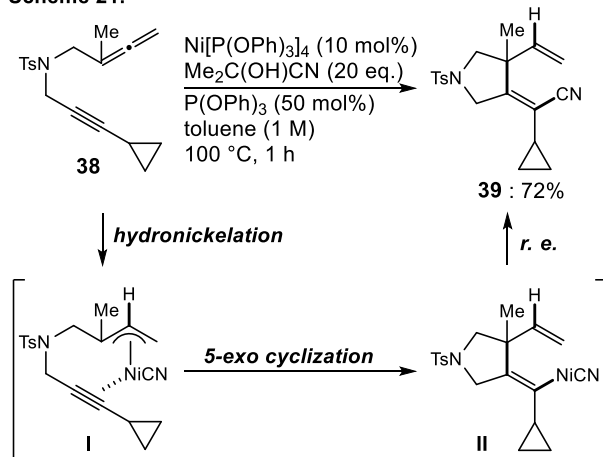
Scheme 20.



b) アレン-イン体の検討

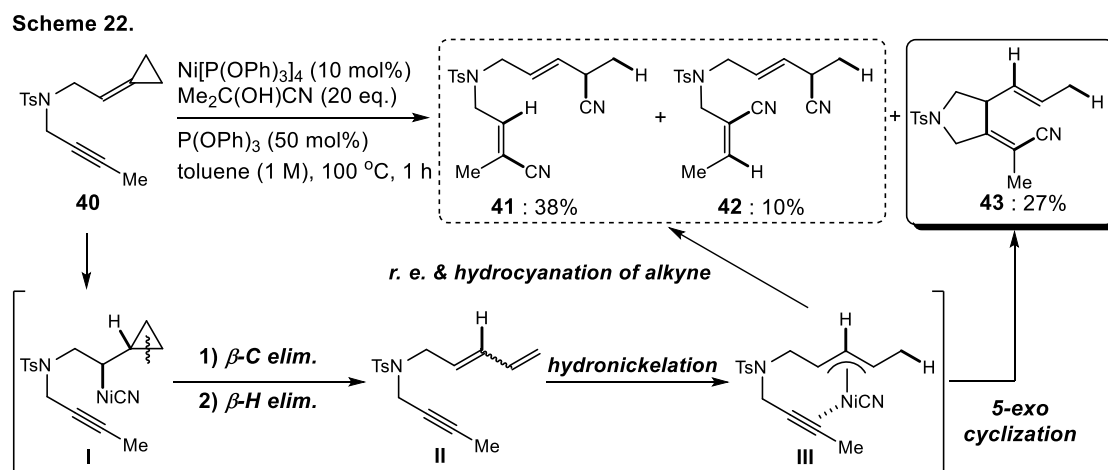
次に、アレン-イン体 **38** のヒドロシアノ化反応を検討したところ、シクロプロパン環が保持された環化体 **39** を収率 72% で与えた (**Scheme 21.**)⁷。この際、反応はアレンから進行しており、 π -アリル Ni 中間体 **I** が生じた後、*5-exo* 環化によりアルケニル Ni 中間体 **II** が生成し、続く還元的脱離によって環化体 **39** を与える。なお、**II** から β -炭素脱離が進行した付加体は一切得られなかった。本結果より、アレンはアルキンよりも高い反応性を有することが確認できた。

Scheme 21.



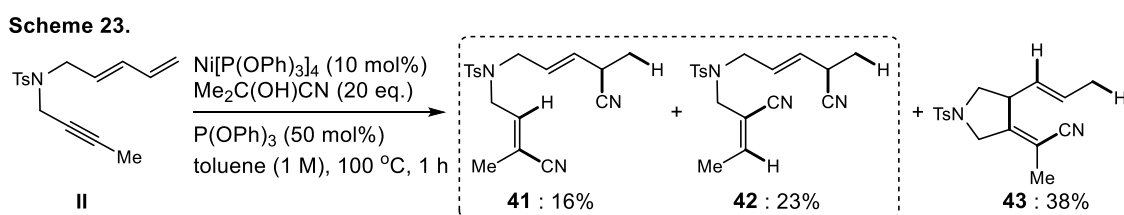
c) メチレンシクロプロパン - イン体の検討

先の検討 a), b)の結果から、ヒドロシアノ化反応条件において、アレンはメチレンシクロプロパンやアルキンよりも高い反応性を示すことが示唆された。そこで更なる検討として、分子内にメチレンシクロプロパン及びアルキンを有する基質 **40** を検討することで、両者の反応性を比較することにした(**Scheme 22.**)。その結果、メチレンシクロプロパン及びアルキンの両方がヒドロシアノ化された非環化体 **41**, **42** をそれぞれ 38%, 10% 与えるとともに、環化体 **43** を 27% の収率で得た。環化体 **43** に至る反応機構は次のように考察した。すなわち、最初にメチレンシクロプロパンに対するヒドロニッケル化によって中間体 **I** が生成した後、 β -炭素脱離、 β -水素脱離を経てジエン-イン中間体 **II** を与える。次に、**II** の末端オレフィンに対する位置選択的なヒドロニッケル化により π -アリル Ni 中間体 **III** が生成し、続いて *5-exo* 環化、還元的脱離が連続して起これば環化体 **43** に至る。一方、中間体 **III** からの還元的脱離シアノ基導入とともにアルキンのヒドロシアノ化反応が進行すれば、非環化体 **41**, **42** を与える。この際、アルキンがヒドロシアノ化されることで環化反応が進行しなかった **41** と **42** が合わせて 48% の収率で得られるのに対し、アルキンがヒドロシアノ化される前に環化反応が進行した **43** が 27% の収率で得られたことから、アルキンの方がメチレンシクロプロパンよりもヒドロニッケル化を受けやすいことが示唆された。



d) ジエン - イン体の検討

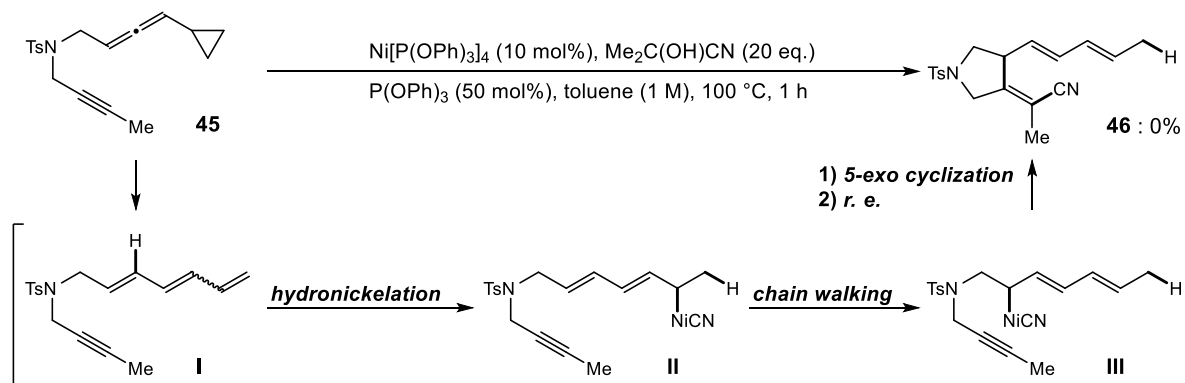
先の環化反応において、ジエン-イン **II** が生じている可能性が示唆されたため、次にジエン-イン体 **II** のヒドロシアノ化反応を検討した(**Scheme 23.**)。その結果、生成比は異なるものの、**Scheme 22.** と同一の非環化体 **41**, **42** 及び環化体 **43** を与えた。このことから、**Scheme 22.** のヒドロシアノ環化反応は、ジエン-イン中間体 **II** を経由していることが確認できた。この際、**Scheme 22.** に比べて環化体 **43** の収率が向上し、鎖状化合物 **41**, **42** の収率が低下したのは、**40** から **II** へ至る過程(**Scheme 22.**)におけるアルキンのヒドロシアノ化反応が **Scheme 23.** では抑制されたためだと考えられる。また、**41** と **42** が合わせて 39% で、**43** が 38% の収率で得られていることから、ジエンとアルキンはヒドロシアノ化反応において同等の反応性を示すことが示唆された。



e) アレニルシクロプロパン - イン体の検討

最後に、アレニルシクロプロパン - イン体 **45** に対し、ヒドロシアノ化反応を検討した(Scheme 24.)。この際、アルキンを持たない場合と同様にトリエン中間体 **I** が生成した後、末端オレフィンへの位置選択的ヒドロニッケル化、続くチェーンウォーキング⁶による炭素-Ni 結合の移動、中間体 **III** からの 5-exo 環化及び還元的脱離を経て環化体 **46** を与えると期待したが、複雑な混合物を与えるにとどまった。

Scheme 24.



以上の検討により、炭素 - 炭素多重結合のヒドロシアノ化反応における反応性の序列は、【アレン >> 共役ジエン ≒ アルキン > メチレンシクロプロパン】であることが示唆された⁷。このような知見は、今後 Ni 触媒を用いるヒドロシアノ化反応条件で基質を設計する上で重要な指針になると考えている。

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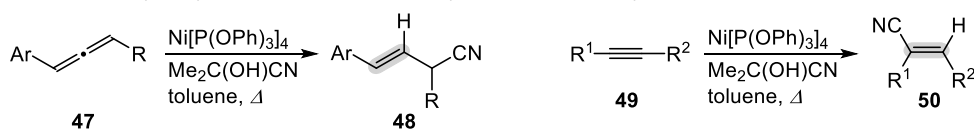
- (1) (a) Taylor, B. W.; Swift, H. E. *J. Catal.*, **1972**, *26*, 254.; (b) Brown, E. S. *Aspects of Homogeneous Catal.*, **1974**, *2*, 57. (c) Funabiki, T.; Yamazaki, Y.; Tarama, K. *J. Chem. Soc., Chem. Commun.*, **1979**, 1110.; (d) Jackson, W. R.; Lovel, C. G. *J. Chem. Soc., Chem. Commun.*, **1982**, 1231.; (e) Fallon, G. D.; Fizmaurice, N. J.; Jackson, W. R.; Perlmutter, P. J. *J. Chem. Soc. Chem. Commun.*, **1985**, 4.; (f) Sakakibara, Y.; Matsuzaka, S.; Nagamine, S.; Sakai, M.; Uchino, N. *Nippon Kagaku Kaishi*, **1985**, 409.; (g) Elmes, P. S., Jackson, W. R. *Aust. J. Chem.*, **1982**, *35*, 2041.; (h) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.*, **1992**, *114*, 6265.; (i) Goertz, V.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Chem. Eur. J.*, **2001**, *7*, 1614.; (j) Wilting, J., Janssen, M., Müller, C., Lutz, M., Spek, A. L., Vogt, D. *Adv. Synth. Catal.*, **2007**, *349*, 350.; (k) Falk, A., Göderz, A.-L., Schmalz, H.-G. *Angew. Chem. Int. Ed.*, **2013**, *52*, 1576.; for a review of nickel-catalyzed hydrocyanation, see: (l) Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. *Adv. Catal.* **1985**, *33*, 1.; (m) Bini, L., Müller, C., Vogt, D. *ChemCatChem*, **2010**, *42*, 590.; (n) Bini, L., Müller, C., Vogt, D. *Chem. Commun.*, **2010**, *46*, 8325. (o) Saha, B., RajanBabu, T. V.; *Org. Lett.* **2006**, *8*, 4657.
- (2) Arai, S.; Hori, H.; Amako, Y.; Nishida, A. *Chem. Commun.* **2015**, *51*, 7493.
- (3) Cyclopropane cleavage by Ni(0) via oxidative addition, see: (a) Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5798.; (b) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350.
- (4) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153.
- (5) For recent applications of the cleavage of MCP under Ni catalysis, see, (a) Ogata, K.; Shimada, D.; Furuya, S.; Fukuzawa, S. *Org. Lett.*, **2013**, *15*, 1182.; (b) Ogata, K.; Shimada, D.; Fukuzawa, S. *Chem. Eur. J.*, **2012**, *18*, 6142.; (c) Saito, S.; Maeda, K.; Yamasaki, R.; Kimura, T.; Nakagawa, M.; Kato, K.; Azumaya, I.; Masu, H. *Angew. Chem. Int. Ed.*, **2010**, *49*, 1830.; (d) Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.*, **2009**, *131*, 11298.; (e) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060.; For review, see (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.*, **2014**, *114*, 7317.
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第二章 Co 触媒によるジェンのラジカル環化反応

序論

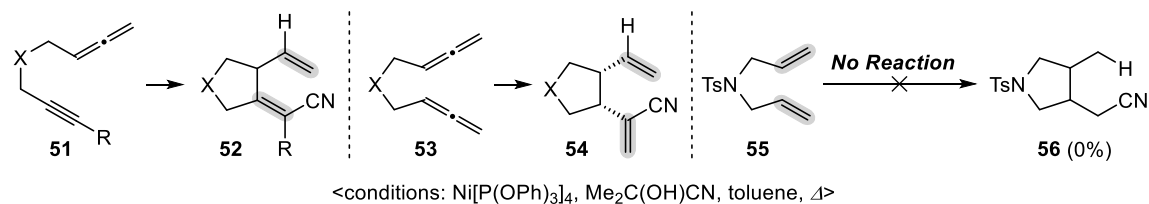
当研究室におけるこれまでの検討により、Ni 触媒とアセトンシアノヒドリンを用いる反応条件では、様々なアレンやアルキンのヒドロシアノ化反応が高い位置及び立体選択性を伴って進行することが判明した(Scheme 25.)¹。この際、アセトンシアノヒドリンを過剰に用いても、生成物であるアルケン体 **48** や **50** が更なるヒドロシアノ化反応を受けないことから、本反応条件においてアルケンはほとんど反応性を示さないことが示唆される。

Scheme 25. Hydrocyanation of allenes and alkynes under Ni-catalysis



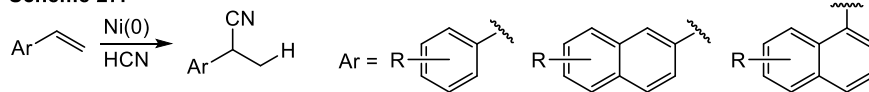
また、同様の反応系はアレン-イン体 **51** やビスアレン体 **53** に適用することで環化反応へ展開可能であることも見出しているが、この際得られる **52** や **54** に含まれるアルケンもヒドロシアノ化反応が進行することはなかった(Scheme 26.)。更に、ジェン体 **55** のヒドロシアノ化反応では出発物質 **55** が定量的に回収されたため、本条件におけるアルケンのヒドロシアノ化反応は困難であると判断した。しかし、アルケンにはアレンやアルキンに比べて簡便な合成手法が数多く知られており、**55** の様なジェン体のヒドロシアノ環化反応が開発できれば、簡便に合成可能な出発物質から様々な環化体を得ることが可能となる。そこで筆者は、従来の Ni 触媒を用いるヒドロシアノ化反応条件に代わる反応系を精査することにした。

Scheme 26. Hydrocyanative cyclization under Ni-catalysis

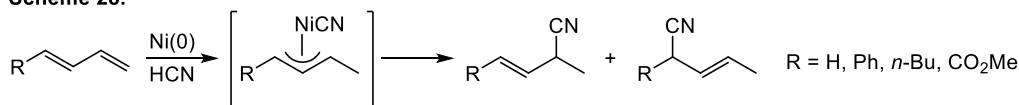


先に述べた通り、Ni 触媒によるアルケンのヒドロシアノ化反応はほとんど進行しない。こうしたアルケンの反応性の低さは先行研究においても報告されており、反応を円滑に進行させるためには、活性化されたアルケンを用いる必要がある。活性化されたアルケンとしてスチレン誘導体を用いた場合、高い位置選択性を伴ったヒドロシアノ化反応が円滑に進行するが、一置換アルケンを出発物質として用いる例が大半を占め、基質一般性は高くない(Scheme 27.)²。また、共役ジェンを用いる報告例もあるが、その多くは出発物質が 1,3-ブタジエンであることに加え、単一生成物を選択的に得ることが困難であり、その基質適用範囲は狭い(Scheme 28.)³。

Scheme 27.




Scheme 28.

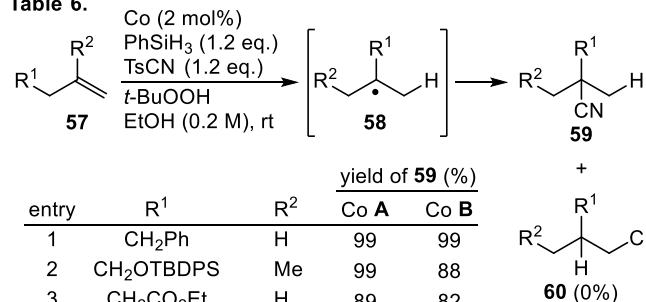


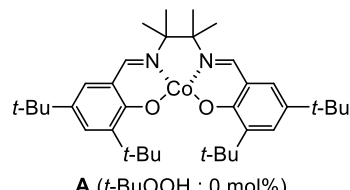
この様に、Ni 触媒と HCN によるアルケンへのヒドロシアノ化反応の多くは活性化されたアルケンを用いており、芳香環や二重結合と共役していない不活性アルケンを経験として用いる場合には、 AlCl_3 や ZnCl_2 などの Lewis 酸を添加する必要がある⁴。

一方、Carreira らによって報告された Co 触媒を用いるアルケンへのヒドロシアノ化反応は、不活性なアルケンを経験として用いることが可能である (Table 6)⁵。本反応では、 PhSiH_3 が水素源、TsCN がシアノ源として添加されており、Ni 触媒の系で用いられる有毒なシアノ化水素を必要としないという特徴がある。また、中間体としてはアルキルラジカルが想定されており、Markovnikov 則に従ってより安定な中間体 **58** が生じるように反応が進行するため、**60** は生成せず、**59** のみを選択的に与える。更に、基質一般性も高く、シリルエーテル、エステル、アミド、ケトン、アルデヒドなど様々な官能基を有するアルケンが適用可能である。本反応では、Co 触媒 **A**, **B** が有用であるが、**B** を用いる際には $t\text{-BuOOH}$ の添加が必要であること、及び **A** を用いた場合の方が収率良くヒドロシアノ化体を与えることから、出発物質にジエンを用いればヒドロシアノ環化反応に展開できると期待した (Scheme 29.)。

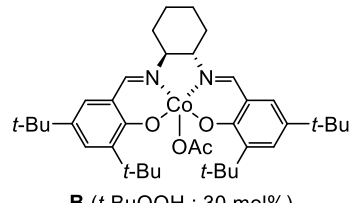
Table 6.

| entry | R ¹ | R ² | yield of 59 (%) | |
|-------|--|----------------|------------------------|------|
| | | | Co A | Co B |
| 1 | CH ₂ Ph | H | 99 | 99 |
| 2 | CH ₂ OTBDPS | Me | 99 | 88 |
| 3 | CH ₂ CO ₂ Et | H | 89 | 82 |
| 4 | C(O)NHPh | Me | 87 | 86 |
| 5 | CH ₂ C(O)Ph | H | 91 | 40 |
| 6 | OHC-  | H | 81 | 64 |



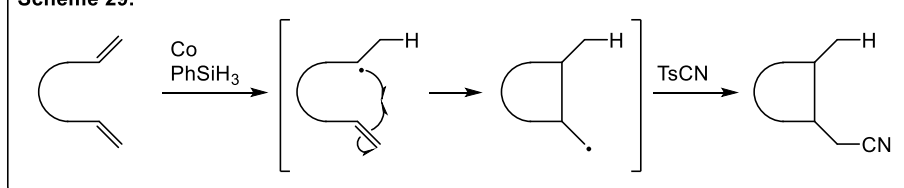


A ($t\text{-BuOOH}$: 0 mol%)



B ($t\text{-BuOOH}$: 30 mol%)

Scheme 29.



本論

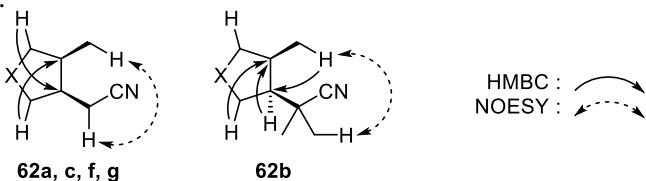
第一節 基質一般性の検討

最初に、Carreira らが報告している最適条件をジエン体 **61a-j** に適用し、五員環形成を検討した (Table 7.)。まず、対称ジエン **61a** を用いたところ環化体 *cis*-**62a** が 81% で得られた。この際、*cis* 体が選択的に得られたのは、**64** の様なコンフォメーションを経て環化反応が進行したためだと考えられる。また、同様の反応は触媒量を 0.5 mol% に減量しても進行し、*cis*-**62a** のみを収率 55% で与えた。なお、得られた環化体の立体化学は NOESY 測定により決定している (Figure 3.)。

Table 7.

| substrate | product | substrate | product |
|----------------|---|----------------|---|
| 61a | Co (2 mol%) : <i>cis</i> - 62a (82%, 4 h) Co (0.5 mol%) : <i>cis</i> - 62a (55%, 24 h) | 61f | rt : 62f (68%, <i>cis/trans</i> = 2.5/1, 6 h) 0 °C : 62f (43%, <i>cis/trans</i> = 2.5/1, 24 h) |
| 61b | <i>cis</i> - 62b (62%, 9 h) | 61g | 62g (47%, <i>cis/trans</i> = 2.3/1, 24 h) |
| 61c | 63c (72%, 9 h) | 61h | 62h (0%, 24 h) |
| 61d | 62d (0%, 5 h) | 61i | 62i (0%, 16 h) |
| 61e | 62e (0%, 7 h) | 61j | 62j (70%, 3 h) <i>single isomer</i> |

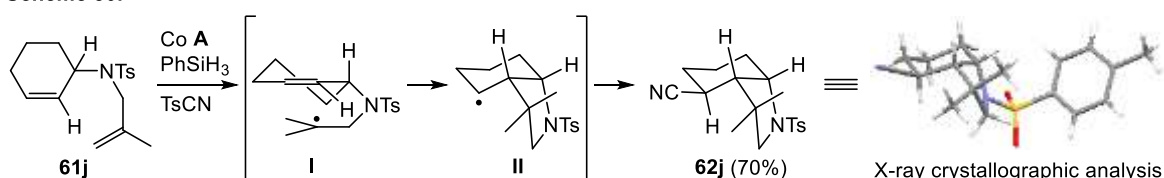
Figure 3.



次に、一方のアルケン末端にメチル基を二つ有する **61b** を検討したところ、**cis-62b** を単一生成物として与えた。この際、三置換アルケンから反応が進行することで、より安定な三級ラジカルを経由する環化反応も考えられるが、**cis-62b** が単一生成物として得られたことから、本基質の場合は立体障害の影響が大きく、一置換の末端アルケンから位置選択的に反応が進行したと考えられる。一方 **61c** を用いた場合は、より安定な三級ラジカルを与える二置換アルケンから位置選択的に環化反応が進行した。また、アルケン末端に Ph 基を有する **61d** を用いた検討では、ベンジル位のラジカルが優先的に生じ、六員環形成が進行することを期待したが、反応は複雑化し、環化体を得ることは出来なかった。アルケン内部にケイ素を有する **61e** の場合も同様に反応は複雑化し、環化体は得られなかった。

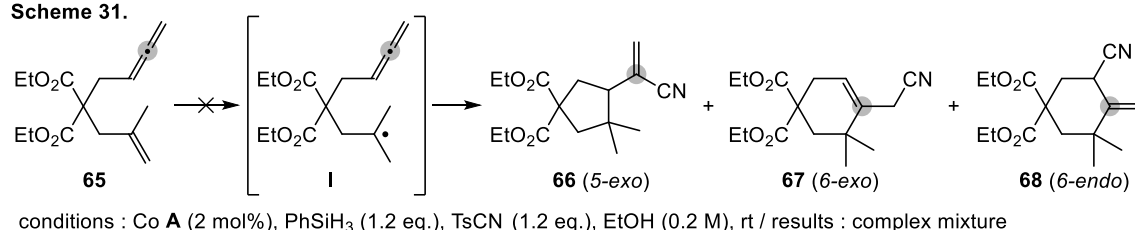
続いて、アルケン部位を窒素及びケイ素で架橋した基質の反応性を検討した(**61f-j**)。まず、**61f** を検討したところ、マロン酸誘導体の場合とは異なり、**cis** 体と **trans** 体の混合物として **62f** を与えた。そこで、ジアステレオ選択性の向上を期待して、0 °C において同様の環化反応を検討したが、ジアステレオマー比を保ったまま収率が低下する結果に終わった。また、アニリン誘導体 **61g** を用いた際も **61f** の場合と同程度のジアステレオマー比で環化体を与えたが、Boc 基で保護した基質 **61h** では反応が複雑化し、環化体は得られなかった。更に、ケイ素で架橋した基質 **61i** も検討したが、こちらの場合も反応は複雑化し、**62i** は得られなかった。最後に、縮環骨格の構築を期待してシクロヘキセンを有する **61j** を検討したところ、環化体 **62j** が単一異性体として得られた。この際、環化体の立体化学は X 線結晶構造解析によって決定された(**Scheme 30**)。環化体 **61j** が単一異性体として得られた理由は、三級ラジカルから環化反応が進行する際に、**I** の様な半イス型のコンフォメーションを経由することで中間体 **II** が立体選択的に生じ、続くシアノ化が convex 面から進行したためだと考えられる。

Scheme 30.

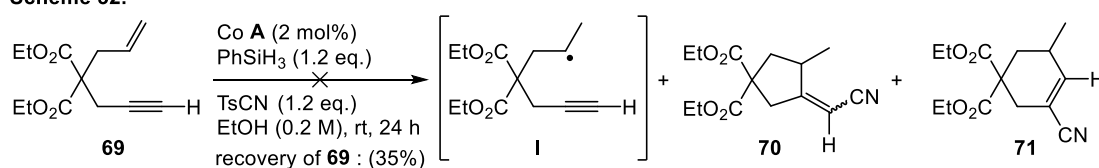


また、ジエンの他にアレン-イン体 **65** 及びエン-イン体 **69** を用いた検討も行ったが、いずれの場合も反応は複雑化し、想定される環化体は得られなかった(**Scheme 31, 32**)。

Scheme 31.

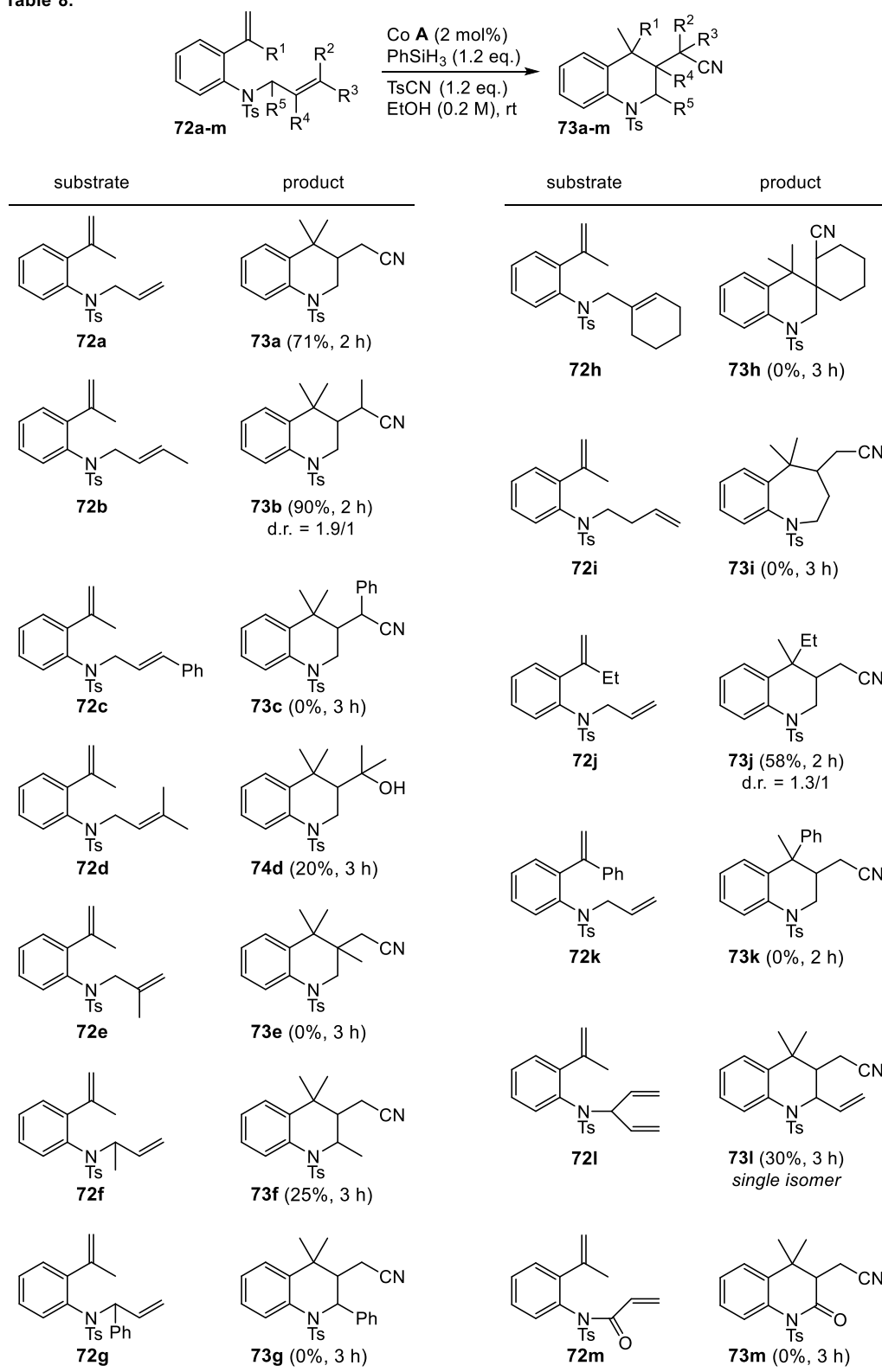


Scheme 32.



次に基質 **72** を用いて六員環形成を検討した(**Table 8.**)。本基質では、ベンジル位かつ三級のラジカルを経由することで、環化体 **73** の生成が期待できる。そこで、まず **72a** を検討したところ、環化 **73a** が収率 71% で得られた。また、アルケン末端にメチル基を導入した場合は環化体 **73b** がジアステレオマー混合物として収率良く得られた。

Table 8.

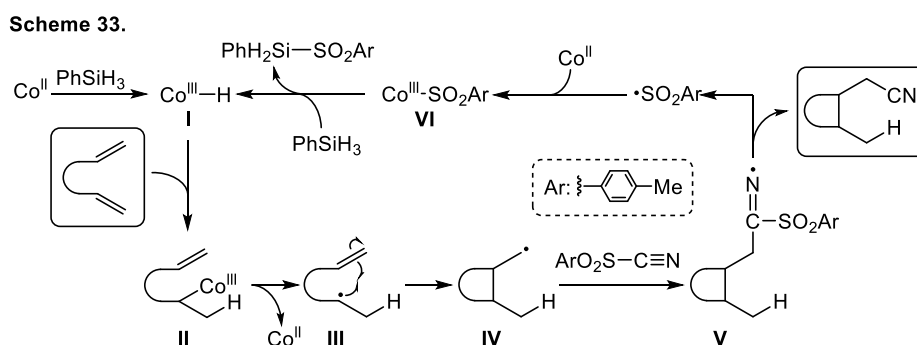


一方、アルケン末端に Ph 基を導入した際には反応が複雑化し、**73c** は得られなかった。また、アルケン末端にメチル基を二つ有する基質 **72d** では、シアノ基ではなく水酸基が導入された環化体 **74d** を得た。本環化体の生成は、環化によって生じた三級ラジカルが立体障害の影響により TsCN と反応せず、溶存酸素と反応したためだと考えられる。また、**72e** を用いた場合、反応が複雑化した。これは、どちらのアルケンが反応しても三級ラジカルを与えるため、位置選択性に有意な差が生じなかったためだと予想される。更に、 R^5 にメチル基を有する基質を検討したところ、低収率ながら環化体 **73f** が得られたが、同じ位置に Ph 基を持つ **72g** では複雑な混合物を与えるのみであった。

次に、**72h** を用いたスピロ環構築、及び **72i** を用いる七員環構築を検討したものの、いずれも望みの環化体を得ることは出来なかった。そこで再度六員環形成の検討に戻り、 R^1 の置換基効果を検証することにした。その結果、エチル基を有する **72j** では環化体を収率 58% で与えたが、Ph 基を導入した際には、環化体は得られなかった。これは、生じたラジカルが立体的に嵩高く、環化反応が進行しなかったためだと考えられる。更に、 R^5 の検討として、ビニル基を有する **72l** を用いたところ、環化体 **73l** を単一異性体として得ることが出来たが、立体化学に関しては未決定である。この際低収率にとどまったのは、得られる環化体 **73l** のオレフィン部位において、更なるヒドロシアノ化や水和反応が進行している為だと考えられるが、それらに相当する生成物を単離することは出来なかった。また、Carreira らによる先行研究において適用可能であったアミドを有する **72m** のヒドロシアノ化では反応が複雑化し、望みの環化体を得ることは出来なかった。

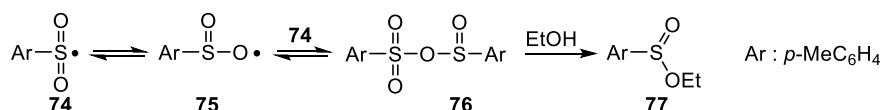
第二節 反応機構の考察

本反応の機構は以下の様に考察している (Scheme 33.)⁶。すなわち、まず二価のコバルト触媒と PhSiH_3 から三価のコバルトヒドリド **I** が生じ、アルケンに対する Markovnikov 則に従ったヒドロコバルト化により中間体 **II** を位置選択的に与える。その後 Co 触媒が脱離することでラジカル中間体 **III** を与え、続くラジカル環化、TsCN への付加を経て中間体 **V** に至り、本中間体からスルホニルラジカルの脱離を伴って環化体を与える。この際生じたスルホニルラジカルは二価コバルト、 PhSiH_3 と順次反応することにより、再度コバルトヒドリド **I** を与えると考えられる。



また、本反応においてスルホン酸エステル **77** が得られることから、スルホニルラジカルは以下の反応にも関与していることが示唆される (Scheme 34.)。すなわち、スルホニルラジカル **74** は **75** と平衡であり、これらから **76** が生じた後、溶媒であるエタノールと反応し、スルホン酸エステル **77** に至ると考えられる。

Scheme 34.

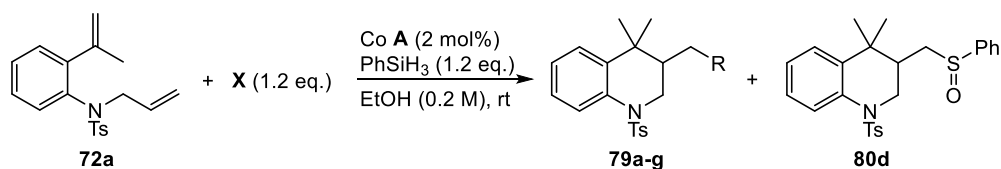


第三節 シアノ基以外の官能基導入を伴う環化反応の検討

前節の反応機構で示した様に、本反応においてスルホニル基は有用な脱離基となることが示唆された。そこで、TsCN と同様にスルホニル基を有する試薬をラジカルアクセプターとして加えれば、シアノ基以外の官能基を導入する手法になると考えた(**Table 9**)。

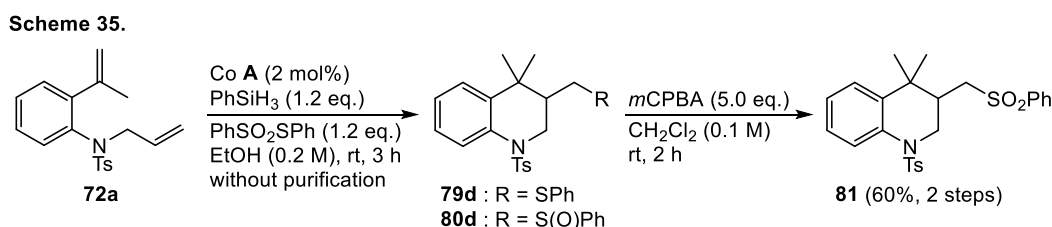
まず、アルケンの両端にベンゼンスルホニル基を有する試薬を検討したが、反応は一切進行しなかった(entry 1)。次に、一端のベンゼンスルホニル基を Ph 基へと変更したところ、この場合は反応が複雑化し、望みの環化体 **79b** は得られなかった(entry 2)。また、生じたアルキルラジカルが窒素と結合を形成した後にスルホニルラジカルが脱離することを期待してスルホニルイミンを検討したが、反応は一切進行しなかった(entry 3)。一方、PhSO₂SPh や TsSePh を用いた場合には反応が円滑に進行し、環化体 **79d,e** をそれぞれ得た(entry 4, 5)。なお、SPh 基が酸化されたスルホキシド体 **80d** も副生した(entry 4)。また、環化体 **79e** の構造は X 線結晶構造解析によって確認している(**Figure 4**)。更に、TsCl⁷ や TsN₃⁸ も検討したが、いずれの場合も望みの環化体を得ることは出来なかった。

Table 9.



| entry | X | time (h) | R | 79 (%) | comment |
|-------|------------------------|----------|----------------|-----------------|------------------|
| 1 | | 16 | | 79a (0) | No Reaction |
| 2 | | 3 | | 79b (0) | complex mixture |
| 3 | | 20 | | 79c (0) | No Reaction |
| 4 | PhO ₂ S-SPh | 3 | SPh | 79d (56) | 80d (23%) |
| 5 | Ts-SePh | 14 | SePh | 79e (61) | - |
| 6 | Ts-Cl | 3 | Cl | 79f (0) | No Reaction |
| 7 | Ts-N ₃ | 24 | N ₃ | 79g (0) | complex mixture |

次に、得られた環化体の変換反応を検討した。先の検討において SPh 基の導入を試みた際、望みの環化体 **79d** に加えてスルホキシド体 **80d** も副生成物として得られたため、これらを酸化してスルホン体 **81** へ収束させることを試みた(Scheme 35.)。検討の結果、一段階目の環化反応で **79d** 及び **80d** の生成を確認後、減圧下で溶媒を留去し、ジクロロメタン及び *m*CPBA を加えて室温で攪拌することによりスルホン体 **81** が単一生成物として得られることを見出した。



また、環化体 **79e** の変換反応の検討により、過酸化水素による酸化、脱離反応を経てエキソメチレン体 **82** を定量的に与えることを見出している(Scheme 36.)。本反応も Scheme 35. のスルホン化と同様にワンポット合成が可能であり、二工程収率 52% で環化体 **82** を与えた。

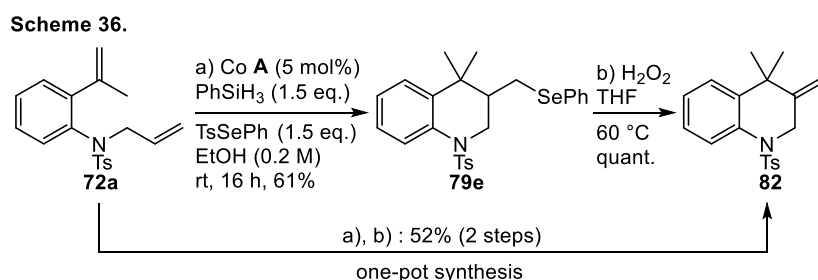
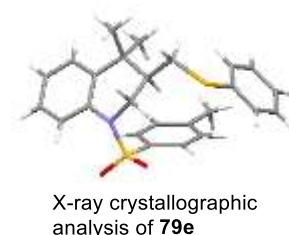
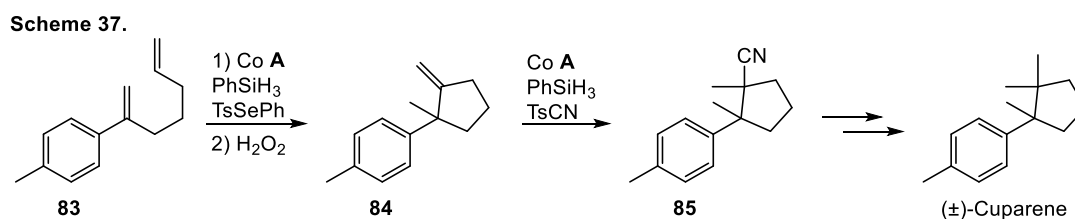


Figure 4.

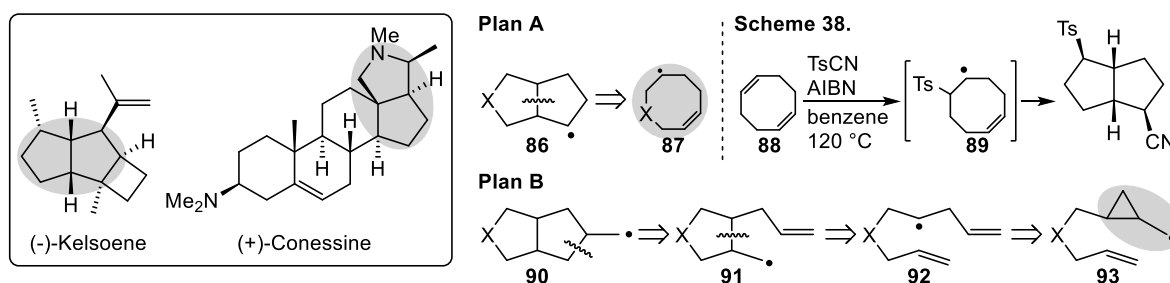


本反応によって生じるエキソメチレンは、Co 触媒によるヒドロシアノ化反応を適用することで四級炭素を与えるため、その利用価値は高い(Scheme 37.)。例えば、ジエン **83** に Scheme 36. で見出した条件を適用すれば、エキソメチレン体 **84** を与え、続くヒドロシアノ化、シアノ基のメチル基への変換による Cuparene の合成が期待でき、今後検討する予定である。

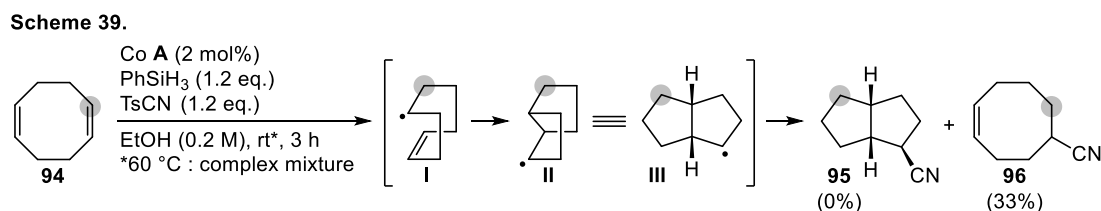


第四節 [3,3,0]オクタン骨格構築法の開発

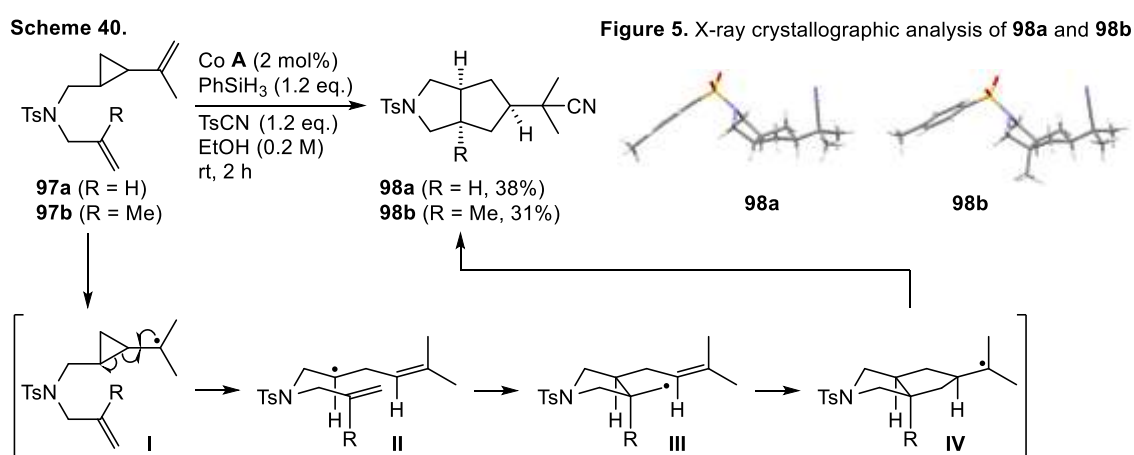
ジエンを用いたラジカル環化反応の更なる展開として、[3,3,0]オクタン骨格の構築を目指すことにした。本骨格は(-)-Kelsoene や(+)-Conessine など様々な天然物に含まれる重要構造であり、その構築法の開発は重要な研究課題である。筆者は、ラジカル環化反応によって本骨格を構築する方法として二種類の合成計画を立てた(Plan A, B)。Plan A では、ラジカル中間体 **86** を鍵中間体として設定し、本中間体はシクロオクテンラジカル **87** からの環化反応により導くことが出来ると考えた。この様なシクロオクテンラジカルを経由する環化反応は既に知られており、シクロオクタジエンに対する TsCN の付加反応がラジカル反応条件下において進行することが見出されている(Scheme 38.)⁹ 一方、Plan B では鍵中間体 **90** を設定した。**90** は連続した二度の五員環形成により中間体 **92** から導くことが可能であると考え、その前駆体にはシクロプロピルラジカル中間体が適切であると判断し¹⁰ それぞれ検討に着手した。



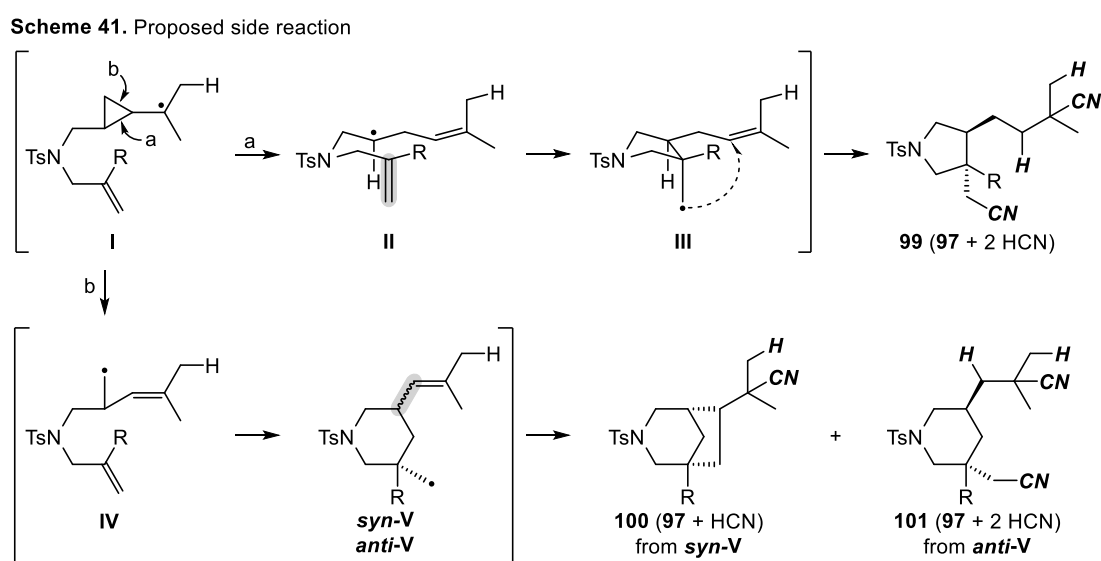
まず、シクロオクタジエンを出発物質とするヒドロシアノ化反応を検討した(Scheme 39.)。本反応では、最初にラジカル中間体 **I** が生じた後、環化反応によって **II** を与え、続くシアノ化が convex 面から進行することで **95** を単一異性体として与えると期待した。しかし、実際には一方のアルケンのみがヒドロシアノ化された **96** しか得られなかった。この際、環化反応が円滑に進行しなかった原因は、室温下において **II** の様なコンフォメーションを取ることが困難であったためだと考え、同様の反応を 60 °C で検討したが、反応は複雑化し **95** 及び **96** のいずれも得られなかった。



次に、ビニルシクロプロパン-エン体 **97** を用いて、シクロプロピルラジカルを経由するタンデム環化反応を検討したところ、望みの環化体 **98** を単一異性体として得ることに成功した (Scheme 40.)。本反応ではまず、ビニルシクロプロパンへのヒドロコバルト化が優先して中間体 **I** を与えた後、位置選択的なシクロプロパン環開裂によって **II** が生じると考えられる。その後、二度の五員環形成が **II**, **III** の様なコンフォメーションを経て進行し、三級ラジカル **IV** を立体選択的に与えることで環化体 **98** が単一異性体として生成したと予想される。なお、環化体 **98a** 及び **98b** の立体化学に関しては X 線結晶構造解析によって決定している (Figure 5.)。この際、アルケン内部に Me 基を導入した **97b** を用いた場合でも、**97a** と同程度の収率で環化体を与えたことから、ビニルシクロプロパンは単純アルケンよりも高い反応性を示すことが示唆された。これは、シクロプロパン環の歪みによって、ビニルシクロプロパン部位が共役ジエンに近い反応性を有している為だと考えられる。



本反応では、望みの環化体 **98** を得ることが出来たものの、低収率にとどまっている。これは以下の副反応が競合している為だと考察した (Scheme 41.)。



まず、 $^1\text{H NMR}$ の測定結果より、環化体 **98** 以外に得られた副生成物は、いずれもアルケンを持たないことが示唆された。また、質量分析を行ったところ、出発物質 **97** に対して HCN が一分子あるいは二分子付加していることが示唆されたため、それらの条件を満たす機構を **Scheme 41.** に示している。

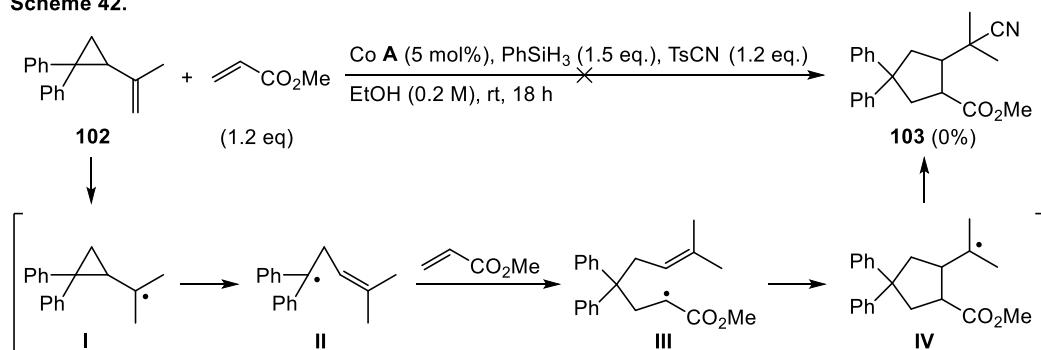
上段に示した経路では、中間体 **I** が生じた後、望みの反応と同様に a で示した結合が開裂することで **II** を与える。この際、環化反応が **II** で示したコンフォメーションを経由すると、続く五員環形成は反応点が遠く、生じる炭素骨格の歪みの為に進行しないことが予想される。そのため、ラジカル **III** は TsCN に捕捉され、反応に関与しなかった三置換アルケンに対するヒドロシアノ化反応が進行することで、出発物質 **97** に HCN が二分子付加した **99** に至ると考えられる。

下段に示した経路では、中間 **I** から b で示した結合の開裂による **IV** の生成を想定している。本中間体から環化反応が進行すると、ラジカルが生じる炭素とアルケン側鎖が *syn* 及び *anti* の位置関係となる二種類の間mediate **V** の生成が想定される。この際、*syn-V* からはラジカル環化反応に続くシアノ化により、出発物質 **97** に HCN が一分子付加した **100** が生成すると考えられる。一方、*anti-V* からの環化反応は困難であることが予想され、 TsCN による補足とアルケン部位のヒドロシアノ化によって出発物質 **97** に HCN が二分子付加した **101** に至ると考えられる。

第五節 分子間反応の検討

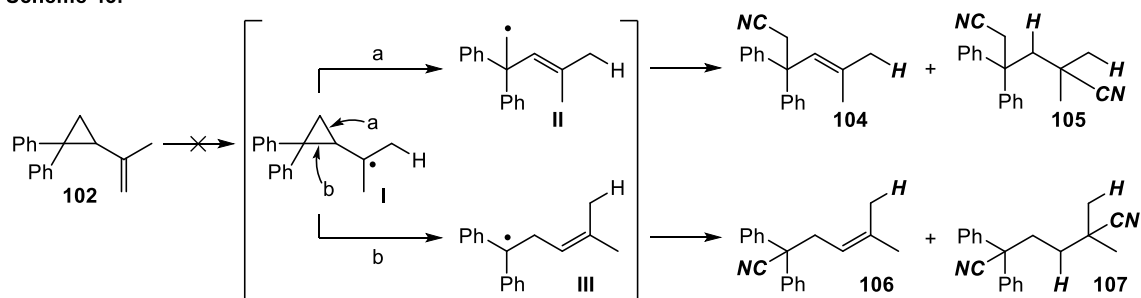
最後に、これまでの検討で得た知見を基に分子間反応による環化反応の構築を試みた (**Scheme 42.**)。そこで、基質にはビニルシクロプロパン **102** 及びラジカルアクセプターとして汎用されるアクリル酸メチルを用いてヒドロシアノ化反応を検討した。本反応では、より高い反応性が予想される **102** へのヒドロコバルト化が優先することで中間体 **I** を与え、続くシクロプロパン環開裂がより安定なベンジルラジカル **II** を与えるように進行すると期待した。その後、生じた **II** のアクリル酸メチルに対するラジカル付加、続く *5-exo* 環化反応が進行すれば **103** が得られると考えたが、実際に検討したところ反応は複雑化し、望みの環化体 **103** を得ることは出来なかった。そこで、本反応を検討するにあたってビニルシクロプロパン **102** が適切な基質であるかを判断するために、アクリル酸メチルを加えずに同様の反応を検討することにした (**Scheme 43.**)。

Scheme 42.



102 をヒドロシアノ化反応条件に付した際、以下に示す反応が予想される。すなわち、**I** が生じた後、**a** で示した結合が開裂すれば **II** を与え、本中間体からは **104** 及び **105** が生じる可能性がある。一方 **b** で示した結合が開裂すれば **III** が生じ、**106** 及び **107** の生成が考えられる。しかし、実際に **102** を用いたヒドロシアノ化反応を検討したところ、反応は複雑化し、これらのシアノ化物を単離することは出来なかった。本結果より、ビニルシクロプロパンを用いた分子間反応は困難であると判断し、検討を断念した。

Scheme 43.



Co A (2 mol%), TsCN (1.2 eq.), PhSiH₃ (1.2 eq.), EtOH (0.2 M), rt, 2 h : complex mixture

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- (2) (a) Nugent, W. A.; McKinney, R. J. *J. Org. Chem.* **1985**, *50*, 5370. (b) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265.
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- (10) Hay, E. B.; Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2015**, *137*, 322.

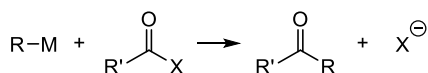
第三章 アルケンのヒドロアシル環化反応

序論

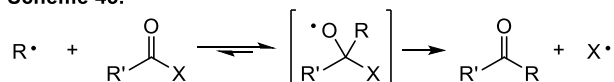
第一章及び第二章の検討では、カルボニル基等価体として有用な官能基であるシアノ基の導入反応を種々開発してきた。特に、第二章の Co 触媒を用いるラジカル反応は穏和な条件下で反応が進行するため、次に同様の反応条件でカルボニル基を直接導入する反応の開発を目指すことにした。

カルボニル基導入法としては、カルボン酸誘導体に対する有機金属試薬の求核付加反応が一般的に用いられているが(Scheme 44.)、アルキルラジカルがカルボニル基に対して付加する反応は可逆反応であり、出発物質が容易に再生してしまうため、これまでほとんど報告されていない(Scheme 45.)。

Scheme 44.

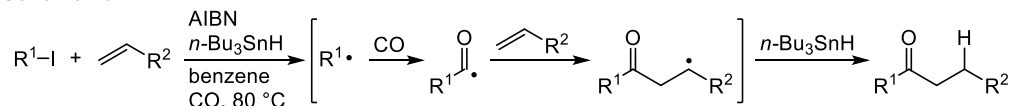


Scheme 45.

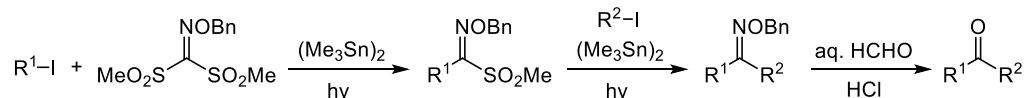


そのため、ラジカル反応条件下でカルボニル基を導入する反応としては、一酸化炭素からアシルラジカルを発生させる手法¹や、オキシムへの付加反応後に加水分解をする手法²が用いられてきた(Scheme 46, 47.)。

Scheme 46.

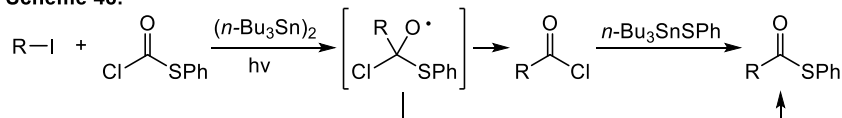


Scheme 47.

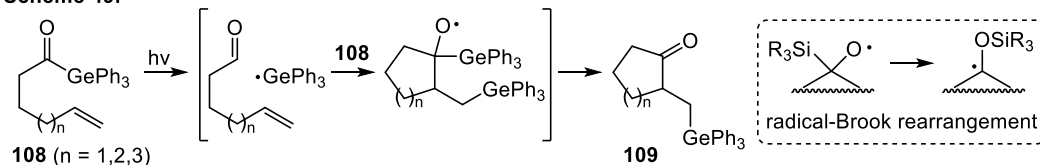


一方、アルキルラジカルがカルボニル基に対する付加反応は、Kim らがクロロチオホルメート³を、清岡らがアシルゲルマン⁴を用いて達成しているが、ラジカルアクセプターとして適用可能なカルボニル基は限られている(Scheme 48, 49.)。なお、Scheme 49.の反応において、ゲルマニウムと同族元素であるケイ素をカルボニル基に導入した場合は、ラジカルブルック転位が進行してしまうため、アシル化に用いることは出来ない。

Scheme 48.

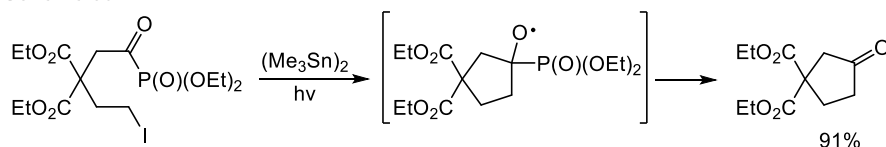


Scheme 49.

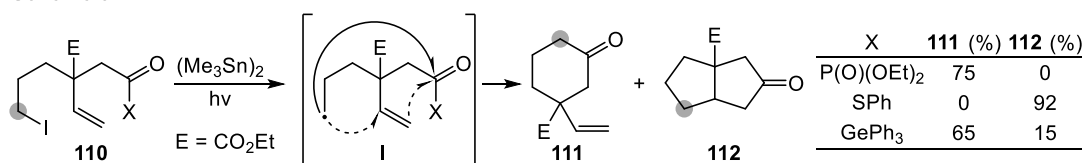


また、2003年にKimらはアシルホスホネートがラジカルアクセプターとして有用であることも見出した(Scheme 50.)⁵。この際、アシルホスホネートのラジカルアクセプターとしての反応性を確認するために、110の様な基質を用いた検討も行っている (Scheme 51.)。すなわち、110からアルキルラジカル I が生じた後に与える生成物としては、カルボニル基に直接付加して生じる111と、アルケンへの付加によって生じたラジカル種のカルボニル基に対する付加により生成する112が考えられるが、基質110のカルボニル基にP(O)(OEt)₂を導入した場合は111のみが得られたことから、アシルホスホネートがラジカルアクセプターとして高い反応性を持つことが示唆された。一方、SPh基を導入した際にはアルケンへの付加を経由する112が選択的に得られたことから、C(O)SPhはアルケンよりもラジカルアクセプターとしての反応性が低いことが予想される。また、清岡らが報告したGePh₃を導入した場合も111を主生成物として与えたが、P(O)(OEt)₂の場合よりも収率が低く、副生成物として112も与えているため、アシルホスホネートのラジカルアクセプターとしての反応性が特に高いことが示唆された。

Scheme 50.

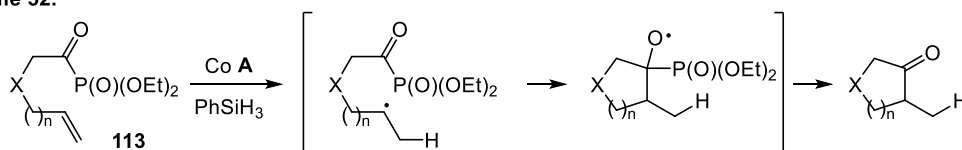


Scheme 51.



そこで、ラジカルドナーとしてアルケン、ラジカルアクセプターとしてアシルホスホネートを持つ基質113を第二章で用いたCo触媒反応条件に付せば、同様の環化反応がより穏和な反応条件下で進行すると期待し、検討することにした(Scheme 52.)。

Scheme 52.

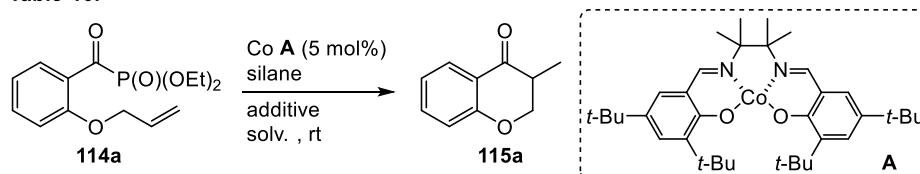


本論

第一節 反応条件の検討

はじめに、基質 **114a** を用いて反応条件の検討を行った(**Table 10.**)。本反応は、第二章で述べたジエンの環化反応とは異なり、分子内にラジカルアクセプターを持つため、0.05 M と低濃度で検討したところ、環化体 **115a** が収率 43% で得られた(entry 1)。次に濃度の効果を検証すべく、0.2 M、1.0 M の条件で検討したところ、それぞれ 65%、52% の収率で **115a** を与えたため、以降の検討は 0.2 M の条件で行っている(entry 2, 3)。また、PhSiH₃ を 3 当量用いても収率は変化せず(entry 2, 4)、Carreira らによる先行研究(第二章、序論、第二節)⁶ を参考に *t*-BuOOH を添加したが、収率は改善されなかった(entry 5)。また、PhSiH₃(TCI, 5 mL, 8000 円)の代わりに、重久ら⁷ が用いた(Me₂SiH)₂O (TCI, 25 mL, 4800 円)を水素源として検討したものの、環化体 **115a** の収率は 20% にとどまった(entry 6)。更に、entry 7-10 では溶媒の効果を検討したが、収率は改善されなかった。

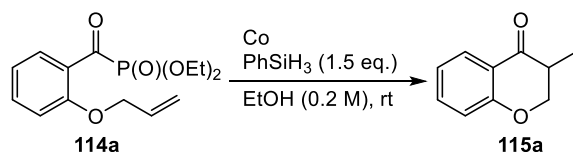
Table 10.



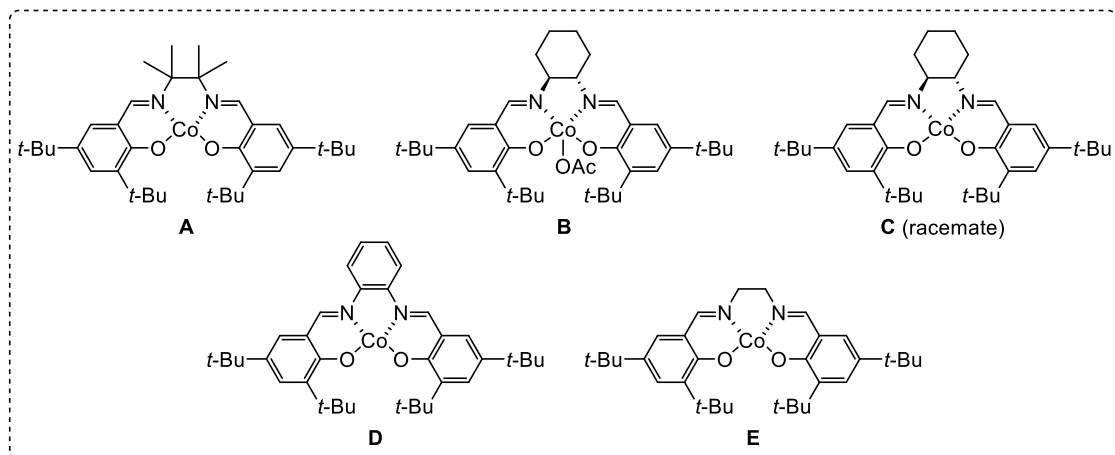
| entry | silane (eq.) | solv. (M) | additive (mol%) | time (h) | 115a (%) |
|-------|--|-------------------------|----------------------|----------|-----------------|
| 1 | PhSiH ₃ (1.5) | EtOH (0.05) | - | 9 | 43 |
| 2 | PhSiH ₃ (1.5) | EtOH (0.2) | - | 4 | 65 |
| 3 | PhSiH ₃ (1.5) | EtOH (1.0) | - | 3 | 52 |
| 4 | PhSiH ₃ (3.0) | EtOH (0.2) | - | 3 | 64 |
| 5 | PhSiH ₃ (1.5) | EtOH (0.2) | <i>t</i> -BuOOH (50) | 1 | 45 |
| 6 | (Me ₂ SiH) ₂ O (4.0) | EtOH (0.2) | - | 3 | 20 |
| 7 | PhSiH ₃ (1.5) | PhCF ₃ (0.2) | - | 24 | 37 |
| 8 | PhSiH ₃ (1.5) | toluene (0.2) | - | 24 | 32 |
| 9 | PhSiH ₃ (1.5) | MeOH (0.2) | - | 3 | 55 |
| 10 | PhSiH ₃ (1.5) | <i>i</i> PrOH (0.2) | - | 12 | 42 |

次に、entry 2 (**Table 10.**) の条件を用いて、Co 触媒のリガンド効果を確認することにした(**Table 11.**)。そこで、Co 触媒 **B-E** を既存の報告例⁸ に倣って合成し、ヒドロアシル化反応を検討したところ、Co 触媒 **B** (ラセミ体) を用いた場合に **115a** が収率 24% で得られたが(entry 2)、Co 触媒 **C-E** は痕跡量の **115a** を与えるのみであった(entry 3-5)。この際、低収率ではあったものの、Co 触媒 **B** (ラセミ体) は環化反応に適用可能であったため、不斉反応への展開を期待してキラルなシクロヘキサジアンから合成した Co 触媒 **B** を用いて検討したところ、entry 2 と同程度の収率で **115a** を与えたが、得られた環化体はラセミ体であった(entry 6)。これらの結果より、最初に検討した Co 触媒 **A** が最も適していると判断し、最後に触媒量の低減を試みたところ、**115a** の収率が低下したため、entry 1 の条件を用いて基質一般性を検討することにした(entry 7)。

Table 11.



| entry | Co (mol%) | time (h) | 115a (%) | % ee |
|-------|-----------------|----------|----------|------|
| 1 | A (5) | 4 | 65 | - |
| 2 | B (racemate, 5) | 24 | 24 | - |
| 3 | C (5) | 24 | trace | - |
| 4 | D (5) | 24 | trace | - |
| 5 | E (5) | 9 | trace | - |
| 6 | B (chiral, 5) | 24 | 20 | 0 |
| 7 | A (2) | 9 | 36 | - |



第二節 基質一般性の検討

基質一般性の検討では、まず条件検討で用いた基質のベンゼン環にメトキシ基、ブロモ基を導入した基質 **114b,c** を用いたところ、環化体 **115b** が収率 69%、**115c** が 59% で得られた (Table 12.)。また、トシルアミド誘導体 **114d** も本反応に適用可能であり、収率 57% で環化体を与えた。この際、ベンゼンスルホニル基に電子供与性基であるメトキシ基や、電子吸引性基であるフッ素を導入しても反応は円滑に進行した (**114e,f**)。また、二置換アルケンを有する **114g** を用いたところ、四級炭素の構築を伴う環化反応が進行し、環化体 **115g** が収率 57% で得られた。そこで、**114h** の様なアルケン末端に二つのメチル基を有する基質を用いれば、三級ラジカルの生成に続く七員環形成が進行すると期待したが、反応は複雑化し、**115h** を得ることは出来なかった。また、アルケン側鎖を一炭素増炭した **114i** を用いる七員環形成も検討したが、この場合も複雑な混合物を与えるのみであった。

次に、マロン酸誘導体を検討したところ、六員環形成は 37% と低収率にとどまったもの (**114j**)、五員環成績体 **115k** は 81% と高収率で得られ、**114l** を用いた際には四級炭素の構築が円滑に進行した。また、カルボニル基の α 位に四級炭素を有する **114m** 及び **114n** も本反応に適用可能であった。この際、環化体 **115n** は単一異性体として得られているが、その立体化学については未決定である。更なる検討として、シクロブタノンを与えることが予想される **114o** をケトン **115o** は一切得られず、ラクトン **116o** を収率 56% で与えた。これは、ラジカル条件で不利な *4-exo* 環化反応が進行せず、酸素の関与による *5-exo* 環化反応が進行したためだと考えられる。また、ラジカルドナーとしてシクロアルケンを有する **114p,q** を検討したところ、主生成物としてスピロケトン **115p,q** をそれぞれ収率 30%、25% で与えるとともに、副生成物としてスピロラクトン **116p,q** が得られた。なお、ラクトン **116o**、スピロケトン **115p**、スピロラクトン **116q** に関してはいずれも X 線結晶構造解析によって構造を決定している (Figure 6.)。

Table 12.

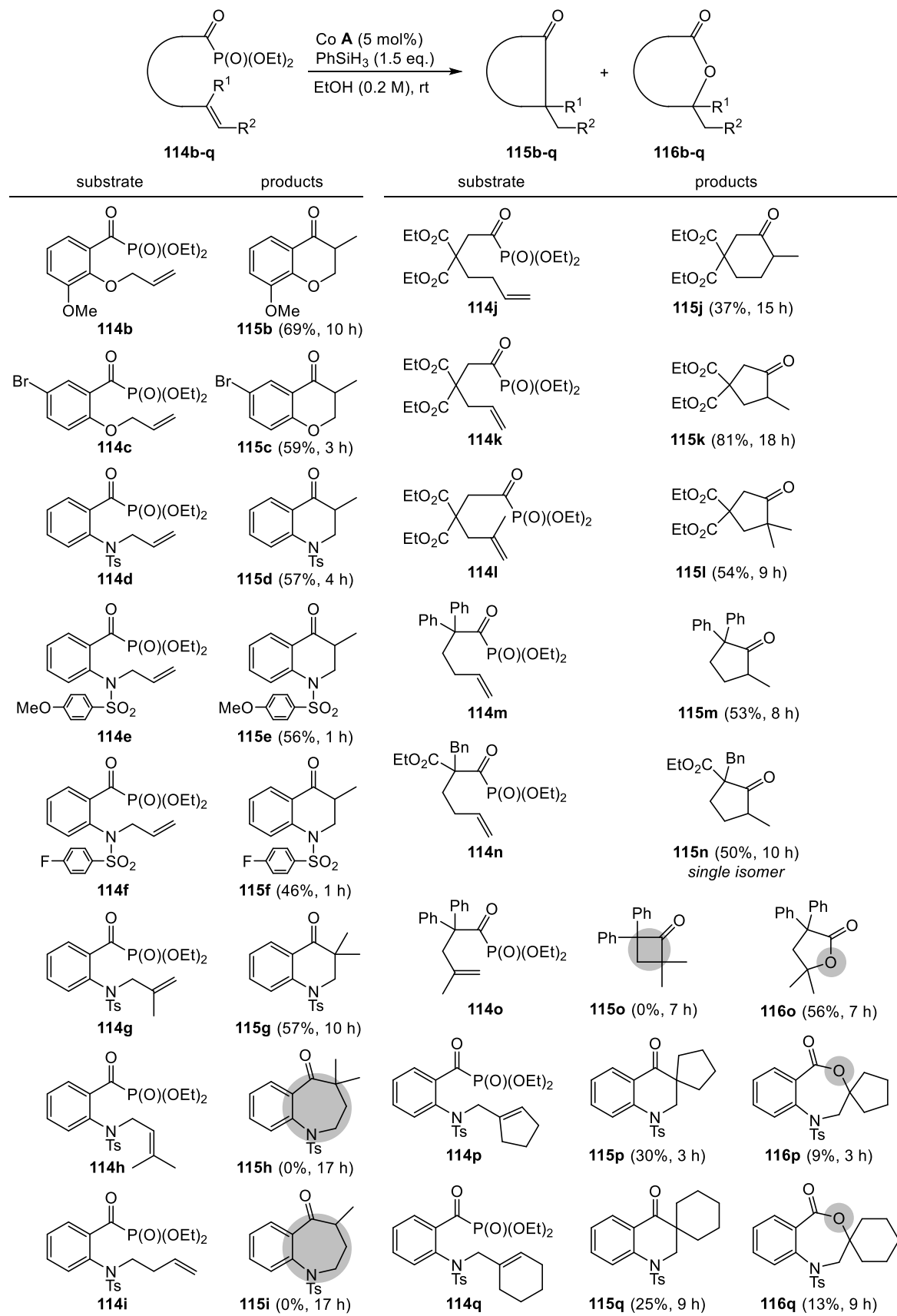
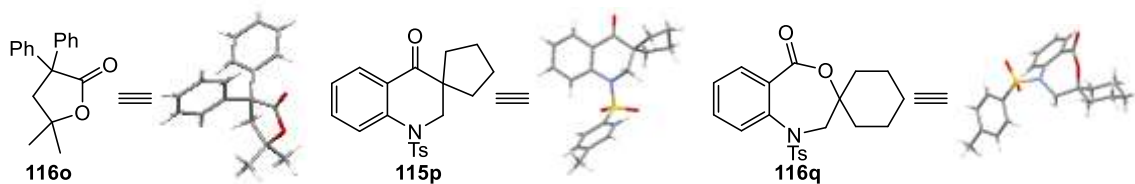
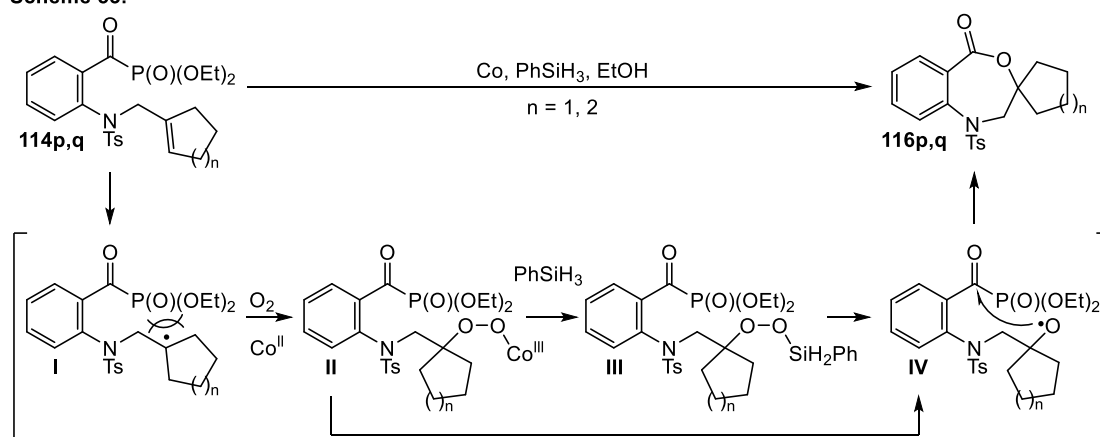


Figure 6. X-ray crystallographic analysis of **116o**, **115p** and **116q**.



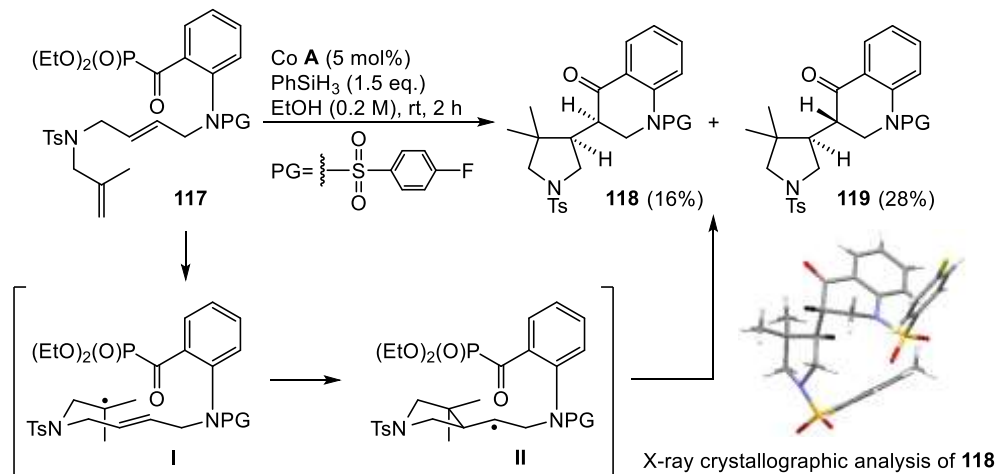
この際、ラクトン体が得られる経路は以下の様に考察した(Scheme 53.)。すなわち、最初に生じた三級ラジカルは立体的に嵩高いため、カルボニル基への付加が起こりにくく、続く酸素との反応を経てコバルト錯体**II**あるいはシリルペルオキシド**III**を与える。その後これらの中間体から酸素-酸素結合の開裂によって生じたアルコキシラジカル**IV**がカルボニル基へ付加することによってラクトン体に至ると考えられる。

Scheme 53.



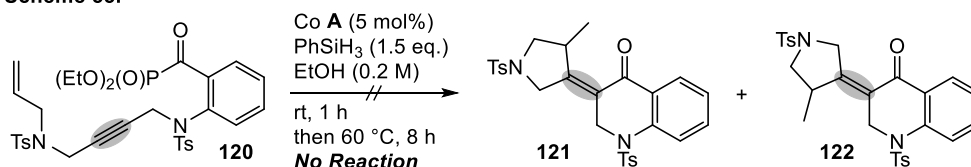
更に、タンデム環化反応も検討した(Scheme 54.)。基質としては、**117**を用いたところ、環化体**118**及びそのジアステレオマーである**119**をそれぞれ収率16%、28%で得た。なお、主生成物**118**の立体化学に関してはX線結晶構造解析により決定している。得られた環化体の構造から、反応は末端アルケンへのヒドロコバルト化による三級ラジカル**I**の生成が最初に起こっており、続く5-*exo*、6-*exo*環化反応が連続して進行することで環化体に至ったと考えられる。

Scheme 54.



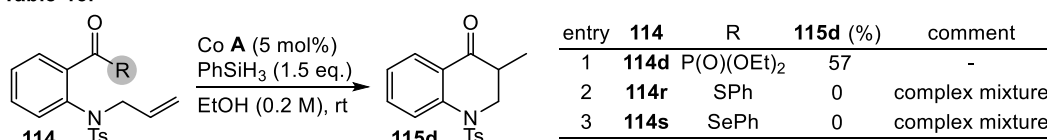
また、**120** の様なエン-イン体を用いた検討も行ったが、こちらに関しては反応が一切進行せず、環化体 **121** や **122** は得られなかった(Scheme 55.)。

Scheme 55.



最後に、アシルホスホネートの有用性を確認するため、SPh 基や SePh 基を脱離基として持つ基質 **114r** や **114s** を検討したところ、複雑な混合物を与えるのみであった(Table 13.)。本結果から、脱離基 R は高い脱離能を持つことに加え、電子吸引力によってカルボニル基を活性化する必要があると示唆された。

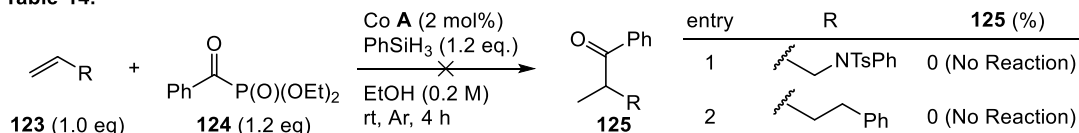
Table 13.



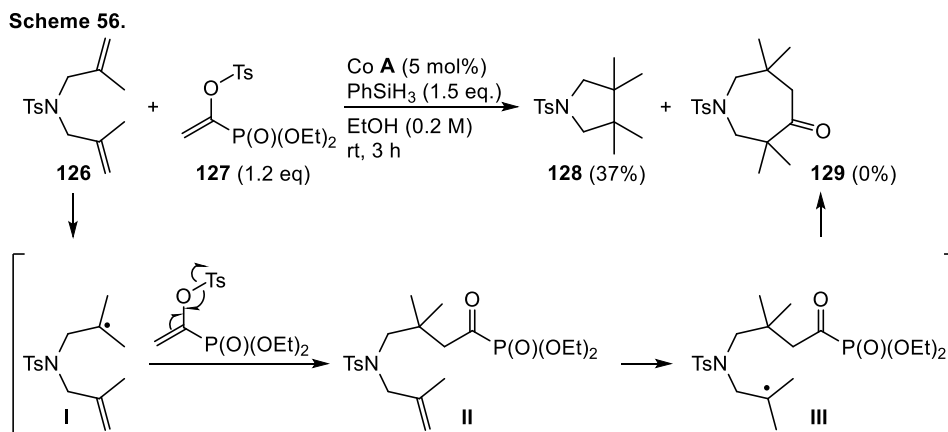
第三節 分子間反応の検討

前節の検討で、様々な基質において分子内アシル化が進行することが見出されたため、次に分子間反応を検討した(Table 14.)。基質としては、一置換アルケン **123** 及びアシル化剤として **124** を用いて検討したが、いずれの場合も反応は一切進行しなかった。

Table 14.

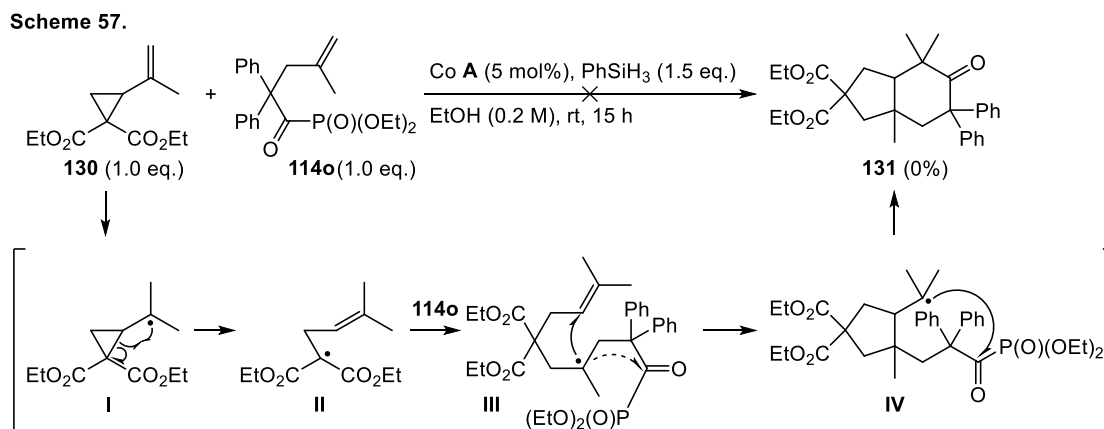


次に、ジエン **126** とアシル化剤 **127** を用いた検討を行った(Scheme 56.)。本反応では、アルキルラジカル **I** の **127** に対する付加と続くスルホニルラジカルの脱離によって **II** を与え、続く分子内アシル化が進行することを期待したが、**129** は得られず、ジエン **126** に水素が一分子付加した環化体 **138** が収率 37%で得られるのみであった。この様な、**127** が関与していない環化体 **138** が主生成物として得られたこと、及び本反応条件において七員環形成が困難であることが、望みの反応が進行しなかった原因だと考えられる。

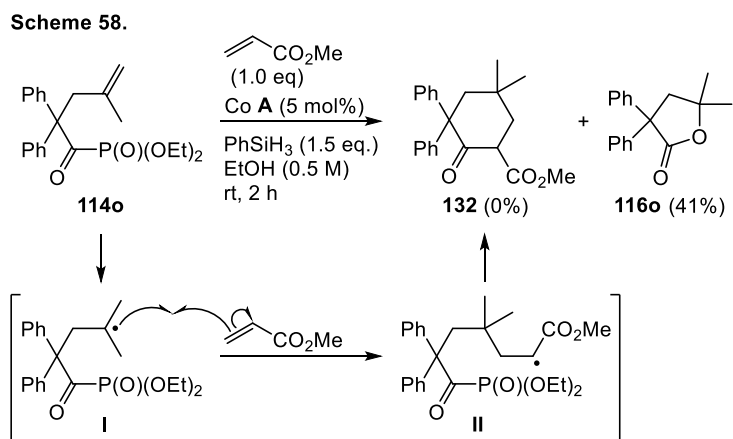


更なる検討として、ヒドロシリル化反応条件に付した際に、ケトンではなくラクトンを与えた基質 **114o** を用いる分子間反応を二種類設計した。

Scheme 57.の検討では、ビニルシクロプロパン **130** と **114o** による分子間反応を検討した。すなわち、より高い反応性が予想されるビニルシクロプロパンへのヒドロコバルト化が優先すれば、まず **I** が生じ、続く環開裂反応、**114o** への付加により、**III** が生成すると考えられる。その後、カルボニル基へのラジカル付加は *4-exo* 環化反応となるため、アルケンへの *5-exo* 環化反応が優先すると予想され、最後に **IV** から *6-exo* 環化反応が進行すれば、双環性化合物 **131** を与えると考えた。しかし、実際に検討したところ反応は複雑化し、**131** を得ることは出来なかった。本反応は分子間反応であることに加え、シクロプロパン環開裂を含むため、想定される副反応が多く、反応が複雑化したと考えられる。そこで、ビニルシクロプロパン **130** をアクリル酸メチルへと変更した分子間反応を検討することにした(**Scheme 58.**)。

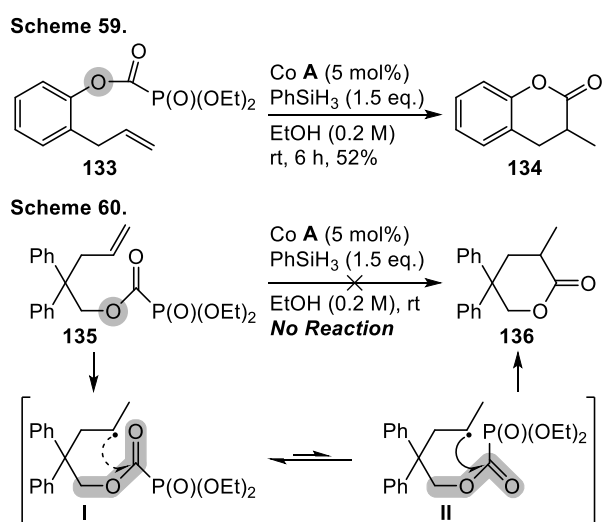


すなわち、アクリル酸メチルはラジカル反応条件においてラジカルアクセプターとしての反応性を示すので、**114o** へのヒドロコバルト化が優先すると考えられる。この際生じるアルキルラジカル **I** は、続く *4-exo* 環化反応が不利な反応であるため、アクリル酸メチルを共存させることで分子間付加反応が進行し、**II** が生じると考えた。その後、分子内アシル化によって環化体 **132** が生成すると期待したが、実際には本反応系でもラクトン体 **116o** が収率 41% で得られるのみであった。



第四節 ラクトン化反応の検討

最後に、Co 触媒条件でのラクトン化を検討した。これまでのアシルホスホネートをラジカルアクセプターとする反応系において、しばしばラクトン体が得られてきたが、それらはアシル化が進行しにくい基質に限定されるものであった。そこで本節では、ホスホノホルメート ^{5b,c} をラジカルアクセプターとするラクトン化を検討した。まず、基質として **133** を用いたところ、ラクトン体 **134** を収率 52% で得ることに成功した (**Scheme 59.**)。しかし、基質一般性の検討として **135** を検討した際には反応が一切進行せず、**135** が定量的に回収された (**Scheme 60.**)。これは、酸素の孤立電子対の電子的な反発により **II** よりも **I** の状態が優先することにより⁹、続くアルキルラジカルの付加反応が進行しなかったためだと考察している。更なる基質の検討も試みたが、アシルホスホネートの場合に比べて基質合成が困難であったことから、以降の検討は断念した。しかし、本反応はホスホノホルメートに対するアルキルラジカルの付加反応としては初の成功例であるため、新たなラクトン合成法として確立していきたいと考えている。



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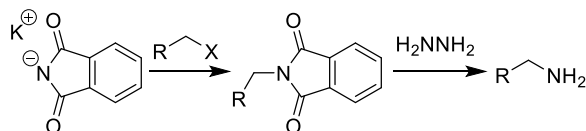
第四章 オキシムへの炭素ラジカル付加反応の開発

序論

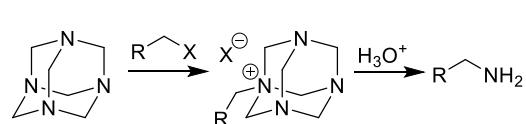
アミン類は医薬品や農薬などの生理活性物質中に含まれる重要な官能基であり、様々なアミン合成法が開発されてきた。一般的なアミン合成法としては、シアノ基やニトロ基、イミンといった含窒素官能基の還元反応が知られている。また、Gabriel アミン合成¹、Delépine 反応²、還元的アミノ化³、Ns アミドを経由する二級アミンの合成⁴などに代表される、窒素求核剤と炭素求電子剤の組み合わせも数多く報告されているが(Scheme 61.)、窒素求電子剤と炭素求核剤を用いる手法は一般性に乏しく、アミン合成としてはあまり用いられていない(Scheme 62.)⁵。

Scheme 61. Representative amine synthesis (Nucleophile: N, Electrophile: C)

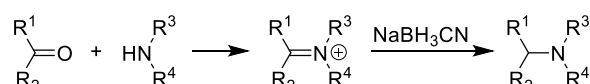
a) Gabriel Amine Synthesis



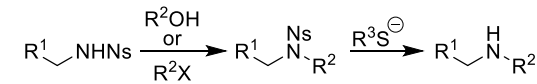
b) Delépine Reaction



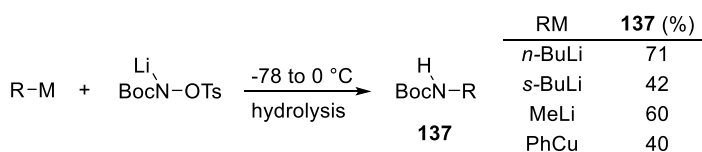
c) Reductive Amination



d) Ns-strategy

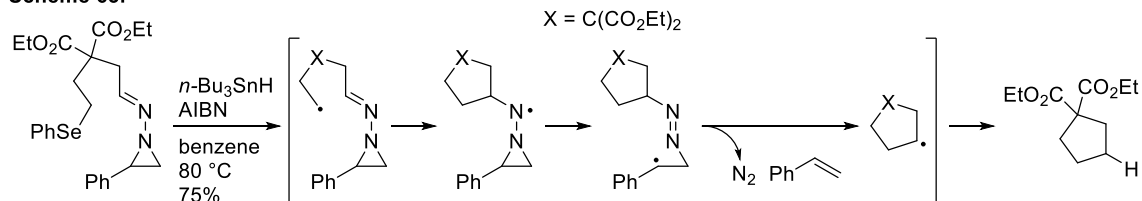


Scheme 62. Representative amine synthesis (Nucleophile: C, Electrophile: N)



アミン合成法としては他に、イミン類に対する水素化や求核付加反応も知られている。しかし、求核付加反応では有機金属試薬の持つ強い塩基性のためにエナミンへの異性化が進行するため、穏和な反応剤である炭素ラジカルのイミンへの付加反応が精力的に開発されてきた。中でもヒドラゾンやオキシムにアルキルラジカルが付加した際に生じるアミニルラジカル種は、隣接するヘテロ原子による安定化を受けやすく、ラジカルアクセプターとして優れている。また、得られるヒドラジンやアルコキシアミンは還元的にアミンへ変換できるため、分子内付加反応を中心に活発な研究がなされてきた。例えば、ヒドラゾンに対するラジカル付加反応は、1991年に Kim らによって初めて報告されている(Scheme 63.)⁶。

Scheme 63.



本反応ではアジリジン環の歪み解消と、窒素及びスチレンの脱離を駆動力としている。一方、1994年に Fallis らは、*N,N*-ジフェニルヒドラゾンを用いたラジカル環化反応を報告している(Table

本論

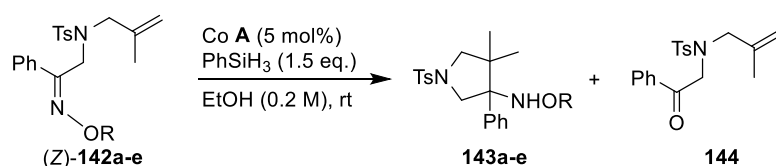
第一節 オキシム上の置換基効果の検討

序論で述べてきたように、オキシムはラジカルアクセプターとして有用であることが知られているが、それらの多くは高温条件や有毒なスズ試薬を必要としている。一方、筆者がこれまで検討してきた Co 触媒条件がオキシムに対しても有効であれば、より温和な反応系での環化反応が達成できると期待し、分子内にアルケンとオキシムを有する基質を用いて検討を開始した(**Table 18.**)。

まず、オキシムの保護基の効果を検証するために、**142** を出発物質として設定し、反応条件には第三章で検討したヒドロシリ化反応の最適条件を用いることにした。この際、出発物質 (*Z*)-**142a** (R = H) の立体化学は X 線結晶構造解析により決定しており (**Figure 7.**)、(*Z*)-**142b-d** はいずれも (*Z*)-**142a** から合成することで、単一異性体として得た。

保護基を検討するにあたり、まず無保護の **142a** を用いたところ、反応は複雑化し、環化体 **143a** は得られなかった。これはラジカル条件において水酸基の水素が関与した副反応が起こっている為だと考えられる (**entry 1**)。次に、オキシムの保護基として汎用される Bn 基を検討したところ、出発物質 **142b** がエタノールにほとんど溶解せず、反応は一切進行しなかった (**entry 2**)。一方、Bz 基を用いた場合は環化体 **143c** が得られたものの、35%と低収率であり、副生成物としてケトン体 **144** を与えた (**entry 3**)。また、Bz 基を有する基質 **142c** も **142b** と同様に結晶性が高かったため、基質の溶解性が向上すれば収率が改善されると判断し、TBS 基を用いたところ、収率 52%で環化体 **143d** を与えた (**entry 4**)。この際、環化体 **143d** の構造は二次元 NMR を用いて決定している (**Figure 8.**)。また、**entry 5** では *E* 体及び *Z* 体の混合物を出発物質として用いたが、この場合も反応は円滑に進行し、環化体 **143d** を収率 60%で与えた。なお、ラジカル反応条件においてシリル保護基を用いている例はこれまでに二例しか報告されておらず¹¹、その効果の詳細についてはほとんど知られていない。また、保護基として Ac 基を用いた場合も TBS 基と同程度の収率で環化体を与えた (**entry 6**)。以上の検討により、オキシム上の保護基は TBS 基及び Ac 基が適切であると判断し、次に基質一般性の検討を行うことにした。

Table 18.



| entry | 142 (R) | <i>E</i> / <i>Z</i> | time (h) | 143 (%) | 144 (%) | comment |
|-------|-------------------|---------------------|----------|------------------|----------------|-----------------|
| 1 | 142a (H) | <i>Z</i> only | 8 | 143a (0) | 0 | complex mixture |
| 2 | 142b (Bn) | <i>Z</i> only | 24 | 143b (0) | 0 | No Reaction |
| 3 | 142c (Bz) | <i>Z</i> only | 4 | 143c (35) | 42 | - |
| 4 | 142d (TBS) | <i>Z</i> only | 5 | 143d (52) | 0 | - |
| 5 | 142d (TBS) | 1/3.1 | 5 | 143d (60) | 0 | - |
| 6 | 142e (Ac) | 1/1.5 | 8 | 143e (61) | 0 | - |

Figure 7.

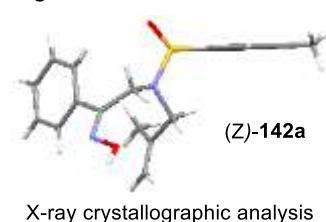
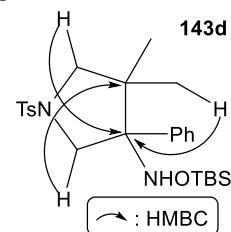


Figure 8.

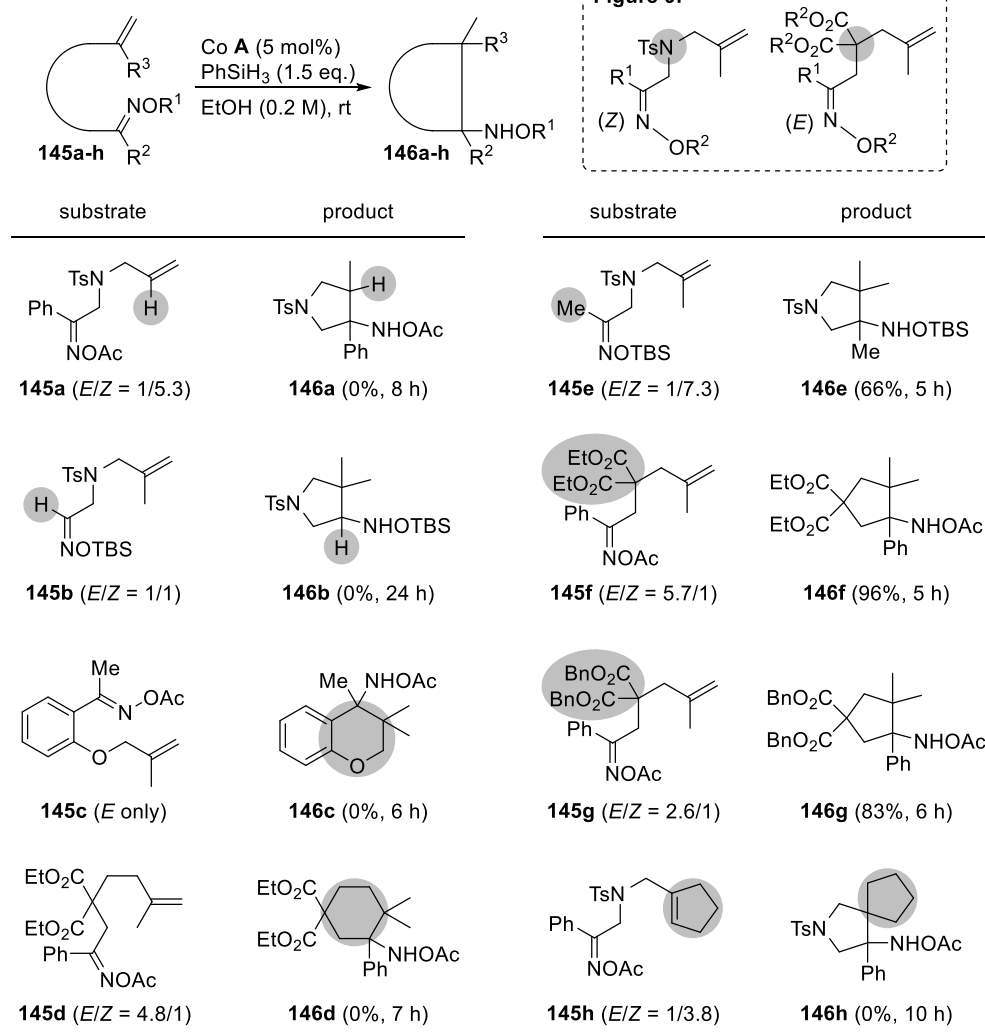


第二節 基質一般性の検討

オキシムの保護基として Ac 基及び TBS 基を有する基質を用いて基質一般性を検討した (Table 19.)。なお、オキシムの立体化学に関しては Figure 9. に示した様に定義している。

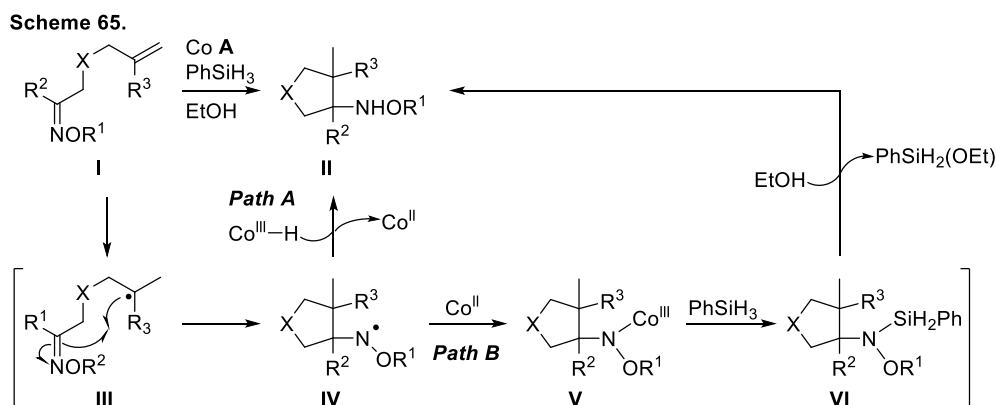
まず、一置換アルケンを持つ **145a**、及びアルドキシム **145b** を検討したところ、いずれの場合も反応は複雑化し、望みの環化体 **146a,b** は得られなかった。これらの結果から、本反応では三級ラジカルを与えるアルケンとケトキシムの組み合わせが必須であると判断し、**145c** 及び **145d** を用いて六員環形成を試みたが、いずれの場合も出発物質はすべて消費したものの、複雑な混合物を与えるのみであった。そこで、五員環形成を再度検討したところ、メチル基を有するケトキシム **145e** は環化反応が進行し、**146e** を収率 66% で与えた。また、マロン酸誘導体 **145f,g** はトシルアミド誘導体に比べてより高い反応性を示し、高収率で環化体 **146f** 及び **146g** を与えた。最後に、ラジカルドナーとしてシクロペンテンを有する **145h** を用いてスピロ環の構築を試みたが反応は複雑化し、環化体 **146h** を得ることは出来なかった。これらの結果から、本反応の進行には【①立体的に嵩高くない三級ラジカルが発生②ケトキシムの利用③五員環形成】が必須であることが分かった。しかし、隣接する四級炭素と四置換炭素をオキシム類のラジカル環化反応によって構築する報告例は二例しかないため¹²、そのような環化体を収率良く合成できる点が本反応最大の特徴であると言える。

Table 19.



第三節 反応機構の考察

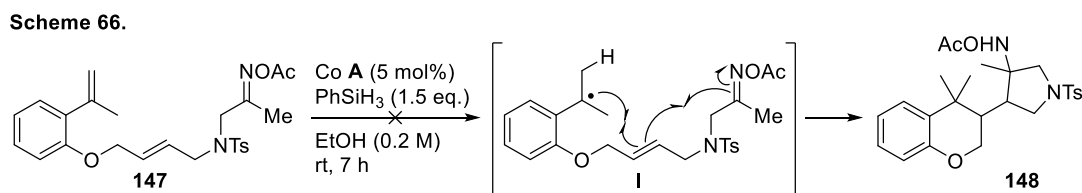
本反応の機構は以下の様に考察した(Scheme 65.)¹³。すなわち、最初にアルキルラジカルIIIが生じた後、オキシムへのラジカル付加によりアミニルラジカルIVを与える。本中間体から環化体IIへの経路は二通り考えられる。Path Aは、コバルトヒドリド種によってアミニルラジカルが捕捉されることで、環化体IIを与える経路で、窒素に結合した水素はPhSiH₃由来である。一方、Path Bでは、まず二価コバルトとIVからコバルト錯体Vが生じた後、PhSiH₃、エタノールと順次反応することで環化体IIを与える経路で、窒素に結合した水素はエタノール由来である。また、本反応では、R²やR³が水素の場合に反応が複雑化したことから、アミニルラジカルIVが生じた際に、分子内で水素の移動が起こっていることが予想されるが、その様な反応を示唆する副生成物は得られていないため、詳細は不明である。今後は、PhSiD₃やアルコール以外の溶媒を用いた検討などを行い、反応機構の詳細を解明する予定である。



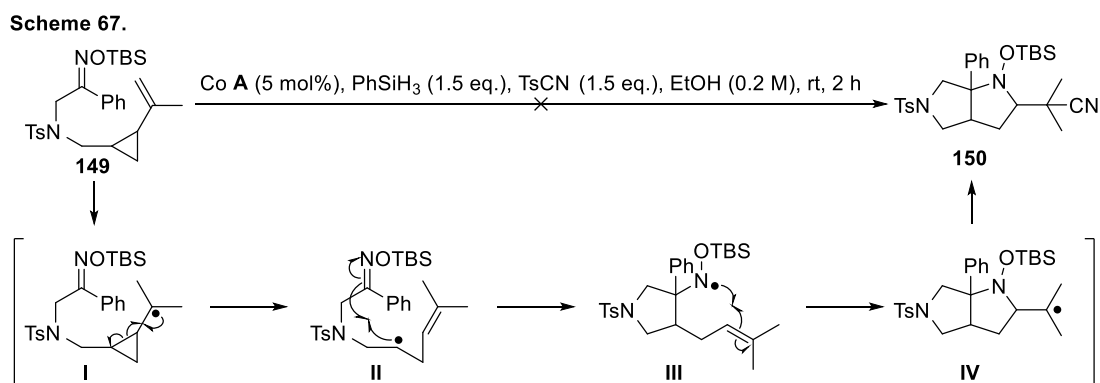
第四節 タンデム環化反応の検討

次に筆者は、タンデム環化反応を検討した。この際、これまで見出してきたシクロプロパン環開裂を伴うタンデム環化反応(第二章、第四節、Scheme 40.)及びヒドロアシル化条件で達成したタンデム環化反応(第三章、第二節、Scheme 54.)を参考に、環化前駆体 **147** (Scheme 66.)及び **149** (Scheme 67.)を設計し、実際の検討に移った。

まず、基質 **147** を検討したところ複雑な混合物を与え、環化体 **148** は得られなかった(Scheme 66.)。本反応では、最初に生じたベンジルラジカルからの *6-exo* 環化反応までは、参考にした反応と同じ形式であるため、進行している可能性が高いと考えられるが、その後オキシムに対して付加するラジカルが二級ラジカルであるために反応が複雑化したと考えられる。

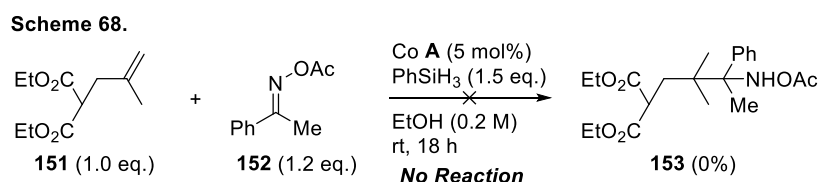


また、ビニルシクロプロパンを有する **149** を用いた際も反応は複雑化し、**150** は得られなかった(Scheme 67.)。本反応でも、シクロプロパン環開裂による **I** の生成までは進行している可能性が高いと考えられるが、この際に生じる中間体 **II** が二級ラジカルであるために、反応が円滑に進行しなかったと考えられる。また、本系ではアミニルラジカル **III** からの環化反応が進行せず窒素上に水素が導入された環化体や、二級ラジカル **II** が TsCN によって捕捉されたシアノ化体などが副生成物として考えられるが、それらに相当する生成物を得ることも出来なかった。

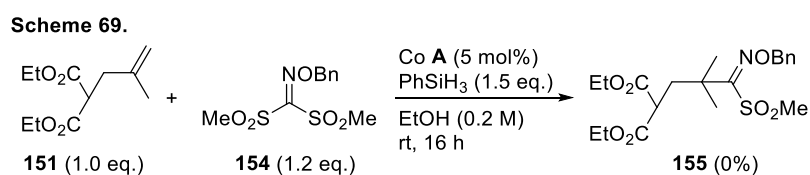


第五節 分子間反応の検討

更なる検討として、分子間反応を試みた。まず、環化反応における基質一般性の結果を踏まえ、三級ラジカルを与えるアルケン **151** 及びケトキシム **152** を用いた反応を検討したところ、反応は一切進行しなかった(Scheme 68.)。



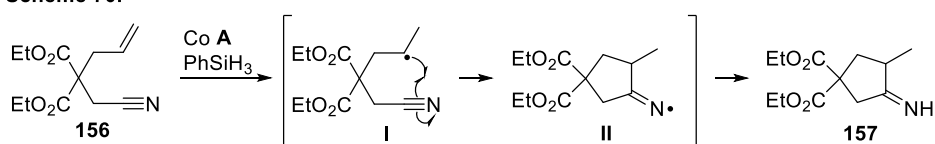
過去の研究においても、オキシムに対するアルキルラジカルの付加反応は分子内反応を中心に検討されており、達成されてきた分子間反応の多くは、オキシムの sp^2 炭素に電子吸引性基としてスルホニル基を有するものであったため¹⁴、次に、より高い反応性が予想される **154** を用いて検討したところ、Scheme 68.とは異なり、出発物質 **151** の消失は確認できたが、望みの **155** を得ることは出来なかった(Scheme 69.)。



第六節 シアノ基に対するラジカル付加反応の検討

ここまでの検討では、ラジカルアクセプターとしてオキシムを用いてきたが、このような炭素 - 窒素多重結合に対するラジカル付加反応は、シアノ基でも進行することが知られている¹⁵。例えば、第二章で示したヒドロシアノ化反応では、TsCNのシアノ基に対してアルキルラジカルが付加することが示唆されている。そこで、分子内にアルケンとシアノ基を持つ基質 **156** を Co 触媒条件に付した場合、アルキルラジカル **I** のシアノ基に対する付加により **II** が生じ、オキシムの場合と同様に窒素上に水素が導入されることでイミン **157** が生成すると考えた(Scheme 70)。

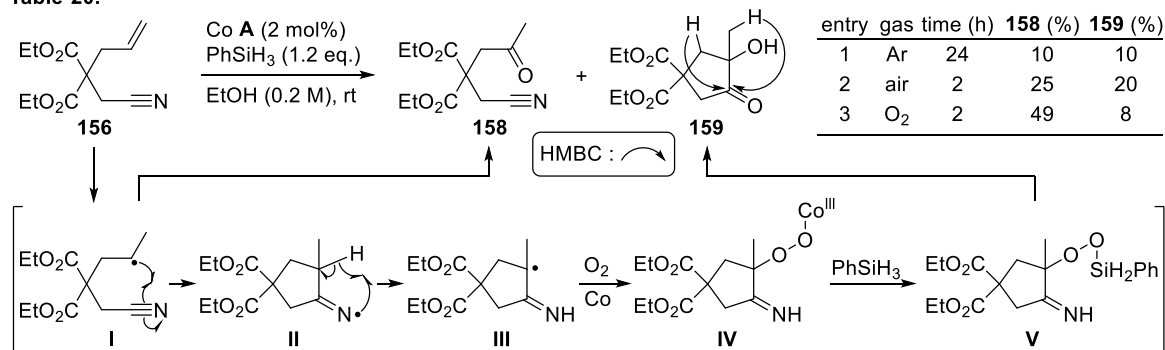
Scheme 70.



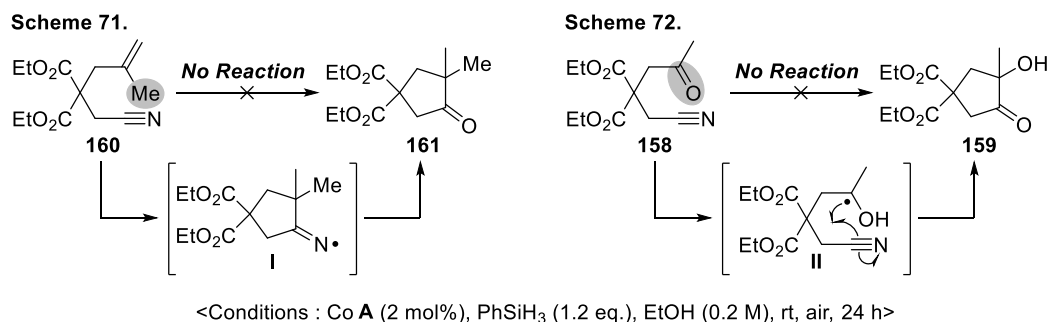
そこで、実際に基質 **156** を Co 触媒条件に付したところ、当初想定したイミン **157** は一切得られず、**158** 及び **159** を得た。(Table 20., entry 1)。環化体 **159** の構造に関しては、HMBC 測定の結果より五員環の存在が示唆され、質量分析及び IR の測定結果からケトン及びアルコールの存在が示唆されたため、それらを満たす構造として推定した。この際、推定した環化体 **159** は既知化合物であり¹⁶、各種機器データの結果が一致したため **159** であると決定した。この際得られた生成物の構造から、酸素が反応に関与していると考え、空气中で同様の反応を検討したところ、ケトン **158** 及び **159** の収率がいずれも向上する結果となった(entry 2)。しかし、酸素雰囲気下で検討した際にはケトン **158** が主生成物として得られ、環化体 **159** の収率は 8%にとどまっている(entry 3)。

本反応において、環化体 **159** に至る反応機構は次のように考察した。すなわち、まず当初予想したようにアルキルラジカルがシアノ基に付加することで、**II** を与えた後、分子内で水素移動が進行し、三級ラジカル **III** が生じる。その後酸素、Co 触媒、PhSiH₃ と順次反応することによってシリルペルオキシド **V** が生成し、酸素 - 酸素結合の開裂、イミンの加水分解が進行することにより **159** が生成したと考えた。この際、**IV** の段階で酸素 - 酸素結合が開裂する可能性も考えられる。しかし、本反応機構は生成物の構造からの推定に過ぎないため、更なる検討によりその妥当性を確かめることにした。

Table 20.

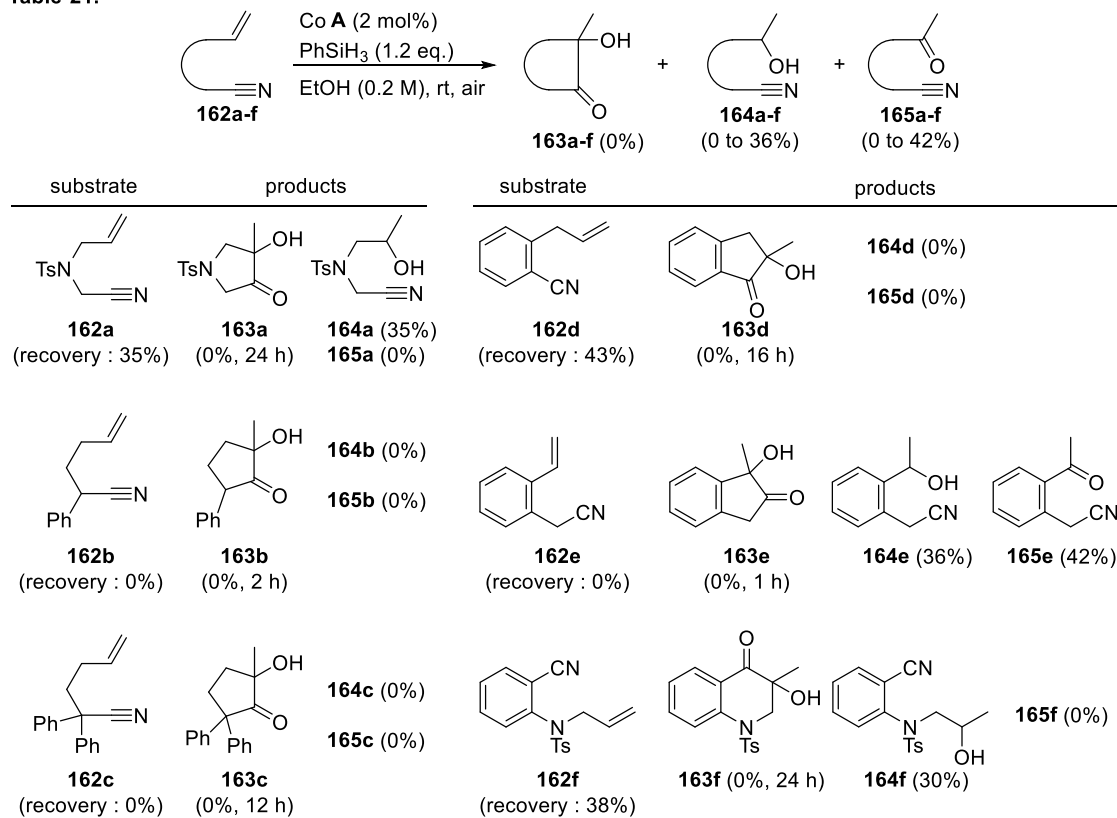


そこで、基質 **160** 及び **158** を空气中で Co 触媒条件に付したところ、いずれの場合も反応は一切進行しなかった。**Scheme 71.**において反応が一切進行しなかったのは、アルケンにメチル基を導入することで、中間体 **I** において分子内移動が可能な水素がなくなり、中間体 **I** から出発物質 **160** が再生しているか、三級ラジカルシアノ基に対する付加反応が進行していない為だと考えられる。一方、**Scheme 72.**の結果より、ケトン体 **158** から環化体 **159** に変換されなかったため、ケトン **158** が環化体 **159** に至る際の反応中間体ではないことが示唆された。



基質 **156** を用いた反応において、当初は予想していなかった興味深い反応の進行が確認されたため、基質一般性の検討を行うことにした(**Table 21.**)。先の検討を踏まえ、一置換アルケンとシアノ基を持つ基質 **162** を種々検討したが、いずれの場合も環化体 **163** を得ることはできず、一部の基質においてアルコール体 **164** やケトン体 **165** を与えるのみであった。これらの検討により、基質一般性が極めて低い反応であることが示唆されたため、本反応に関する更なる検討は断念することにした。

Table 21.



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第五章 Taiwaniaquinoids の合成研究

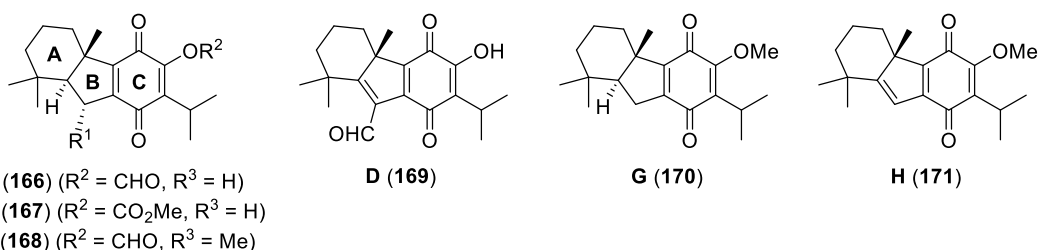
序論

第一節 Taiwaniaquinoids について

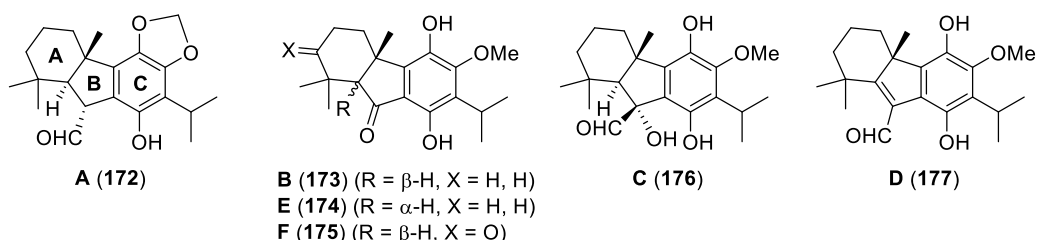
Taiwaniaquinoids は 1995 年、Cheng らによって台湾に自生する *Taiwania cryptomerioides* Hayata (タイワンスギ) の葉^{1a,b}より、2003 年には Kuo らによって樹皮^{1c,d}より単離構造決定された三環性ジテルペノイドであり、*p*-キノン構造を有する Taiwaniaquinone 類とフェノール構造を有する Taiwaniaquinol 類に分類される(**Figure 10**)。

Figure 10. Taiwaniaquinoids

<Taiwaniaquinones>



<Taiwaniaquinols>



Taiwaniaquinoids の構造決定には質量分析、赤外分光、紫外分光、一次元及び二次元 NMR が用いられている。最初に構造が決定された Taiwaniaquinone **A(166)** を例にとると、質量分析では m/z 330 ($\text{C}_{20}\text{H}_{26}\text{O}_4$) の分子イオンピークが観測されており、*p*-キノンに特徴的な吸収として赤外分光では 1659, 1639 cm^{-1} の吸収が、紫外分光では 432, 284, 207 nm の吸収が観測されている。また、 ^1H NMR では 9.84 ppm (d, 1H, $J = 4.0$ Hz) のピークが、 ^{13}C NMR では 200.2 ppm のピークが確認されたことからアルデヒドの存在が示唆された。更に、二次元 NMR 解析では、COSY、HMBC の解析により 6-5-6 縮環構造を含有することが決定された^{1a}。

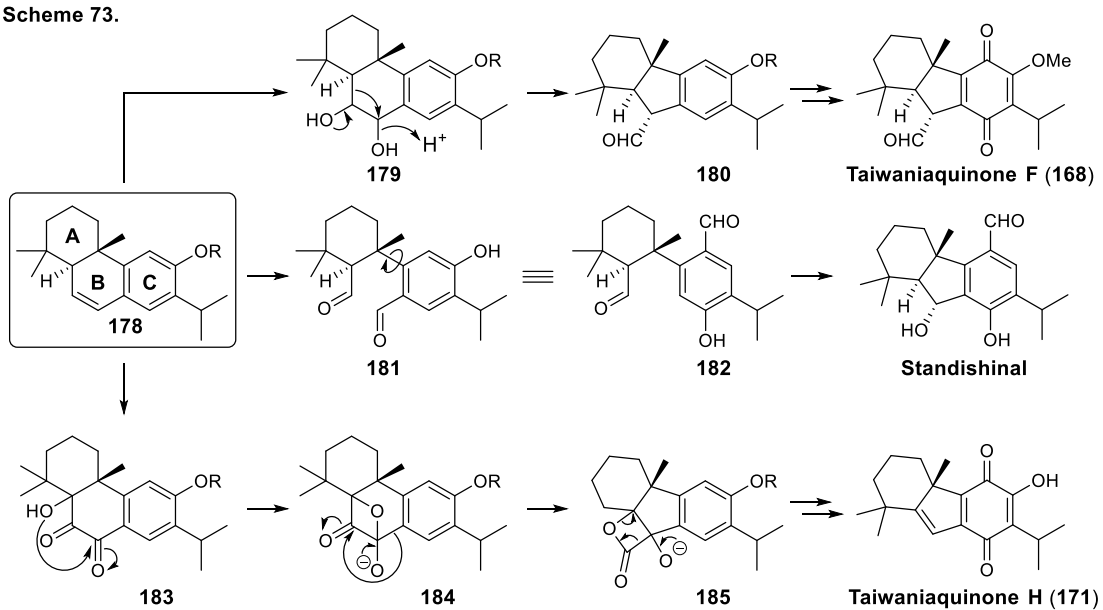
また、Taiwaniaquinoids の中で B 環部分にホルミル基を有する Taiwaniaquinone **A, D, F** 及び Taiwaniaquinol **A, C, D** に関しては、ヒト口腔類表皮癌細胞 (KB 細胞) に対して活性を示すことが報告されており、医薬品としての活用が期待されている (**Table 22**).^{1d}

Table 22. Cytotoxic effect to KB cells.

| <Taiwaniaquinones> | | <Taiwaniaquinols> | |
|--------------------|-----------------------|-------------------|-----------------------|
| Compound | IC ₅₀ (μM) | Compound | IC ₅₀ (μM) |
| etoposide | 1.1 ± 0.02 | etoposide | 1.1 ± 0.02 |
| A (166) | 6.9 ± 0.26 | A (172) | 8.3 ± 0.43 |
| D (169) | 7.2 ± 0.50 | B (173) | > 10 |
| E (167) | > 10 | C (176) | 8.1 ± 0.66 |
| F (168) | 4.4 ± 3.4 | D (177) | 3.5 ± 0.10 |
| G (170) | > 10 | E (174) | > 10 |
| H (171) | > 10 | F (175) | > 10 |

Taiwaniaquinoids を単離した Cheng らは、生合成経路を以下の様に提唱している(Scheme 73.)^{1a, 2}。すなわち、Ferruginol 誘導体 **178** からジヒドロキシ体 **179** が生じる経路では、ピナコール転位により Taiwaniaquinone F (**168**) に代表される Taiwaniaquinoids が生合成される。一方、**178** の B 環二重結合部の酸化的開裂によってジアルデヒド体 **181** が生じる経路では、Prins 型反応によって Standishinal タイプの化合物が生成する。また、**183** の様なジケトンを与えた場合は、ベンジル酸転位と脱炭酸を経て Taiwaniaquinone H (**171**) に代表される化合物が生合成されると考えられる。

Scheme 73.

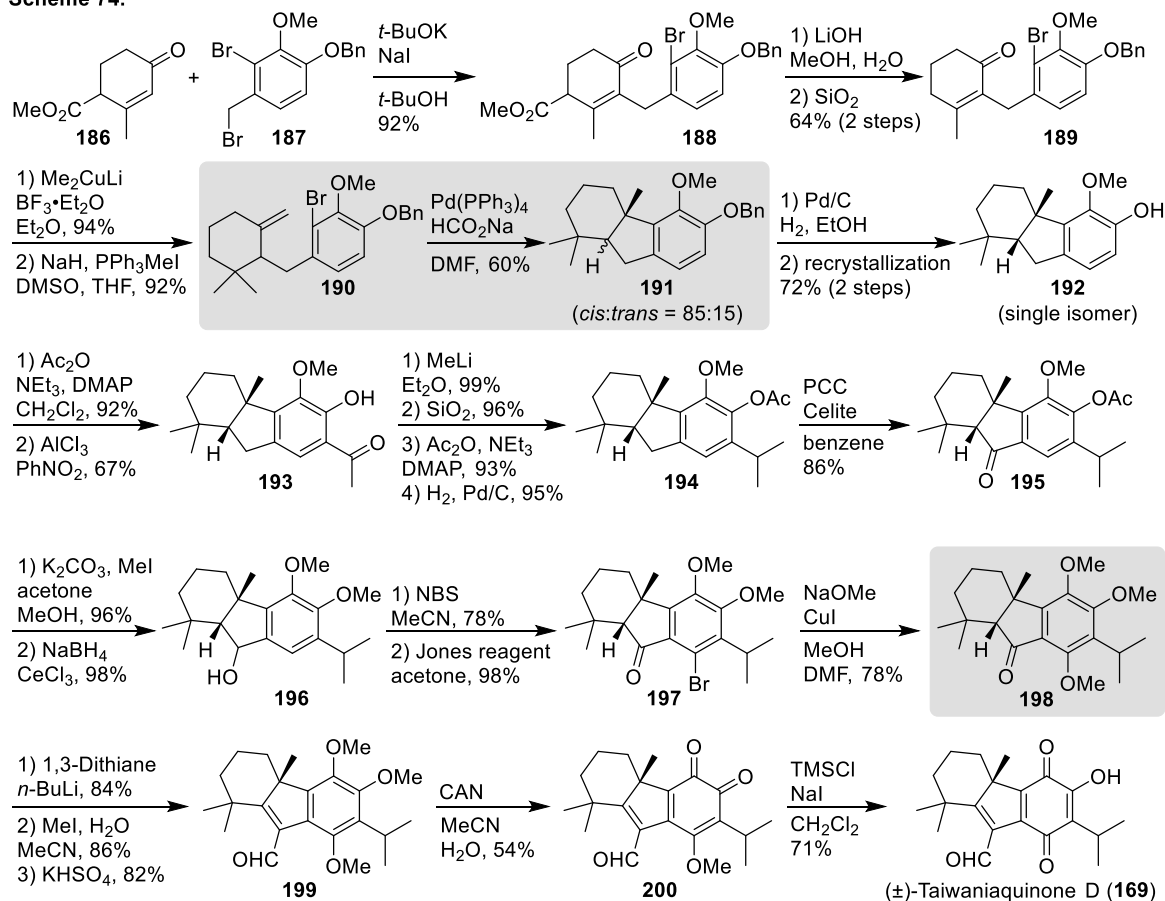


第二節 (±)-Taiwaniaquinone D の合成研究例

1) Banerjee らによる全合成 (2006 年)³

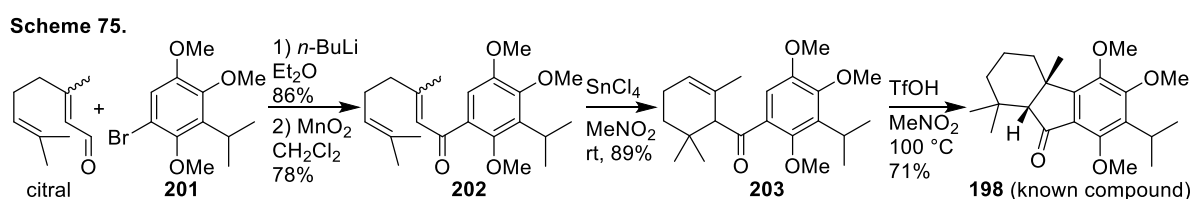
Banerjee らは Heck 反応を鍵工程とする逆合成解析を行い、Taiwaniaquinone D の全合成を達成している(Scheme 74)。すなわち、**186** と **187** から 5 工程の変換により環化前駆体 **190** を合成し、ギ酸ナトリウムを用いる還元的 Heck 反応により環化体 **191** をジアステレオマー混合物として得た。なお、続く脱ベンジル化によって生じるアルコール体 **192** は再結晶により単一異性体として得ている。その後、Fries 転位により導入した Ac 基を *i*Pr 基へと変換して得られた **194** のベンジル位を酸化することでインダノン **195** を合成した。更に、ベンゼン環の臭素化を経て MeO 基を導入した後、アルデヒド等価体として 1,3-ジチアンを用いることで、アルデヒド体 **199** を得ている。この際、インダノン **195** に対して NBS を用いる臭素化を行うと、縮環部位の水素が定量的に臭素へと置換されてしまったが、アルコール体 **196** を経由することでベンゼン環上への臭素化に成功している。最終段階での CAN を用いる酸化反応では、期待した *p*-キノンではなく、*o*-キノン **200** を与えたが、続く脱メチル化反応に付すことで Taiwaniaquinone D の全合成を達成した。

Scheme 74.



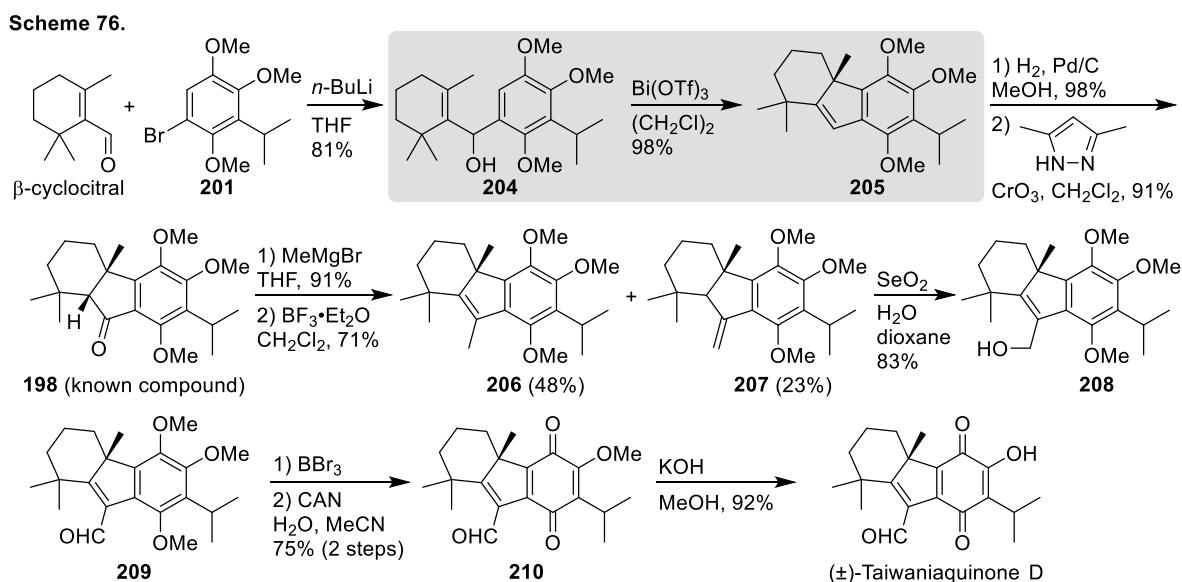
2) Chiu らによる形式合成 (2008 年)⁴

Scheme 74.に示した Banerjee らの合成では、三環性骨格の構築後にベンゼン環上の置換基を導入するため、工程数が多くなるという課題があった。一方、Chiu らは、1,2,4-トリメトキシベンゼンから 4 工程の変換によって、ベンゼン環上にあらかじめ必要な官能基を導入した **201** を合成し、続くリチオ化、citral への付加を経て環化前駆体 **202** を得ている(**Scheme 75.**)。当初の計画では、タンデム環化反応により **202** から **198** を直接合成する予定であったが、酸として TMSOTf を用い、100 °C で加熱した際に 11% の収率で **198** を得たのが唯一の成功例であり、多くの場合は **203** が主生成物として得られたため、段階的な環化反応により Banerjee らが報告している既知中間体 **198** へと導いた。



3) Bisai らによる全合成 (2016 年)⁵

Bisai らも **201** を出発物質とし、 β -cyclocitral への付加を経て環化前駆体 **204** を得ている(**Scheme 76.**)。その後、Lewis 酸を用いる Nazarov 型の環化反応によって得られた環化体 **205** は、オレフィン部位の還元続くベンジル位の酸化により既知中間体 **198** へと導いている。Banerjee らは本中間体から 5 工程、収率 23% で Taiwaniaquinone D を合成しているが、Bisai らは更に改良を重ね、6 工程、収率 37% で合成している。

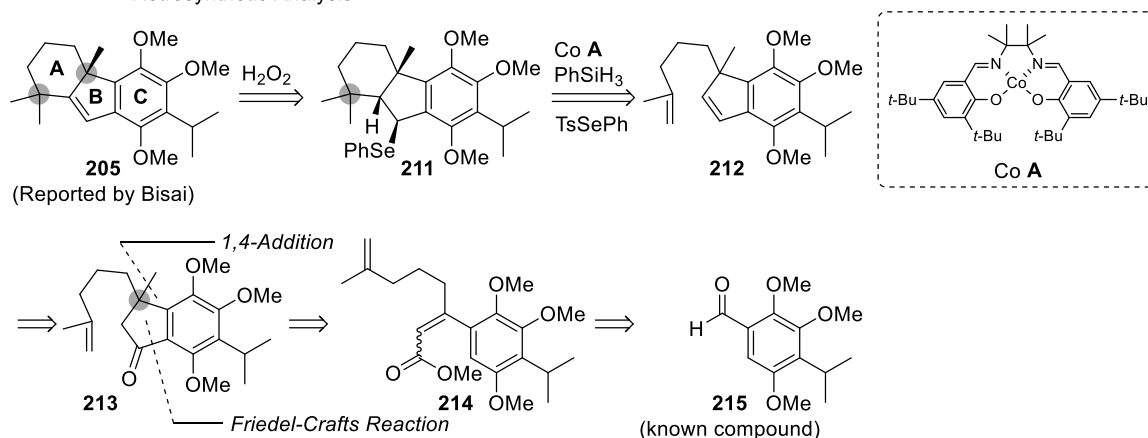


本論

第一節 Taiwaniaquinone D の逆合成解析

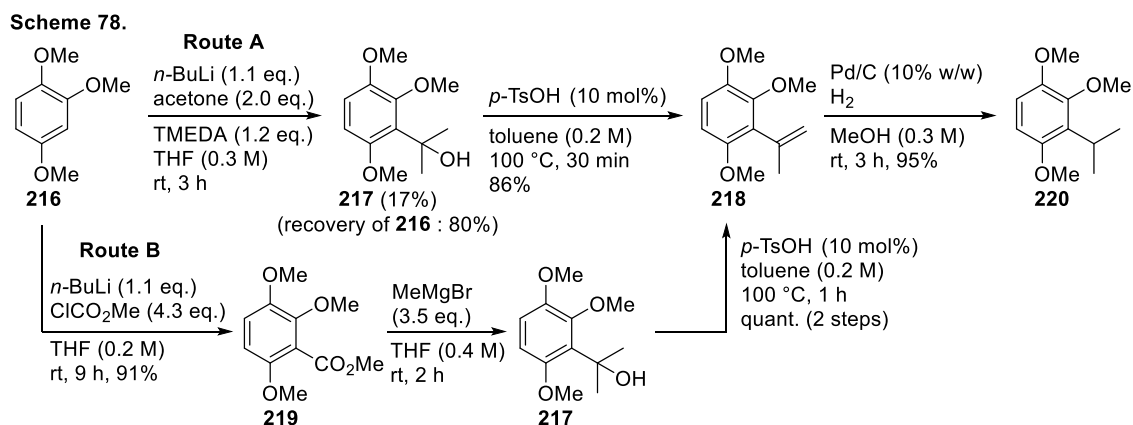
Taiwaniaquinone D の合成を計画する上で、筆者は Bisai らが報告した **205** に着目した(Scheme 77.)。すなわち、**205** は **211** からの *syn* 脱離によって得られると考え、**211** の A 環は自身が見出した Co 触媒を用いるラジカル環化反応によりジエン **212** から構築可能であると期待した。ジエン **212** はインダノン **213** から導けると考え、**213** の四級炭素は α,β -不飽和エステル **214** への 1,4-付加によって導入し、続く分子内 Friedel-Crafts 反応により B 環を構築するものとした。そこで、本合成計画へ着手するにあたり、最初に既知のアルデヒド体 **215** を合成することにした。

Scheme 77. Retrosynthetic Analysis



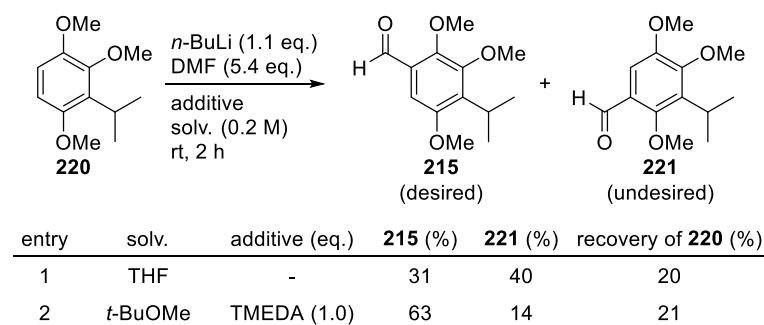
第二節 1,4-付加による四級炭素構築の検討

アルデヒド体 **215** を合成するにあたり、既存の報告例⁶に従って **215** の合成を計画したが、1 工程目のアセトンに対する付加反応の再現性が低かった為、別法を検討することにした(Scheme 78., Route A)。そこで、Majetich らによって報告されたエステル **219** を経由する手法⁷を用いたところ収率良くアルコール体 **217** を得ることに成功し、続く脱水と還元により **220** を合成した(Route B)。



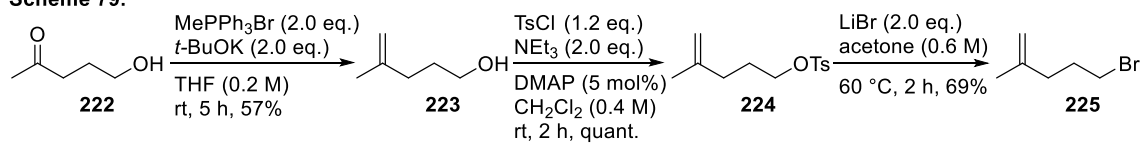
次に、アルデヒドの導入を試みた(**Table 23.**)。はじめに、既知の手法⁸に従い THF を溶媒とした条件で検討したところ、再現性が得られず位置異性体 **221** を主生成物として与えたが(entry 1)、本工程に関しても Majetich らによって報告された反応条件⁷を用いることで、望みのアルデヒド体 **215** を収率 63%で得ている(entry 2)。

Table 23.



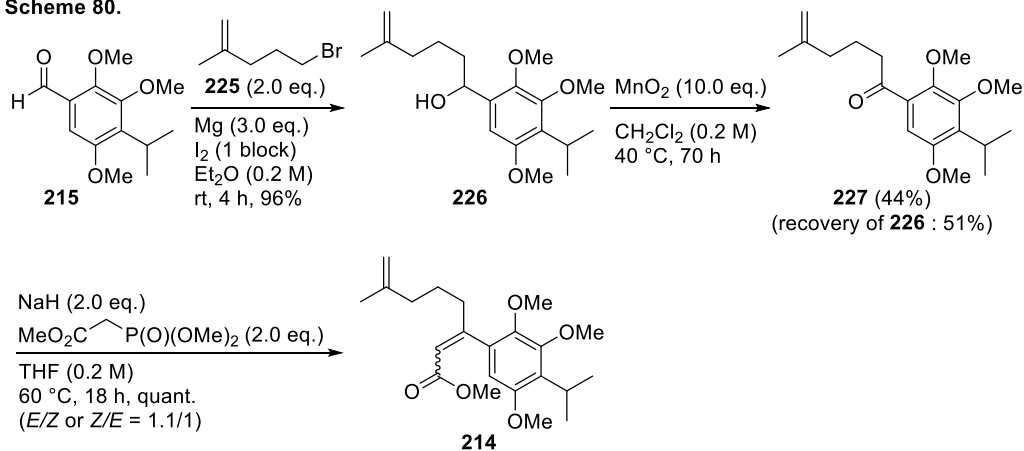
また、導入するアルケン側鎖は市販のケトアルコール **222** から 3 工程で合成した(**Scheme 79.**)。

Scheme 79.



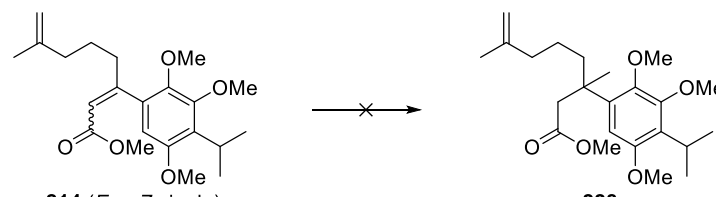
次に、アルデヒド **215** に対して **225** から調製した Grignard 試薬を付加させ、続くアルコールの酸化、不飽和エステルを導入を経て **214** を得た(**Scheme 80.**)。なお、この際生じる *E* 及び *Z* 体は、カラムクロマトグラフィーにより分離可能であったが、立体化学は帰属していない。

Scheme 80.



α,β -不飽和エステル **214** を得ることが出来たため、次に 1,4-付加によるメチル基の導入を検討した(**Table 24.**)。しかし、メチル化剤として MeMgBr 及び MeLi を用いた条件を種々検討したもののいずれの場合も反応は一切進行せず **228** を得ることは出来なかった。

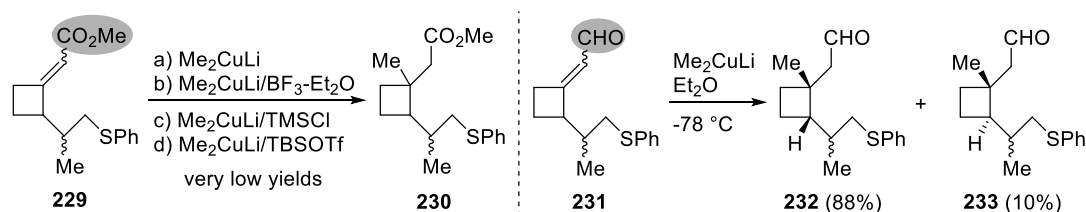
Table 24.



| entry | Me-[M] (eq.) | CuX (eq.) | LiCl (eq.) | TMSCl (eq.) | solv. (M) | comment |
|-------|-----------------------|---------------------|------------|-------------|-----------------------------------|-------------|
| 1 | MeMgBr (1.6) | CuBr (0.2) | 0.4 | 1.1 | THF (0.3) | No Reaction |
| 2 | MeMgBr (1.4) | CuCl (0.1) | - | 1.2 | THF (0.6) | No Reaction |
| 3 | MeMgBr (2.0) | CuCN (3.0) | 6.0 | 2.0 | THF (0.2) | No Reaction |
| 4 | MeLi (6.0) | CuI (3.0) | - | 3.0 | CH_2Cl_2 (0.06 M) | No Reaction |

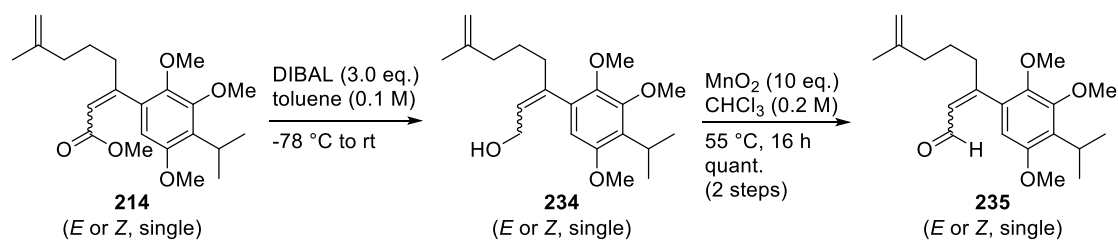
この様な三置換の α,β -不飽和エステルに対する 1,4-付加が円滑に進行しない例は、過去に Bernard らによって報告されている(**Scheme 81.**)⁹。この際、エステル **229** を用いた 1,4-付加は様々な添加剤を用いても低収率であったのに対し、アルデヒド体 **231** へと変換した場合は収率良く **232** 及び **233** が得られている。そこで、自身の系でも同様に反応性が向上することを期待して α,β -不飽和アルデヒドに対する 1,4-付加を検討することにした。

Scheme 81.



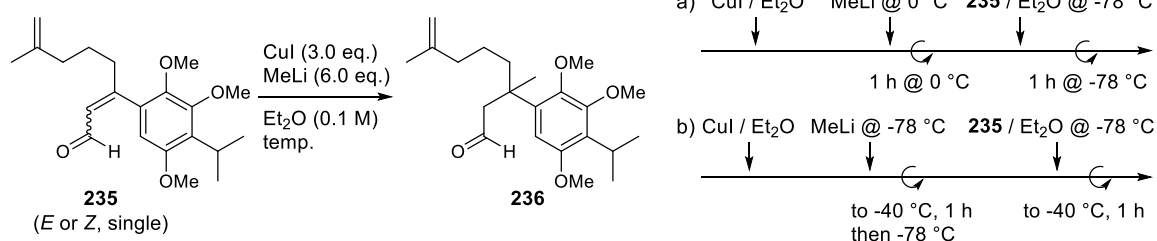
検討に用いるアルデヒド体 **235** は、エステル体 **214** の還元が続く酸化により定量的に合成している(**Scheme 82.**)。

Scheme 82.



合成した α,β -不飽和アルデヒド **235** を用いて 1,4-付加を検討した(Scheme 83.)。まず、a)に示した様に 0 °C で有機銅試薬を調製した後、-78 °C で **235** を加えたところ、望みの **236** は一切得られなかった。この際、粗生成物の ¹H NMR においてアルデヒドの消失が確認されたため、1,4-付加体 **236** 及び出発物質 **235** のアルデヒド部分に対するメチル基の付加が起こっていることが予想される。また、b)に示した様にヨウ化銅の溶液に対して MeLi を-78 °C で滴下し、-40 °C で有機銅試薬を調製した場合は反応が一切進行せず、出発物質を定量的に回収した。これらの検討により、1,4-付加による四級炭素の構築は困難であると判断し、合成計画を変更することにした。

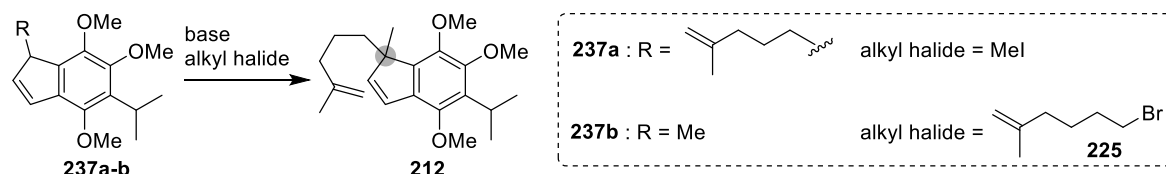
Scheme 83.



第三節 インデンのアルキル化による四級炭素構築の検討

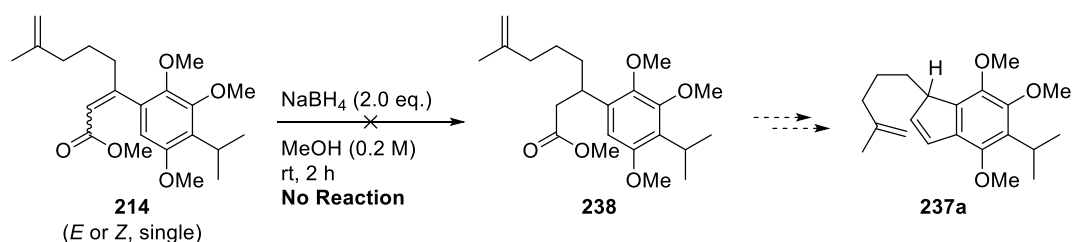
新たな合成経路として、インデン **237** のアルキル化を計画した(Scheme 84.)。インデンのベンジル位かつアリル位の水素は酸性度が高く、塩基による脱プロトン化が可能であるため、対応するアルキルハライドの添加によって四級炭素を有する **212** の合成が期待できる。

Scheme 84.



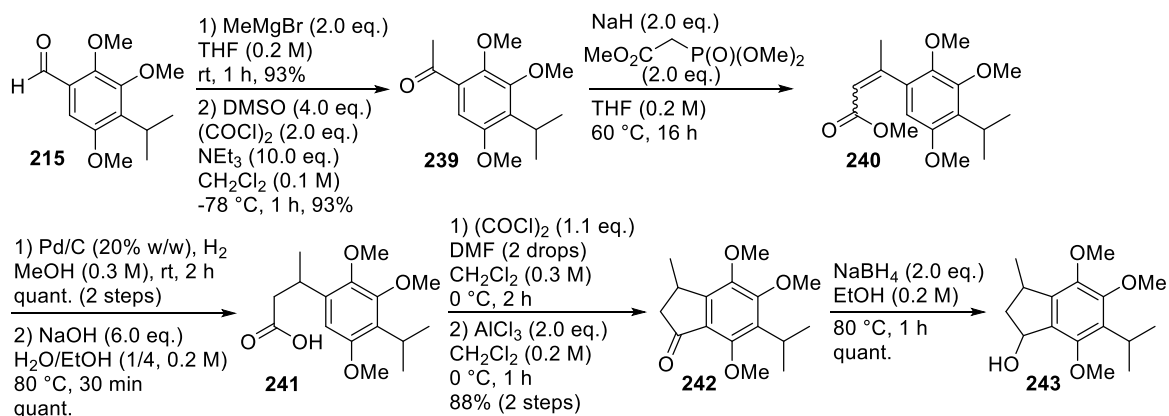
237a は、先の検討で用いたエステル体 **214** の 1,4-還元によって得られる **238** から合成できると期待したが、還元反応は一切進行しなかった(Scheme 85.)。先の 1,4-付加の検討においても **214** の反応性の低さは示唆されていたため、本基質に対する適切な還元条件を精査するよりも、インデン **237b** を用いた検討を行う方が適切であると判断し、**237a** の合成は断念した。

Scheme 85.



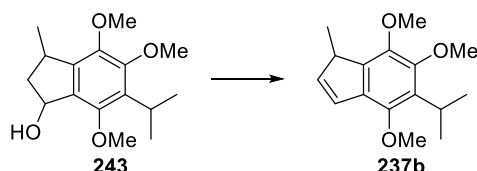
そこで、インデン **237b** の合成を試みた(Scheme 86.)。まず、アルデヒド **215** に対する MeMgBr の付加、続く Swern 酸化、Horner-Wadsworth-Emmons 反応により不飽和エステル **240** を得た。次に、水素添加によるオレフィン部位の還元、生じたエステルの加水分解によりカルボン酸 **241** とし、これを酸クロライドへと変換後、分子内 Friedel-Crafts 反応によってインダノン **242** へと導き、続く還元反応によりアルコール体 **243** を合成した。

Scheme 86.



合成したアルコール体 **243** からの脱水反応を検討したところ、*p*-TsOH を用いる反応条件では反応が複雑化し、**237b** を得ることは出来なかった(Table 25., entry 1)。本結果より、脱水によって生じたインデン **237b** は酸性条件において不安定であることが示唆されたため、塩基性条件での脱離反応を試みた。その結果、水酸基の Ms 化が進行したことを確認後、炭酸カリウム水溶液を加えて 30 分攪拌することで **237b** を合成することに成功した(entry 2)。

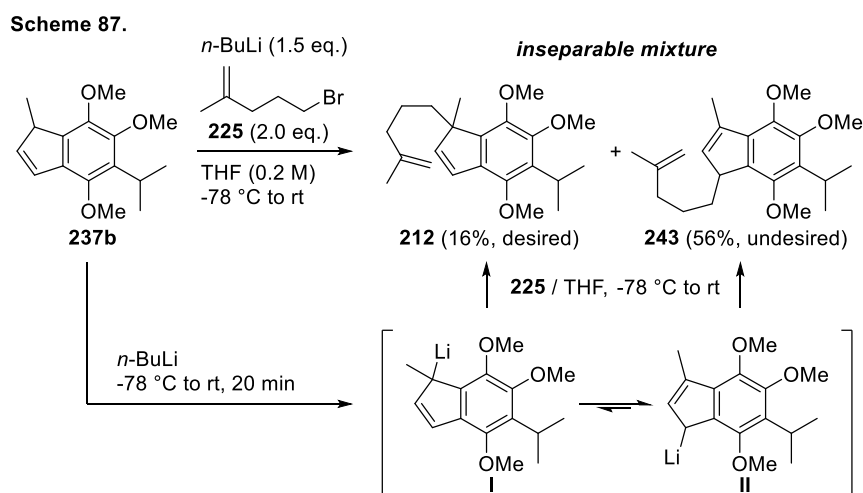
Table 25.



| entry | conditions | 237b (%) | comment |
|-------|---|-----------------|-----------------|
| 1 | <i>p</i> -TsOH (10 mol%), toluene (0.2 M), 100 °C, 30 min | 0 | complex mixture |
| 2 | MsCl (4.0 eq.), NEt ₃ (6.0 eq.), CH ₂ Cl ₂ (0.06 M), 0 °C to rt, 20 h then K ₂ CO ₃ aq., rt, 30 min | 96 | - |

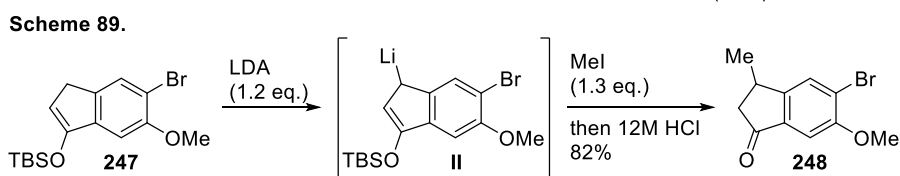
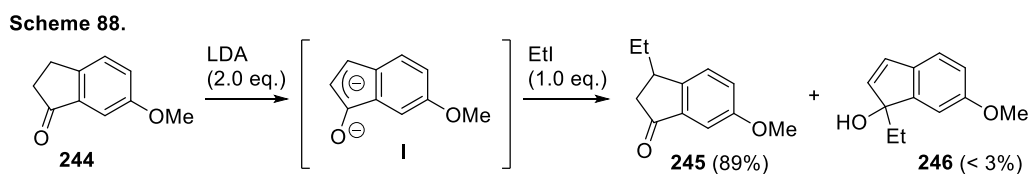
次に、合成した **237b** のアルキル化を検討した(Scheme 87.)。まず、**237b** の THF 溶液 (薄い黄色) に対して *n*-BuLi を滴下し、20 分攪拌したところ濃い赤紫色を呈したため、脱プロトン化によってアニオンが生じていると判断し、アルキルブロミド **225** の THF 溶液を滴下した。その結果、**212** 及び **243** をそれぞれ、16%、56%の収率で与えたが、これらはカラムクロマトグラフィーによって分離することが困難であった。合成計画時には、リチオ化によって中間体 **I** が生じた際、隣接するメトキシ基の酸素がリチウムに配位することで **II** への異性化を抑制できると考えていたが、実際には中間体 **II** への異性化が速やかに進行してしまうこと、及び **212** と **243** の分離が困難

であったことから、インデンのアルキル化による四級炭素構築は断念することにした。



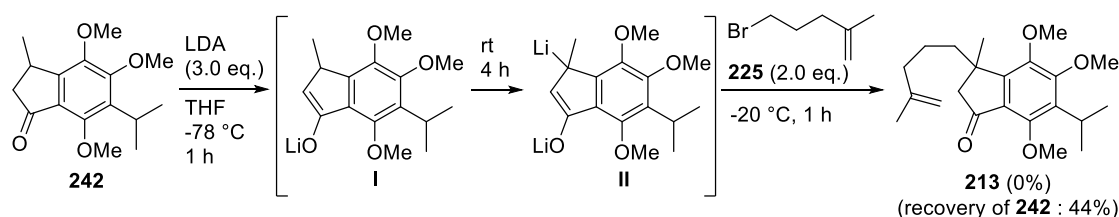
第四節 インダノンのアルキル化による四級炭素構築及び環化反応の検討

先の検討で、インデンの位置選択的なアルキル化が達成できなかったため、次にインダノン **242** の段階で四級炭素を構築することにした。インダノンのカルボニル基β位にアルキル化を行う方法としては、ジアニオン中間体を経由する手法が Trost らによって報告されている (**Scheme 88.**)¹⁰。すなわち、インダノン **244** に対して LDA を二等量加えると、まず一等量目の LDA によりエノラートが生じ、二等量目の LDA によってベンジル位の水素がインデンの場合と同様に脱プロトン化され、ジアニオン中間体 **I** を与える。この際、二等量目の LDA によって生じたアニオンが、酸素上の負電荷との電子的な反発を避けることにより、位置選択的にアルキル化が進行し、**245** が主生成物として得られる。また、インダノンから合成したシリルエノールエーテルをリチオ化する方法も知られており、本手法ではアルキル化を行った後、酸性条件で脱シリル化を行うことでカルボニル基のβ位をメチル化することに成功している (**Scheme 89.**)¹¹。そこで筆者は、これらの手法をインダノン **242** に適用することで四級炭素の構築が達成できると期待し、検討に着手した。



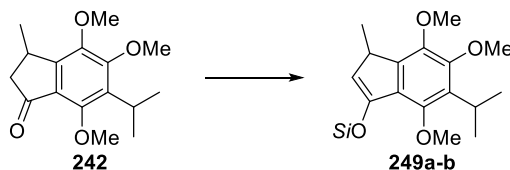
まず、Trost らの報告例に従い、ジアニオン中間体を経由するアルキル化を検討したところ、出発物質である **242** が回収されるのみで、**213** を得ることは出来なかった(Scheme 90.)。

Scheme 90.



次に、Scheme 89.の手法を検討するためにインダノン **242** のシリルエノールエーテル化を試みた(Table 26.)。まず TBS 基を検討したところ、TLC 上では **249a** の生成が確認できたが、精製過程において脱シリル化が進行してしまったため、単離することが出来なかった(entry 1)。次に、生じるシリルエノールエーテルの安定性の向上を期待して TIPS 基を検討したところ、定量的に **249b** を単離することが出来た(entry 2)。

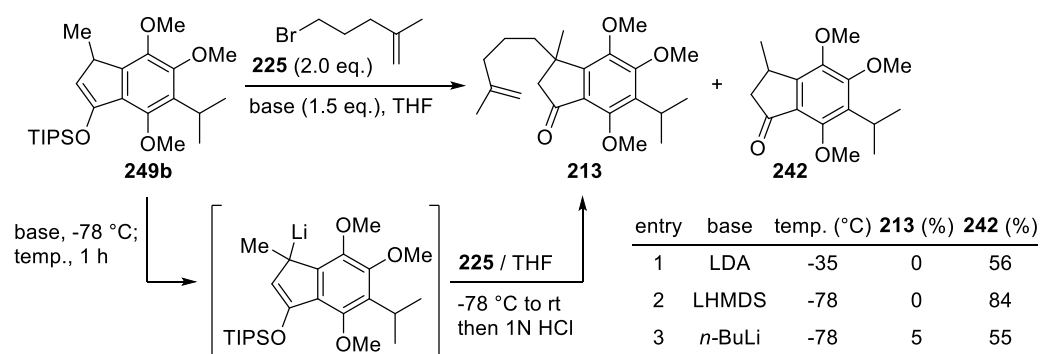
Table 26. Synthesis of silyl enol ether



| entry | conditions | Si | 249 (%) | recovery of 242 (%) |
|-------|--|------|----------------------|----------------------------|
| 1 | DBU (3.0 eq.), TBSOTf (2.0 eq.), CH ₂ Cl ₂ (0.2 M), rt, 1 h | TBS | 249a (0) | 92 |
| 2 | NEt ₃ (3.0 eq.), TIPSOTf (2.0 eq.), CH ₂ Cl ₂ (0.2 M), 0 °C, 30 min | TIPS | 249b (quant.) | 0 |

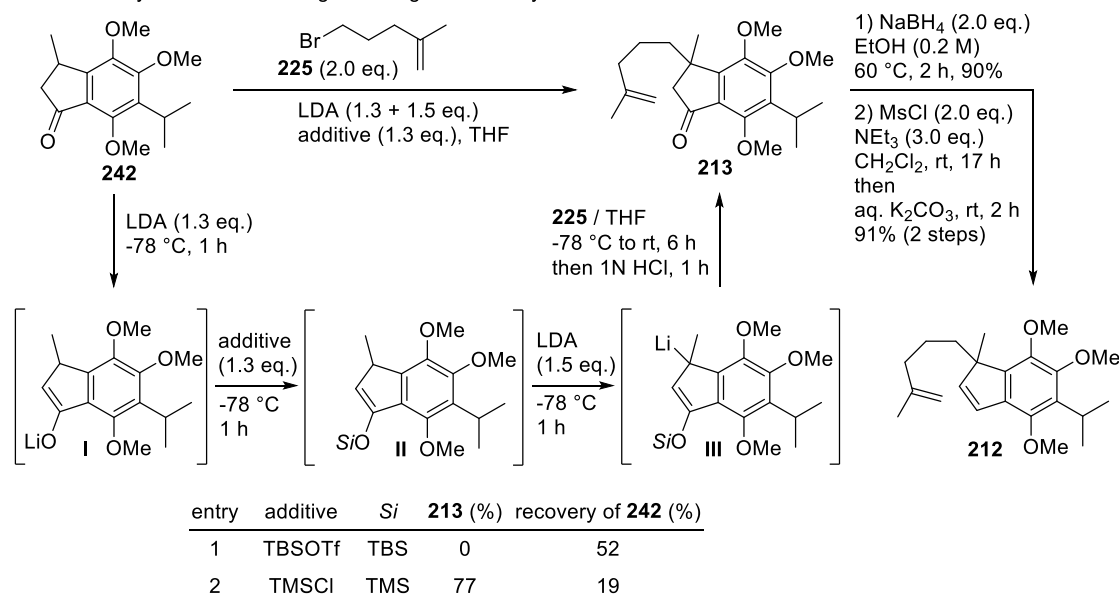
得られたシリルエノールエーテル **249b** を用いた検討結果を以下に示す(Table 27.)。まず LDA を用いて検討したところ、インダノン **242** と共に構造不明の副生成物を回収するのみであり、**213** は得られなかった(entry 1)。また、塩基として LHMDS を用いた際はほとんど反応が進行せず、**242** が収率 84%で得られた(entry 2)。一方、*n*-BuLi を用いた際には **213** が得られたものの 5%と低収率であり、**242** が主生成物として得られた(entry 3)。

Table 27. Alkylation of silyl enol ether **249b**



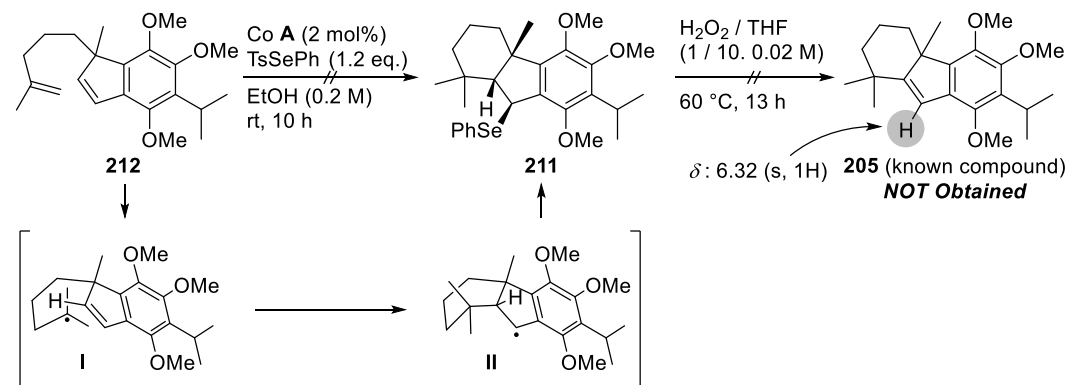
更なる検討として、単離が困難であると予想されるシリルエノールエーテルを反応系中で発生させることにした(**Table 28.**)。まず、LDA 及び TBSOTf を用いて検討したところ、シリルエノールエーテル **II** の生成は TLC で確認できたものの、望みの **213** を得ることは出来ず、出発物質 **242** を回収するのみであった(entry 1)。一方、シリル化剤として TMSCl を添加した際は反応が円滑に進行し、**213** を収率 77% で得ることが出来た(entry 2)。得られたインダノン **213** は先の検討と同様に、ケトンの還元続く Ms 化を経て鍵中間体であるジエン **212** に導くことが出来たため、次に Co 触媒によるラジカル環化反応を検討することにした。

Table 28. Alkylation of **242** through in situ generated silyl enol ether



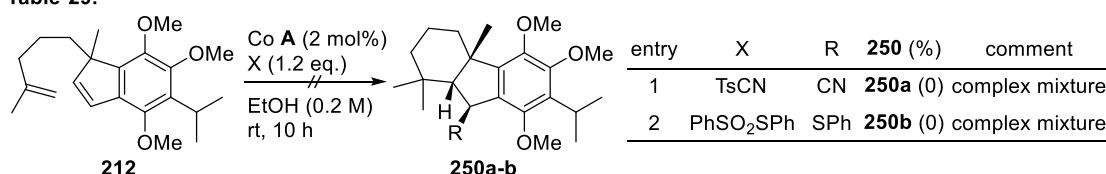
ジエン **212** を Co 触媒条件に付した場合、三級ラジカル **I** の生成に続く立体選択的なラジカル環化反応により中間体 **II** が生じ、TsSePh が convex 面から接近することで環化体 **211** が立体選択的に得られると考えられる(**Scheme 91.**)。実際に下記の条件で検討を行ったところ、一段階目の反応終了後に粗生成物の $^1\text{H NMR}$ の観測において、出発物質 **212** のオレフィンピークが消失していることが確認できたため、続く脱離反応条件に付したものの、複雑な混合物を与えるのみであった。この際、得られた化合物の $^1\text{H NMR}$ スペクトルにおいて、**205** のオレフィン水素に相当するピークは一切観測されなかったため、TsSePh 以外のラジカルアクセプターを用いて同様の環化反応を検討することにした。

Scheme 91.



そこで、ラジカルアクセプターとして TsCN,及び PhSO₂SPh を検討したが、いずれの場合も反応は複雑化し、望みの環化体を得ることが出来なかった(**Table 29.**)。これらの検討において反応が円滑に進行しなかったのは、アルケン側鎖へのヒドロコバルト化による三級ラジカル生成と、インデンへのヒドロコバルト化によるベンジルラジカル生成が競合したためだと考えている。そのため、ジエン **212** は Co 触媒条件において不適切な基質であり、条件検討による収率の改善は困難であると判断し、新たな環化前駆体を設計することにした。

Table 29.



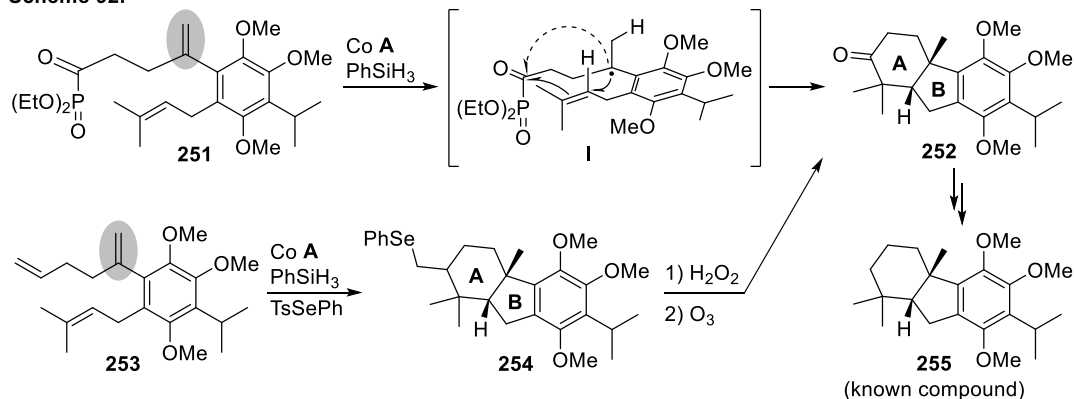
第五節 タンデム環化反応による A 及び B 環構築の検討

先の検討において、ベンジルラジカル生成が反応の複雑化につながったと考えたため、ベンジルラジカルを与えるアルケンが反応の起点となる基質 **251** 及び **253** を設計した(**Scheme 92.**)。

アシルホスホネートを有する基質 **251** の場合、まずベンジルラジカル **I** が生じた後、立体選択的な環化反応により **252** が立体選択的に得られると期待した。この際、最初に生じたベンジルラジカルのアシルホスホネートに対する付加反応は 4-*exo* 環化となるため、アルケンに対する 5-*exo* 環化が優先すると考えられる。しかし、第三章に示したヒドロアシル化の基質検討を行う過程で、スチレンユニットを有する基質に対してアシルホスホネートを導入することが出来なかったため、基質 **251** の合成は困難であることが予想される。

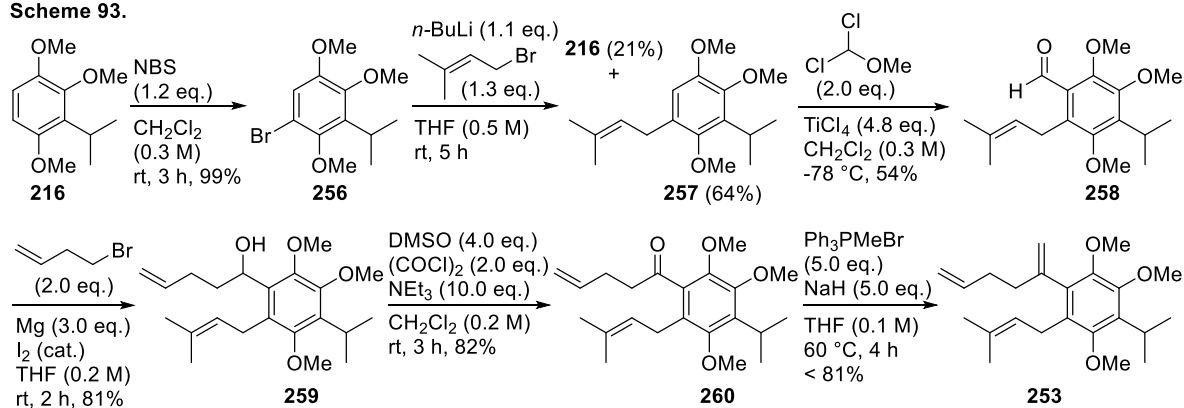
そこで、環化体 **252** をトリエン **253** のタンデム環化反応によって合成する経路を考案した。すなわち、本基質でも最初にベンジルラジカルが生じれば、**251** の場合と同様に環化体 **254** が立体選択的に生成し、続く *syn* 脱離、オゾン分解を経て **252** が合成できると考えた。

Scheme 92.



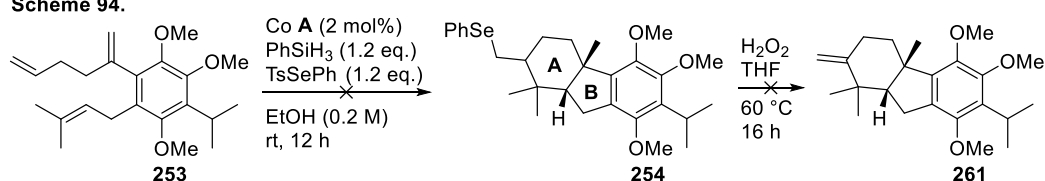
先の合成計画に基づき、トリエン **253** の合成を検討した(Scheme 93.)。まず、**216** のブロモ化、続くアリル化により **257** 及び副生成物として **216** を得た後、TiCl₄ とジクロロメチルメチルエーテルを用いるホルミル化により、アルデヒド体 **258** を合成した。得られた **258** は Grignard 試薬の付加、Swern 酸化、Wittig 反応の 3 工程によって環化前駆体であるトリエン **253** に導いている。なお、トリエン **253** はカラムクロマトグラフィーで完全に精製することは出来なかったため、不純物を含んだ状態で環化反応を検討することにした(Scheme 94.)。

Scheme 93.



まず、**253** を Co 触媒条件に付したところ、**253** の消失が TLC で確認出来たので、溶媒を留去して ¹H NMR を測定した。その結果、オレフィンのピークがすべて消失していることが確認されたため、環化体 **254** が生成していると期待し、続く脱離反応条件に付したが、粗生成物の ¹H NMR スペクトルにおいて、新たに生じるエキソメチレンに該当するピークが観測されなかったため、本基質も環化前駆体として不適切な設計であると判断した。この際反応が複雑化したのは、トリエン **253** には、反応の起点となりうるアルケンが三か所あり、ジエンの場合に比べて位置選択性の制御が困難になったからだと考えている。

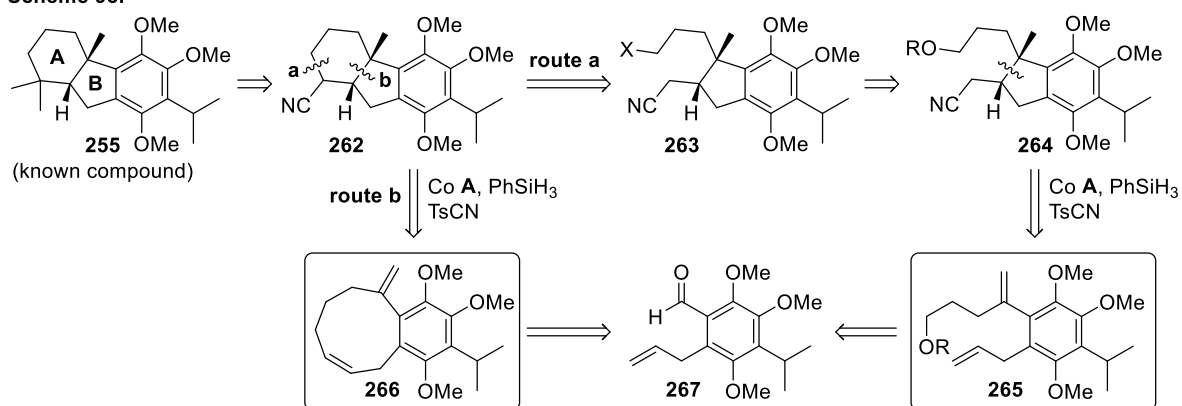
Scheme 94.



第六節 モデル基質による三環性骨格構築法の確立

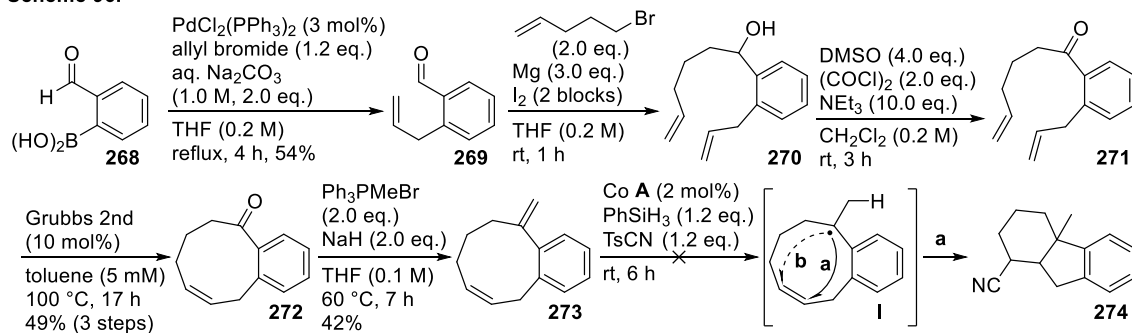
前節での結果を踏まえ、タンデム環化反応によって A 及び B 環を一挙に構築する経路は困難であると判断した。そこで、トリエン **253** と同様に、ベンジル位かつ三級のラジカルを与えるアルケンが反応の起点となるジエンとして **265** 及び **266** を新たに設計した(Scheme 95.)。ジエン **265** の場合、Co 触媒を用いるヒドロシアノ環化反応によって B 環が構築でき、続く A 環構築は **263** からの分子内 S_N2 反応により達成できると期待した。一方、ジエン **266** の場合は九員環構造を有するため、ヒドロシアノ環化反応により A 及び B 環を一挙に構築可能であると考えた。これらのジエンはいずれもアルデヒド体 **267** から合成できると考え、本経路の妥当性を確認するために、ベンゼン環上に置換基を持たないモデル基質を用いて環化反応を検討することにした。

Scheme 95.

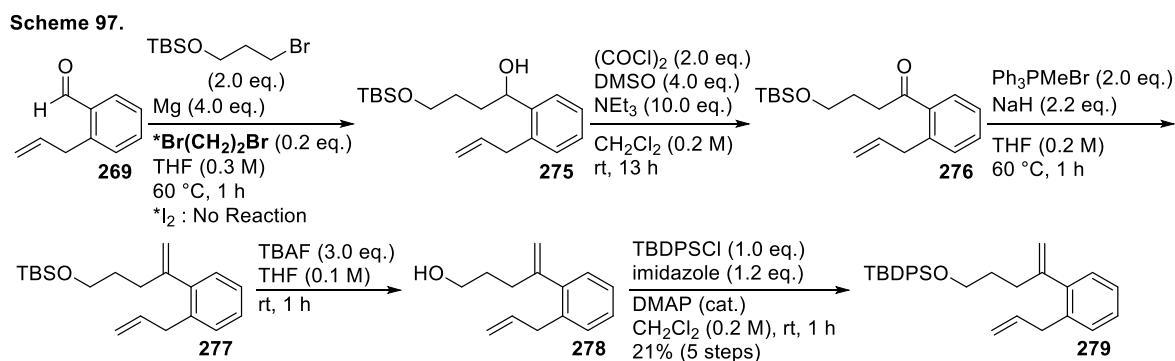


新たに設計したジエン **266** のモデル基質 **273** は、カップリング反応によって合成したアルデヒド **269** への Grignard 試薬の付加、Swern 酸化、閉環メタセシス、Wittig 反応によって得られたため、Co 触媒によるヒドロシアノ環化反応を検討した(Scheme 96.)。しかし、本基質においても反応は複雑化し、環化体 **274** を得ることは出来なかった。この際反応が複雑化したのは、ラジカル中間体 **I** から環化反応が進行する際に実線で示した望みの経路 a と破線で示した経路 b が競合したためだと考えられる。そこで次に、この様な競合が起こらないジエン **265** の環化反応を、モデル基質で検討することにした。

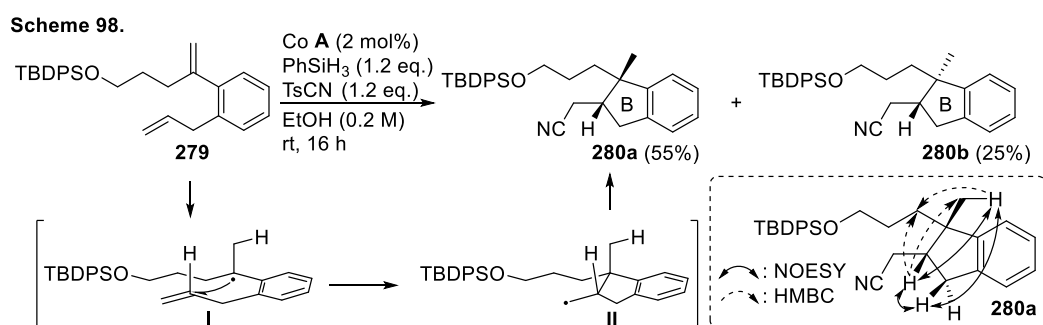
Scheme 96.



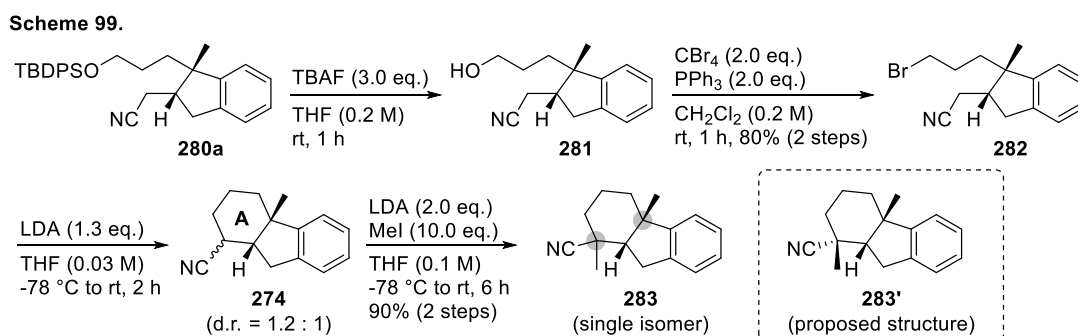
まず、アルデヒド **269** に対する Grignard 試薬の付加を検討したところ、Grignard 試薬の調製における活性化剤としてこれまでと同様にヨウ素を用いた場合は反応が一切進行しなかった (Scheme 97.)。そこで、ジブロモエタンを用いたところ反応は円滑に進行し、アルコール体 **275** を得ることが出来た。続く Swern 酸化、Wittig 反応によりモデル基質 **277** を合成することが出来たが、TLC での視認性向上を期待して、保護基を TBDPS に変更した環化前駆体 **279** に変換した。



次に、ジエン **279** のヒドロシアノ環化反応を検討した (Scheme 98.)。その結果、望みの立体化学を有する **280a** 及びジアステレオマー **280b** をそれぞれ 55%、25% の収率で得た。なお、環化体 **280a** の立体化学に関しては NOESY 測定により決定している。この際 **280a** が主生成物として得られたのは、環化反応が進行する際に **I** の様なコンフォメーションを経由するためだと考えられる。



更なる検討として A 環構築を試みた (Scheme 99.)。検討の結果、TBAF による脱シリル化、Appel 反応により合成した **282** に対して -78°C で LDA を滴下すると環化体 **274** が得られることを見出した。また、LDA とヨードメタンを用いることで続くメチル化も円滑に進行し、三環性骨格及び二つの四級炭素を有する **283** を単一異性体として得た。立体化学は未決定だが、メチル化が convex 面から進行した **283'** であると考えている。

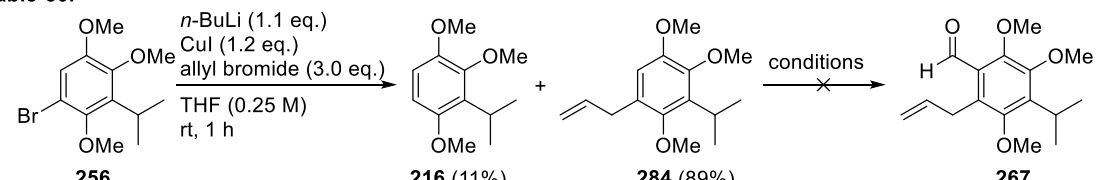


第七節 六置換ベンゼンを有するジェンの合成

前節のモデル基質を用いた検討により、Taiwaniaquinone D の骨格を構築する合成経路が確立できたため、次に、ベンゼン環上の置換基を揃えたジェン **265** の合成を検討することにした。この際、アルデヒド **267** を合成出来ればモデル基質と同じ手法でジェンに導くことが出来ると期待し、アルデヒド体 **267** は、第五節の **Scheme 93** と同様の経路で合成可能であると考えた (**Table 30**)。

そこで、まず **256** のアリル化を行ったところ収率 89% で **284** を得ることが出来たが、続くホルミル化は円滑に進行しなかった。Entry 1, 2 では、TiCl₄ を用いて検討したが、望みの **267** を得ることは出来なかった。この際、¹H NMR においてアルデヒドに相当するピークが観測される生成物を得たが、オレフィン部分が異性化したと思われる構造を有していた。次に、AgOTf を用いたところ、こちらの場合は反応が複雑化する結果となった (entry 3)。更に、*n*-BuLi によってベンゼン環上の水素を脱プロトン化し、DMF を加えることで **267** が得られると期待したが反応は複雑化し、**267** は得られなかった (entry 4)。

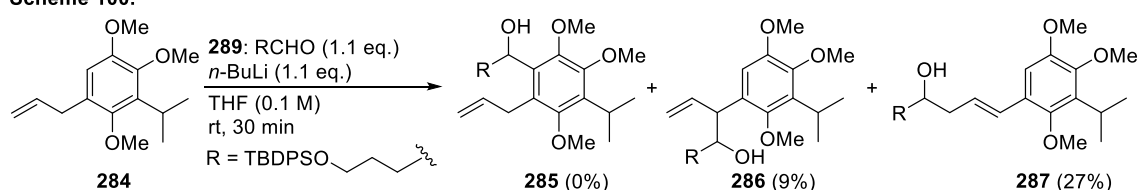
Table 30.



| entry | conditions | 267 (%) | recovery of 284 (%) | comment |
|-------|---|----------------|----------------------------|--------------------|
| 1 | Cl ₂ CHOMe (2.0 eq.), TiCl ₄ (4.8 eq.), CH ₂ Cl ₂ (0.3 M), -78 °C | 0 | 0 | undesired aldehyde |
| 2 | Cl ₂ CHOMe (1.0 eq.), TiCl ₄ (2.0 eq.), CH ₂ Cl ₂ (0.3 M), -78 °C | 0 | 0 | undesired aldehyde |
| 3 | Cl ₂ CHOMe (3.0 eq.), AgOTf (1.0 eq.), CH ₂ Cl ₂ (0.2 M), -78 to 0 °C | 0 | 0 | complex mixture |
| 4 | <i>n</i> -BuLi (1.1 eq.), DMF (5.0 eq.), THF (0.2 M), -78 °C to rt | 0 | 30 | complex mixture |

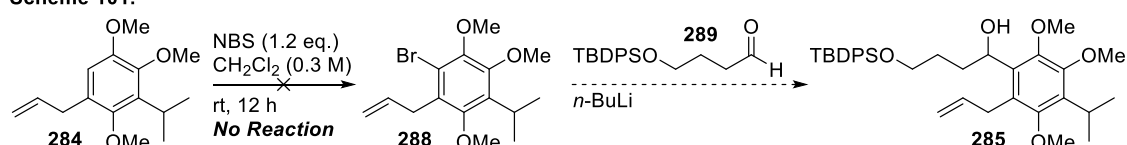
先の検討で、**284** に対して *n*-BuLi を滴下した際に反応溶液が濃い黄色を呈したことから、リチオ化は進行していると考えた。そこで、アルデヒドを加えれば **285** が得られると期待したが、実際にはアリル位の脱プロトン化が進行しており **286** 及び **287** を与えるのみであった (**Scheme 100**)。

Scheme 100.

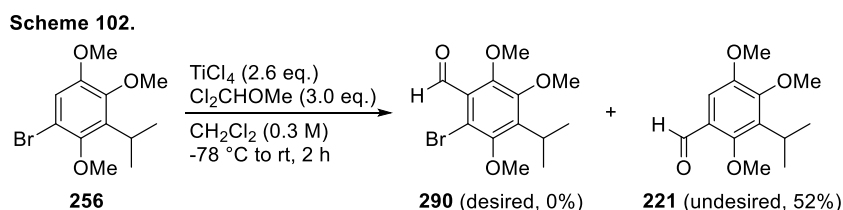


本結果を受け、まずベンゼン環に臭素を導入すればリチオ化に続くアルデヒドの付加が進行すると期待したが、NBS を用いる臭素化条件において **284** は一切反応しなかった (**Scheme 101**)。

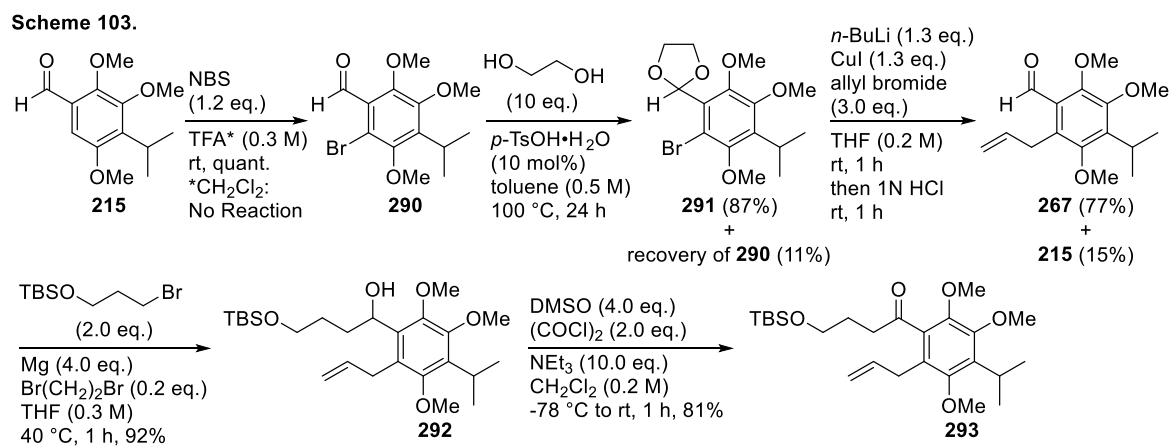
Scheme 101.



ここまでの結果を踏まえ、アリル基の導入はベンゼン環のホルミル化後に行うべきであると判断し、ブロモベンゼン **256** のホルミル化を検討した(Scheme 102.)。その結果望みの **290** は一切得られず、**221** が収率 52%で得られる結果となった。



そこで、アルデヒド体 **215** の臭素化を検討した(Scheme 103.)。その結果、溶媒としてジクロロメタンを用いた際には反応が一切進行しなかったものの、TFAに変更したところ定量的にブロモ体 **290** を得ることが出来た。得られた **290** はアルデヒドの保護、アリル化、脱保護を経てアルデヒド体 **267** へと導き、続く Grignard 試薬の付加、Swern 酸化によってケトン **293** を合成した。

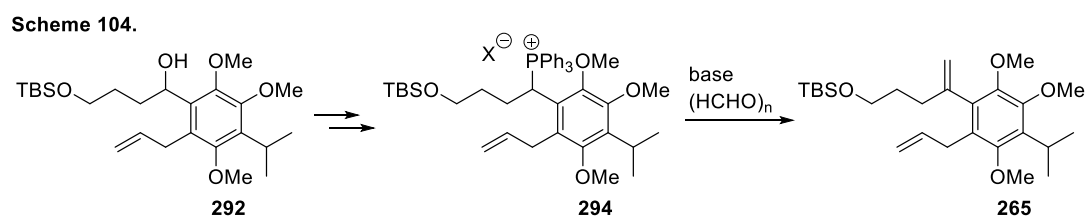


最後に、ケトン **293** のオレフィン化を試みた(Table 31.)。entry 1 では、モデル基質と同様の条件を検討したものの反応は一切進行しなかった。また、塩基として *n*-BuLi や *t*-BuOK も検討したが、いずれも原料を定量的に回収するのみであった(entry 3, 4)。更に、Peterson 反応や Tebbe 試薬によるオレフィン化を試みたもののいずれもジエン **265** を与えることはなかった。オレフィン化が進行しなかった原因としては、基質がエノール化しやすいこと、立体障害の影響、電子豊富な芳香環によりケトンの求電子性が低下していることなどが考えられるが、第五節の Scheme 93. に示した様に類似のケトン **260** ではオレフィン化が進行しているため、詳細は不明である。

Table 31.

| entry | conditions | 265 (%) | comment |
|-------|--|----------------|------------------------------|
| 1 | NaH (5.0 eq.), PPh ₃ MeBr (5.0 eq.), THF (0.1 M), 60 °C | 0 | No Reaction |
| 2 | <i>n</i> -BuLi (5.0 eq.), PPh ₃ MeBr (5.0 eq.), THF (0.1 M), 60 °C | 0 | No Reaction |
| 3 | <i>t</i> -BuOK (5.0 eq.), PPh ₃ MeBr (5.0 eq.), toluene (0.1 M), 100 °C | 0 | No Reaction |
| 4 | TMSCH ₂ MgCl (5.0 eq.), THF (0.1 M), 60 °C | 0 | No Reaction |
| 5 | Tebbe Reagent (2.0 eq.), THF (0.2 M), -78 °C to rt | 0 | recovery of 293 : 43% |

今後は、引き続きケトン体 **293** のオレフィン化を検討するとともに、**Scheme 104.**に示した様にアルコール体 **292** から **294** を合成し、パラホルムアルデヒドを用いた Wittig 反応によりジエン **265** を合成する予定である。



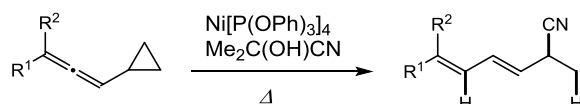
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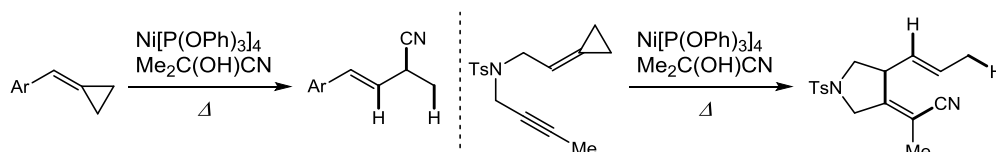
総括

筆者は、遷移金属触媒と炭素-炭素多重結合を用いる新規反応の開発、及び開発した環化反応を用いた天然物の合成研究を行い、以下に示す成果を得た。

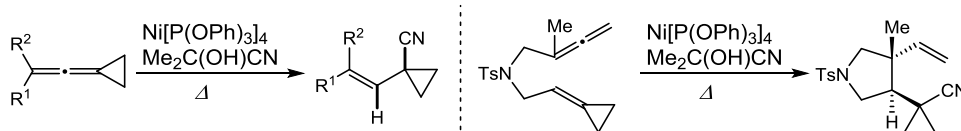
1. アレニルシクロプロパンのシアノ基導入型環開裂反応の開発に成功した。また、トリエンへのヒドロシアノ化反応やヒドリド源非存在下での検証、重水素化実験により反応機構を考察した。



2. メチレンシクロプロパンのシアノ基導入型環開裂反応の開発に成功した。また、メチレンシクロプロパンイン体を用いると環開裂に続く環化反応が進行することを見出した。

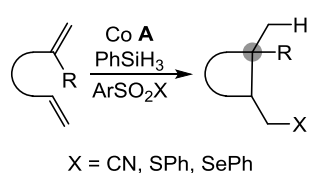


3. ビニリデンシクロプロパンのヒドロシアノ化では、基質がアレンとしての性質を示し、環開裂を伴わない位置及び立体選択的なヒドロシアノ化体が見出された。また、アレンメチレンシクロプロパン体のヒドロシアノ環化では、アレンから反応が進行することを見出した。

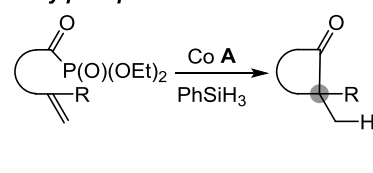


4. ジエンのヒドロシアノ環化反応の検討では、より安定なラジカルを与えるアルケンから位置選択的に反応が進行することを見出した。この際、シアノ基の他に SPh 基や SePh 基も導入可能であった。また、分子内にラジカルアクセプターとしてオキシムやアシルホスホネートを導入した場合にも環化反応が円滑に進行した。これらの反応ではいずれも四級炭素の構築が可能であった。

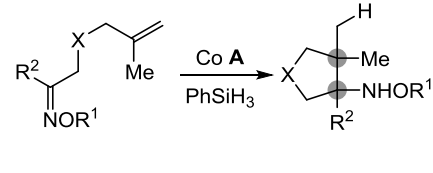
<Dienes>



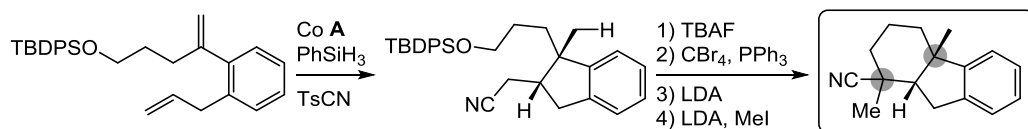
<Acylphosphonates>



<Oximes>



5. 合成経路を種々検討した結果、ジエンのヒドロシアノ化反応を用いて、Taiwaniaquinoids が共通して有する 6-5-6 員環骨格及び、2つの四級炭素が構築可能であることを見出した。

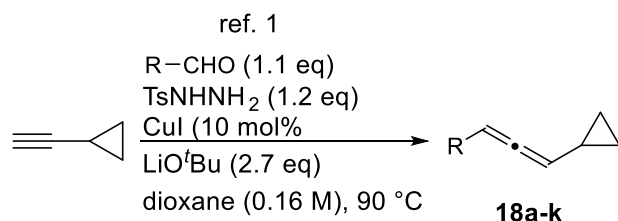


第一章の実験

General remarks: All reactions were performed with dry solvents and reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel (Fuji Silysia, PSQ-60B) DIOL-silica (Fuji Silysia, MB100-40/75) or NH-silica (Fuji Silysia, DM2035). NMR spectra were recorded with calibration using residual undeuterated solvent as an internal reference. High resolution mass spectra were performed on a TOF LC/MS spectrometer (Ionization method: ESI).

General procedure for hydrocyanation: A solution of starting material (1.0 eq.), P(OPh)₃ (50 mol%), Ni[P(OPh)₃]₄ (10 mol%), and acetone cyanohydrin (20.0 eq.) in toluene (0.02 M for starting material) was heated at 100 °C under an argon atmosphere. The reaction mixture was pored into silica gel to be purified by column chromatography (hexane/AcOEt = 15/1), and the desired product was given.

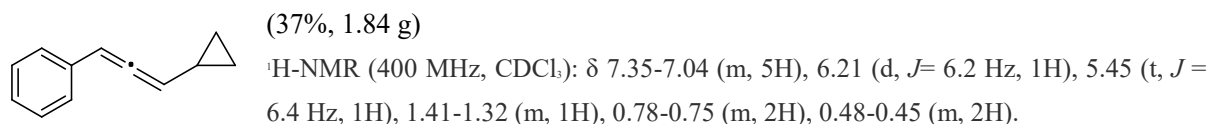
General procedure for the synthesis of cyclopropylallens (18a-k)



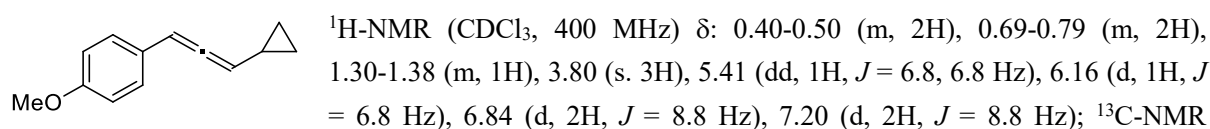
18a-k were synthesized according to the reported procedure¹.

To a 1,4-dioxane (40 ml) solution of TsNHNH₂ (7.1 g, 38.2 mmol) was added benzaldehyde (3.5 ml, 34.5 mmol) at 60 °C under argon. The resulting solution was allowed to stir for an additional 1 h at same temperature. To this solution was added 1,4-dioxane (160 ml), CuI (608 mg, 3.2 mmol), cyclopropyl acetylene (2.7 ml, 31.8 mmol), LiOtBu (8.0 g, 85.9 mmol) at 90 °C. The mixture was stirred for an additional 2 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature and was filtered through a short silica gel column eluting with AcOEt. The solvent was removed in vacuum to leave a crude mixture, which was purified by column chromatography on silica gel (eluting with hexane) to afford pure xxa as a colorless oil (1.84 g, 37%)

(3-cyclopropylpropa-1,2-dien-1-yl)benzene (18a) (CAS-Reg# 200417-79-4)

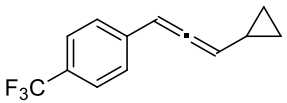


1-(3-cyclopropylpropa-1,2-dien-1-yl)-4-methoxybenzene (18b)

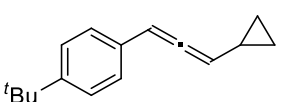


(CDCl₃, 100 MHz) δ : 6.8, 7.0, 9.6, 55.3, 95.6, 99.4, 114.1, 127.2, 127.7, 158.7, 204.0 ; IR (ATR) ν : 2928, 1717, 1599, 1510, 1253, 1161, 1023 cm⁻¹; HRMS (APPI) Calcd for C₁₃H₁₅O, [M+H]⁺ 187.1117, found 187.1117; yellow oil (25%, 250 mg)

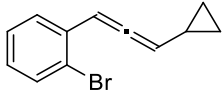
1-(3-cyclopropylpropa-1,2-dien-1-yl)-4-(trifluoromethyl)benzene (18c)

¹H-NMR (CDCl₃, 400 MHz) δ : 0.42-0.52 (m, 2H), 0.78 (dd, 2H, *J* = 8.4, 2.4 Hz), 1.33-1.41 (m, 1H), 5.50 (dd, 1H, *J* = 6.4, 6.4 Hz), 6.22 (d, 2H, *J* = 6.4 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 7.0, 7.0, 9.2, 95.4, 100.2, 125.5, 126.7, 128.5, 138.9, 205.9 ; IR (ATR) ν : 3007, 1948, 1615, 1321, 1119, 1106, 1065, 844 cm⁻¹; HRMS (APPI) Calcd for C₁₃H₁₁F₃, [M]⁺ 224.0807, found 224.0803; Yellow oil (23%, 225 mg)

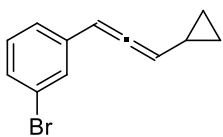
1-(tert-butyl)-4-(3-cyclopropylpropa-1,2-dien-1-yl)benzene (18d)

¹H-NMR (CDCl₃, 400 MHz) δ : 0.42-0.44 (m, 2H), 0.70-0.74 (m, 2H), 1.29-1.30 (m, 10H), 5.42 (dd, 1H, *J* = 6.4, 6.4 Hz), 6.17 (d, 1H, *J* = 6.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 6.8, 7.1, 31.3, 34.5, 95.9, 99.2, 125.5, 126.3, 131.9, 149.8, 204.6; IR (ATR) ν : 2961, 1947, 1514, 1268, 1018, 875, 836 cm⁻¹; HRMS (APPI) Calcd for C₁₆H₂₀, [M]⁺ 212.1560, found 212.1556; Yellow oil (23%, 228.9 mg)

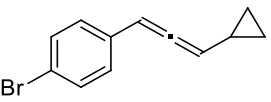
1-bromo-2-(3-cyclopropylpropa-1,2-dien-1-yl)benzene (18e)

¹H-NMR (CDCl₃, 400 MHz) δ : 0.39-0.50 (m, 2H), 0.69-0.82 (m, 2H), 1.31-1.39 (m, 1H), 5.45 (dd, 1H, *J* = 6.8, 6.8 Hz), 6.64 (d, 1H, *J* = 6.8 Hz), 7.00 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.21 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.42 (d, 1H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 6.9, 7.0, 9.3, 95.2, 99.7, 122.4, 127.3, 128.0, 128.2, 132.9, 134.2, 205.9 ; IR (ATR) ν : 3003, 1947, 1473, 1019, 740 cm⁻¹; HRMS (APPI) Calcd for C₁₂H₁₁Br, [M]⁺ 234.0039, found 234.0036; Yellow oil (11%, 108.4 mg)

1-bromo-3-(3-cyclopropylpropa-1,2-dien-1-yl)benzene (18f)

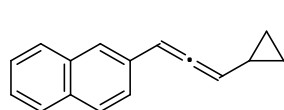
¹H-NMR (CDCl₃, 400 MHz) δ : 0.36-0.49 (m, 2H), 0.70-0.80 (m, 2H), 1.30-1.36 (m, 1H), 5.43 (dd, 1H, *J* = 6.4, 6.4 Hz), 6.10 (d, 1H, *J* = 6.4 Hz), 7.09-7.17 (m, 2H), 7.26 (d, 1H, *J* = 7.6 Hz), 7.41 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ : 7.0, 9.4, 95.1, 100.0, 122.7, 125.2, 129.3, 129.6, 129.9, 137.2, 205.1; IR (ATR) ν : 3080, 3003, 1947, 1588, 1564, 1474, 883, 784, 679 cm⁻¹; HRMS (APPI) Calcd for C₁₂H₁₁Br, [M]⁺ 234.0039, found 234.0036; Yellow oil (20%, 201.2 mg)

1-bromo-4-(3-cyclopropylpropa-1,2-dien-1-yl)benzene (18g)

¹H-NMR (CDCl₃, 400 MHz) δ : 0.38-0.50 (m, 2H), 0.72-0.81 (m, 2H), 1.30-1.39 (m, 1H), 5.43 (dd, 1H, *J* = 6.8, 6.8 Hz), 6.13 (d, 1H, *J* = 6.8 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 7.40 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 7.0, 7.1, 9.3, 95.3, 99.9, 120.3, 128.1, 131.5, 133.9, 204.9; IR (ATR) ν : 3079, 3003, 1946, 1487, 1068, 1009, 828 cm⁻¹; HRMS (APPI) Calcd for C₁₂H₁₂Br, [M+H]⁺ 235.0117, found 235.0111;

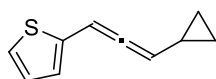
Yellow oil (41%, 823.6 mg)

2-(3-cyclopropylpropa-1,2-dien-1-yl)naphthalene (18i)



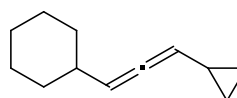
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.45-0.53 (m, 2H), 0.72-0.81 (m, 2H), 1.36-1.43 (m, 1H), 5.51 (dd, 1H, $J = 6.8, 6.8$ Hz), 6.38 (d, 1H, $J = 6.8$ Hz), 7.40-7.50 (m, 3H), 7.65 (s, 1H), 7.75-7.80 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 6.9, 7.1, 9.5, 96.6, 99.7, 124.6, 125.4, 125.5, 126.1, 127.6, 127.7, 128.1, 132.4, 132.6, 133.7, 205.4; IR (ATR) ν : 3054, 3003, 1944, 1629, 1597, 1508, 1248 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{16}\text{H}_{14}$, $[\text{M}]^+ 206.1090$, found 206.1085; Colorless solid (mp: 45-48 $^\circ\text{C}$, 27%, 269 mg)

2-(3-cyclopropylpropa-1,2-dien-1-yl)thiophene (18j)



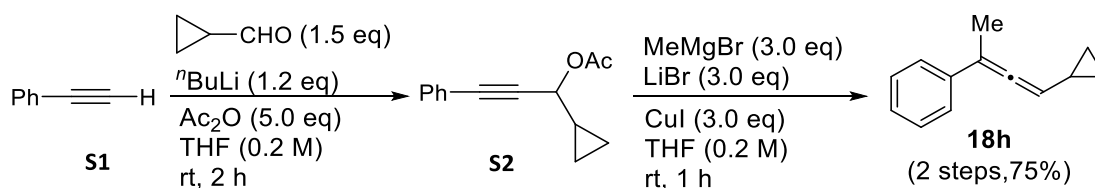
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.43-0.51 (m, 2H), 0.74-0.78 (m, 2H), 1.30-1.38 (m, 1H), 5.47 (dd, 1H, $J = 6.4, 6.4$ Hz), 6.41 (d, 1H, $J = 6.4$ Hz), 6.89 (d, 1H, $J = 3.6$ Hz), 6.94 (dd, 1H, $J = 4.8, 3.6$ Hz), 7.13 (d, 1H, $J = 4.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 6.8, 7.4, 9.5, 90.6, 99.9, 124.2, 124.4, 127.4, 139.5, 204.0; IR (ATR) ν : 3079, 3002, 1653, 1428, 1256 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{10}\text{H}_{10}\text{S}$, $[\text{M}]^+ 162.0498$, found 162.0494; Yellow oil (14%, 143.4 mg)

(3-cyclopropylpropa-1,2-dien-1-yl)cyclohexane (18k)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.27-0.41 (m, 2H), 0.62-0.70 (m, 2H), 1.01-1.11 (m, 2H), 1.13-1.32 (m, 4H), 1.60-1.64 (m, 1H), 1.69-1.76 (m, 4H), 1.89-1.98 (m, 1H), 5.04 (ddd, 1H, $J = 6.4, 6.4, 2.8$ Hz), 5.16 (ddd, 1H, $J = 6.4, 6.4, 1.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 6.4, 6.9, 9.5, 26.0, 26.2, 33.1, 37.4, 95.9, 99.0, 201.8; IR (ATR) ν : 2922, 2850, 1447, 1017, 889 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{12}\text{H}_{19}$, $[\text{M}+\text{H}]^+ 163.1481$, found 163.1479; Colorless oil (23%, 180 mg)

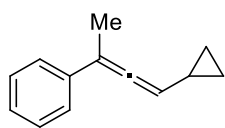
Synthesis of 18h



S1 to S2 : To a THF (23.4 ml) solution of ethynylbenzene (0.51 ml, 4.7 mmol) was added butyllithium (3.6 ml, 1.55 M in THF, 5.6 mmol) at -78 $^\circ\text{C}$ under argon. The resulting solution was allowed to stir for an additional 30 min at same temperature. To this solution was added cyclopropanecarboxaldehyde (0.2 ml, 7.0 mmol) at -78 $^\circ\text{C}$. The mixture was stirred for an additional 30 min, then warmed to 0 $^\circ\text{C}$ over 2 h. After acetic anhydride (2.2 ml, 23.4 mmol) was added, the mixture was allowed to stir for 1 h keeping 0 $^\circ\text{C}$. The reaction was quenched with saturated aqueous ammonium chloride, and the products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue (1.24 g) was used directly in the next step without further purification.

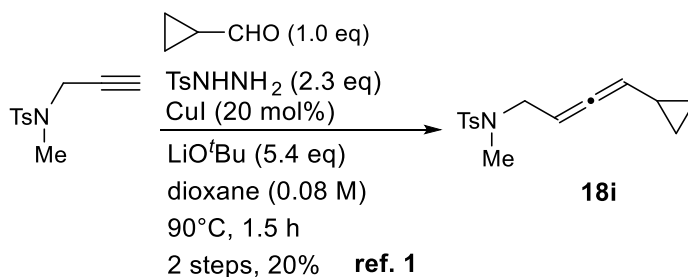
18h was synthesized from **S2** according to the reported procedure².

(4-cyclopropylbuta-2,3-dien-2-yl)benzene (**18h**)

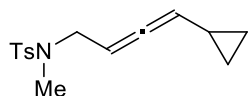


¹H-NMR (CDCl₃, 400 MHz) δ: 0.39-0.43 (m, 2H), 0.69-0.73 (m, 2H), 1.27-1.36 (m, 1H), 2.08 (dd, 3H, *J* = 2.8, 0.8 Hz), 5.29 (dd, 1H, *J* = 6.8, 2.8 Hz), 7.17 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.30 (dd, 2H, *J* = 8.4, 8.4 Hz), 7.39 (dd, 2H, *J* = 8.4, 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 6.9, 6.9, 9.7, 17.3, 97.4, 102.0, 125.6, 126.4, 128.2, 137.5, 203.6; IR (ATR) ν: 3734, 3669, 3081, 3003, 1943, 1597, 1492, 1442, 1370, 1258 cm⁻¹; HRMS (APPI) Calcd for C₁₃H₁₄, [M]⁺ 170.1090, found 170.1088; Yellow oil (597.5 mg)

Synthesis of **18i**

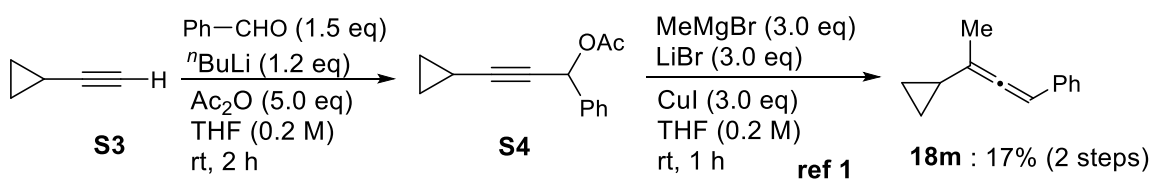


N-(4-cyclopropylbuta-2,3-dien-1-yl)-N,4-dimethylbenzenesulfonamide (**18i**)



¹H-NMR (CDCl₃, 400 MHz) δ: 0.26-0.34 (m, 2H), 0.66-0.73 (m, 2H), 1.14-1.23 (m, 1H), 2.42 (s, 3H), 2.73 (s, 3H), 3.63 (d, 2H, *J* = 6.0 Hz), 5.00-5.06 (m, 2H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.66 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 6.6, 6.7, 9.2, 34.0, 50.0, 88.0, 97.0, 127.3, 129.6, 134.6, 143.3, 204.9; IR (ATR) ν: 3004, 1597, 1451, 1338, 1158, 1089, 1019 cm⁻¹; HRMS (ESI) Calcd for C₁₅H₂₀N₁O₂S, [M+H]⁺ 278.1215, found 278.1220; Colorless oil (20%, 133.4 mg)

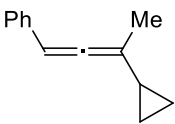
Synthesis of **18m**



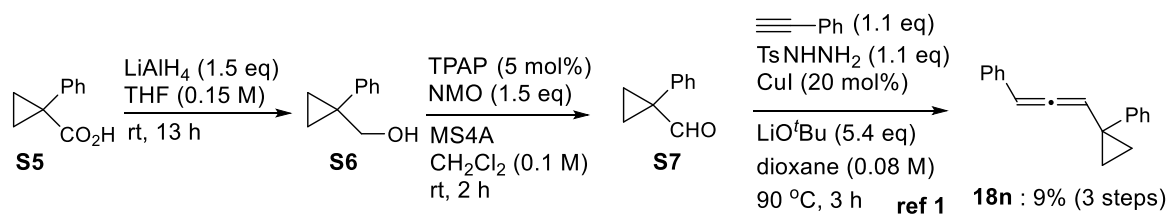
S3 to **S4** : To a THF (23.4 ml) solution of **S1** (4.7 mmol) was added *n*-BuLi (3.6 ml, 1.55 M in THF, 5.6 mmol) at -78 °C under argon. The resulting solution was allowed to stir for an additional 30 min at same temperature. To this solution was added benzaldehyde (7.0 mmol) at -78 °C. The mixture was stirred for an additional 30 min, then warmed to 0 °C over 2 h. After Ac₂O (2.2 mL, 23.4 mmol) was added, the mixture was allowed to be stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous solution of NH₄Cl, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue (1.24 g) was used directly in the next step without further purification.

S4 to 18m : To a stirred suspension of LiBr (1.22 g, 14.1 mmol) and CuI (2.68 g, 14.1 mmol) in THF (10 mL) at 0 °C was slowly added a solution of MeMgBr (4.7 mL, 3.0 M in Et₂O, 14.1 mmol). After the mixture was stirred for 15 min, a solution of **S2** (4.7 mmol) in THF (14 mL) was added. The reaction mixture was allowed to warm to rt over 1 h, and then a saturated solution of NH₄Cl was added and the reaction was extracted with AcOEt. After drying (Na₂SO₄), concentration, and flash column chromatography (*n*-Hexane), cyclopropylallene **18m** was obtained.

(3-cyclopropylbuta-1,2-dien-1-yl)benzene (**18m**)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 0.45-0.50 (m, 2H), 0.64-0.72 (m, 2H), 1.24-1.30 (m, 1H), 1.84 (dd, 3H, *J* = 2.4, 2.4 Hz), 6.09 (brs, 1H), 7.14-7.18 (m, 1H), 7.22-7.30 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 5.96, 6.48, 13.7, 18.0, 95.1, 106.6, 126.5, 126.5, 128.5, 135.7, 202.1; IR (ATR) ν: 3730, 3665, 3077, 3000, 1946, 1590, 14929 14438 1373, 1250 cm⁻¹; HRMS (APPI) Calcd for C₁₃H₁₄, [M]⁺ 170.1090, found 170.1088: Yellow oil (2 steps 17%, 450 mg)

Synthesis of **18n**



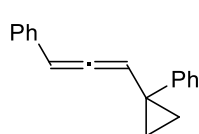
S5 to S6 : To a solution of LiAlH₄ (421 mg, 11.1 mmol) in THF (30 mL) at 0 °C was added slowly **S5** (1.22 g, 7.4 mmol) in THF (20 mL). The reaction was then stirred at room temperature for 13 h. To the reaction mixture was then added H₂O, 15% aqueous solution of NaOH, and water while stirring. The mixture was stirred for 20 min at room temperature, filtered and concentrated to give the crude **S6**, which was used for the next step without purification.

S6 to S7 : To a solution of **S6** and NMO (1.2 mL, 11.3 mmol) in CH₂Cl₂ (75 mL) was added ground molecular sieves (3.0 g, 4 Å). The mixture was stirred for 10 min at room temperature under argon atmosphere before TPAP (134 mg, 0.38 mmol) was added. After stirring for an additional 2 h, the solution was filtered through celite. The solvent was then carefully evaporated and the remaining oil was used for the next step without purification.

S7 to 18n : To a 1,4-dioxane (8.0 mL) solution of TsNHNH₂ (622.8 mg, 3.34 mmol) was added **S7** (444.4 mg, 3.04 mmol) at 60 °C under argon. The resulting solution was allowed to stir for an additional 1 h at same temperature. To this solution was added 1,4-dioxane (30.0 mL), CuI (115.8 mg, 0.61 mmol), phenylacetylene (0.37 mL, 3.34 mmol), LiO^tBu (1.31 g, 16.4 mmol) at 90 °C. The mixture was stirred for an additional 3 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature and was filtered through a short silica gel column eluting with AcOEt. The solvent was removed in vacuum to leave a crude mixture, which was purified by column

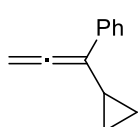
chromatography on silica gel (eluting with *n*-Hexane) to afford pure **18n** as a colorless oil (3 steps 9%, 63.3 mg)

(3-(1-phenylcyclopropyl)propa-1,2-dien-1-yl)benzene (18n)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.07-1.17 (m, 4H), 5.89 (d, 1H, *J* = 6.4 Hz), 6.19 (d, 1H, *J* = 6.4 Hz), 7.08-7.38 (m, 10H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 15.9, 15.9, 24.3, 97.2, 102.7, 126.2, 126.6, 126.9, 128.0, 128.2, 128.5, 134.5, 144.1, 204.3; IR (ATR) v: 3027, 1948, 1598, 1493, 1025, 756, 690 cm⁻¹; HRMS (ESI) Calcd for C₁₈H₁₆Na, [M+Na]⁺ 255.1150, found 255.1151; Colorless oil (3 steps 9%, 63.3 mg)

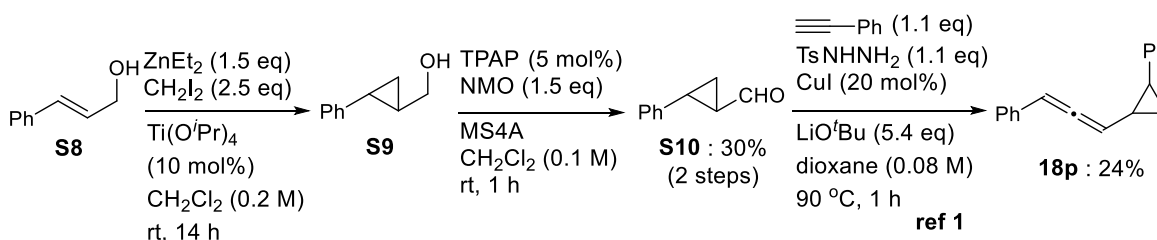
(1-cyclopropylpropa-1,2-dien-1-yl)benzene (18o)



(CAS-Reg# 85914-04-1)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.52–0.58 (m, 2H), 0.84–0.91 (m, 2H), 1.60–1.53 (m, 1H), 5.09 (d, *J* = 2.9 Hz, 2H), 7.18–7.24 (m, 1H), 7.31–7.37 (m, 2H), 7.54–7.60 (m, 2H),

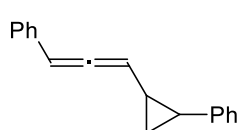
Synthesis of 18p



S8 to S9: To a solution of ZnEt₂ (15 mL, 1.06 M in *n*-Hexane, 15.9 mmol) in 53 mL dry CH₂Cl₂ at -10 °C was added dropwise CH₂I₂ (2.1 mL, 26.5 mmol). The resulting solution was stirred at that temperature for 15 min and a white precipitate was formed. Then the alcohol **S6** (1.4 mL, 10.6 mmol) and Ti(O*i*-Pr)₄ (0.32 mL, 1.06 mmol) were added successively. The reaction mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched with saturated aqueous solution of NH₄Cl and extracted with Et₂O. The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated. The crude product was used for the next step without purification.

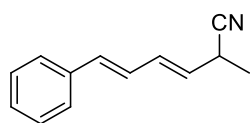
S9 to S10 : Same as **S6 to S7** // **S10 to 18p :** Same as **S7 to 18n**

(3-(2-phenylcyclopropyl)propa-1,2-dien-1-yl)benzene (18p)



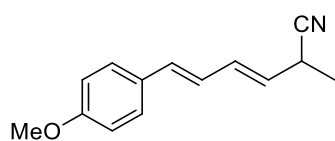
¹H-NMR (CDCl₃, 400 MHz) δ: 1.12-1.26 (m, 2H), 1.54-1.67 (m, 1H), 1.96-2.02 (m, 1H), 5.61-5.67 (m, 1H), 6.25-6.27 (m, 1H), 7.07-7.33 (m, 10H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.9, 17.0, 21.1, 21.5, 25.8, 25.9, 96.8, 98.2, 125.7, 125.9, 126.7, 127.0, 128.4, 128.6, 134.7, 142.2, 205.0, 205.2; IR (ATR) v: 3028, 1944, 1603, 1495, 1457, 1028, 876, 746, 690 cm⁻¹; HRMS (ESI) Calcd for C₁₈H₁₆Na, [M+Na]⁺ 255.1150, found 255.1151; Colorless oil (24%, 58.8 mg)

(3E,5E)-2-methyl-6-phenylhexa-3,5-dienitrile (20a)



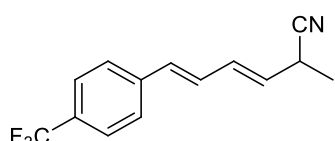
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.46 (d, 3H, $J = 6.8$ Hz), 3.44 (qd, 1H, $J = 6.8, 6.0$ Hz), 5.67 (dd, 1H, $J = 10.4, 6.4$ Hz), 6.52 (dd, 1H, $J = 15.2, 10.4$ Hz), 6.60 (d, 1H, $J = 15.6$ Hz), 6.74 (dd, 1H, $J = 15.6, 10.4$ Hz), 7.23-7.27 (m, 1H), 7.33 (dd, 2H, $J = 7.2, 7.2$ Hz), 7.40 (d, 2H, $J = 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.0, 28.1, 120.8, 126.5, 126.9, 127.6, 127.9, 128.6, 132.8, 134.1, 136.7; IR (ATR) ν : 3025, 2984, 2937, 2240, 2216, 985, 747, 691 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{13}\text{H}_{13}\text{N}$, $[\text{M}+\text{H}]^+$ 184.1121, found 184.1115; Colorless oil (72%, 28.4 mg)

(3E,5E)-6-(4-methoxyphenyl)-2-methylhexa-3,5-dienitrile (20b)



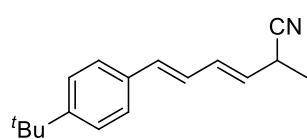
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.45 (d, 3H, $J = 6.8$ Hz), 3.43 (dq, 1H, $J = 6.8, 6.0$ Hz), 3.82 (s, 3H), 5.61 (dd, 1H, $J = 14.8, 6.0$ Hz), 6.48 (dd, 1H, $J = 15.2, 9.6$ Hz), 6.54 (d, 1H, $J = 15.2$ Hz), 6.61 (dd, 1H, $J = 15.2, 9.6$ Hz), 6.86 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.0, 28.1, 55.3, 114.1, 120.9, 124.9, 126.4, 127.7, 129.5, 133.0, 133.6, 159.5; IR (ATR) ν : 2935, 2240, 1603, 1509, 1247, 1174, 1030, 984, 831 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{14}\text{H}_{15}\text{ON}$, $[\text{M}]^+$ 213.1148, found 213.1141; Colorless solid (mp: 52-55 $^\circ\text{C}$; 49%, 17.6 mg)

(3E,5E)-2-methyl-6-(4-(trifluoromethyl)phenyl)hexa-3,5-dienitrile (20c)



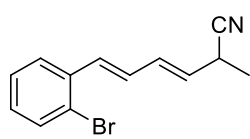
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.47 (d, 3H, $J = 6.8$ Hz), 3.43-3.50 (m, 1H), 5.74 (dd, 1H, $J = 15.6, 6.4$ Hz), 6.51-6.58 (m, 1H), 6.62 (d, 1H, $J = 15.6$ Hz), 6.81 (dd, 1H, $J = 15.6, 10.4$ Hz), 7.48 (d, 2H, $J = 8.4$ Hz), 7.57 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 120.6, 125.6, 125.6, 126.6, 129.3, 129.4, 132.2, 132.4, 140.1; IR (ATR) ν : 2989, 2243, 1613, 1415, 1321, 1163, 1118, 1106, 1065, 985, 839 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{14}\text{H}_{12}\text{NF}_3$, $[\text{M}]^+$ 251.0916, found 251.0908; Yellow oil (65%, 49.0 mg)

(3E,5E)-6-(4-(tert-butyl)phenyl)-2-methylhexa-3,5-dienitrile (20d)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.31 (s, 9H), 1.44 (d, 3H, $J = 7.2$ Hz), 3.38-3.45 (m, 1H), 5.62 (dd, 1H, $J = 15.2, 6.4$ Hz), 6.49 (dd, 1H, $J = 15.2, 10.4$ Hz), 6.57 (d, 1H, $J = 15.2$ Hz), 6.70 (dd, 1H, $J = 15.2, 10.4$ Hz), 7.28-7.38 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 31.2, 34.6, 120.8, 125.6, 126.1, 126.2, 127.1, 132.9, 133.9, 151.1; IR (ATR) ν : 2961, 2242, 1459, 1363, 1269, 985, 835, 732 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{17}\text{H}_{21}\text{N}$, $[\text{M}]^+$ 239.1669, found 239.1660; Yellow oil (74%, 41.7 mg)

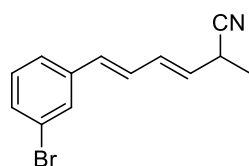
(3E,5E)-6-(2-bromophenyl)-2-methylhexa-3,5-dienitrile (20e)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.47-1.48 (d, 3H, $J = 7.6$ Hz), 3.45 (dq, 1H, $J = 7.6, 6.0$ Hz), 5.72 (dd, 1H, $J = 15.2, 6.0$ Hz), 6.58 (dd, 1H, $J = 15.2, 10.4$ Hz), 6.69 (dd, 1H, $J = 10.4, 15.2$ Hz), 6.96 (d, 1H, $J = 15.2$ Hz), 7.10 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.22-7.29 (m, 1H), 7.55 (dd, 2H, $J = 7.2, 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.8, 28.1, 120.7, 124.0, 126.5, 127.5, 128.9, 129.1, 129.5, 132.6, 132.6, 133.1, 136.4; IR (ATR)

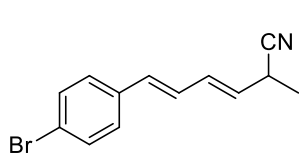
v: 2934, 2242, 1465, 1437, 984, 747 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{13}\text{H}_{12}\text{NBr}$, $[\text{M}]^+$ 261.0148, found 261.0138; Colorless oil (60%, 25.0 mg)

(3E,5E)-6-(3-bromophenyl)-2-methylhexa-3,5-dienitrile (20f)



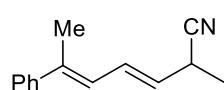
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.45 (d, 3H, $J = 7.2$ Hz), 3.44 (dq, 1H, $J = 7.2$, 6.4 Hz), 5.69 (dd, 1H, $J = 16.0$, 6.4 Hz), 6.46-6.54 (m, 2H), 6.72 (dd, 1H, $J = 16.0$, 10.8 Hz), 7.18 (dd, 1H, $J = 7.6$, 7.6 Hz), 7.29 (d, 1H, $J = 7.6$ Hz), 7.35-7.38 (m, 1H), 7.54 (dd, 1H, $J = 1.6$, 1.6 Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 120.6, 122.8, 125.1, 128.3, 128.8, 129.1, 130.1, 130.7, 132.3, 132.3, 138.8; IR (ATR) v: 2985, 2243, 1588, 1471, 984, 731 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{13}\text{H}_{12}\text{NBr}$, $[\text{M}]^+$ 261.0148, found 261.0142; Colorless oil (67%, 33.6 mg)

(3E,5E)-6-(4-bromophenyl)-2-methylhexa-3,5-dienitrile (20g)



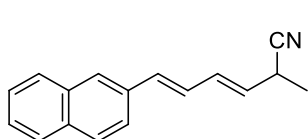
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.45 (d, 3H, $J = 6.8$ Hz), 3.43 (dq, 1H, $J = 6.8$, 6.4 Hz), 5.68 (dd, 1H, $J = 15.2$, 6.4 Hz), 6.46-6.55 (m, 2H), 6.71 (dd, 1H, $J = 15.2$, 10.8 Hz), 7.24 (d, 2H, $J = 8.4$ Hz), 7.43 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 120.6, 121.7, 127.6, 127.9, 128.3, 131.7, 132.4, 132.7, 135.6; IR (ATR) v: 2986, 2241, 1486, 1071, 984, 827, 731 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{13}\text{H}_{12}\text{NBr}$, $[\text{M}+\text{H}]^+$ 261.0148, found 261.0140; Colorless solid (mp: 35-39 $^{\circ}\text{C}$, 68%, 61.8 mg)

(3E,5E)-2-methyl-6-phenylhepta-3,5-dienitrile (20h)



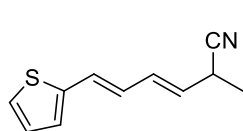
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.42 (d, 3H, $J = 7.2$ Hz), 2.17 (s, 3H, $J = 7.2$, 6.4 Hz), 3.41 (qd, 1H, $J = 7.2$, 6.4 Hz), 5.61 (dd, 1H, $J = 14.8$, 6.4 Hz), 6.38 (d, 1H, $J = 11.2$ Hz), 6.73 (ddd, 1H, $J = 14.8$, 11.2, 1.6 Hz), 7.29-7.34 (m, 3H), 7.42 (d, 2H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 16.1, 19.0, 28.2, 120.9, 124.9, 125.6, 127.3, 127.8, 128.2, 129.1, 138.1, 142.5; IR (ATR) v: 3065, 2985, 2937, 2237, 1467, 1437, 1024, 963 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{14}\text{H}_{16}\text{N}$, $[\text{M}+\text{H}]^+$ 198.1277, found 198.1273; Colorless oil (97%, 104.0 mg)

(3E,5E)-2-methyl-6-(naphthalen-2-yl)hexa-3,5-dienitrile (20i)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.46 (d, 3H, $J = 7.2$ Hz), 3.42-3.48 (m, 1H), 5.69 (dd, 1H, $J = 15.2$, 6.4 Hz), 6.56 (dd, 1H, $J = 15.2$, 9.6 Hz), 6.75 (d, 1H, $J = 15.2$, 9.6 Hz), 7.42-7.49 (m, 2H), 7.59 (dd, 1H, $J = 8.4$, 1.6 Hz), 7.74 (s, 1H), 7.77-7.83 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.0, 28.2, 120.8, 123.3, 126.1, 126.4, 126.8, 127.2, 127.7, 127.8, 128.0, 128.3, 132.8, 133.1, 133.5, 134.2; IR (ATR) v: 2996, 2239, 2215, 1507, 1454 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{17}\text{H}_{15}\text{N}$, $[\text{M}]^+$ 233.1199, found 233.1190; Colorless solid (mp: 117-122 $^{\circ}\text{C}$, 76%, 51.1 mg)

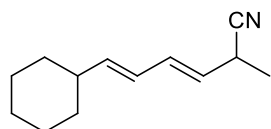
(3E,5E)-2-methyl-6-(thiophen-2-yl)hexa-3,5-dienitrile (20j)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.45 (d, 3H, $J = 6.8$ Hz), 3.40-3.46 (m, 1H), 5.63 (dd, 1H, $J = 15.2$, 6.0 Hz), 6.45 (dd, 1H, $J = 15.2$, 10.4 Hz), 6.73 (d, 1H, $J = 15.2$ Hz), 6.97-7.00 (m, 2H), 7.18 (d, 1H, $J = 5.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 120.7, 124.9, 126.5, 126.8, 127.4, 127.6, 129.7, 132.2, 142.0; IR (ATR)

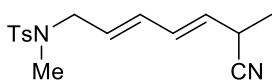
v: 3022, 2984, 2936, 2241, 1593, 1452, 1210 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{11}\text{H}_{11}\text{NS}$, $[\text{M}]^+$ 189.0607, found 189.0601; Yellow oil (50%, 38.1 mg)

(3E,5E)-6-cyclohexyl-2-methylhexa-3,5-dienitrile (20k)



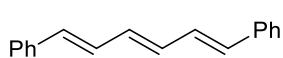
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.04-1.33 (m, 6H), 1.40 (d, 3H, $J = 7.2$ Hz), 1.68-1.75 (m, 4H), 1.96-2.05 (m, 1H), 3.31-3.39 (m, 1H), 5.43 (dd, 1H, $J = 15.6$, 6.4 Hz), 5.72 (dd, 1H, $J = 15.6$, 6.4 Hz), 5.94 (dd, 1H, $J = 15.2$, 10.8 Hz), 6.29 (ddd, 1H, $J = 15.2$, 10.4, 0.8 Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.0, 25.9, 26.2, 28.0, 32.7, 40.7, 120.9, 125.1, 126.0, 133.3, 142.7; IR (ATR) v: 2923, 2850, 2241, 1655, 1448, 986 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{13}\text{H}_{20}\text{N}$, $[\text{M}+\text{H}]^+$ 190.1590, found 190.1584; Colorless oil (52%, 73.4 mg)

N-((2E,4E)-6-cyanohepta-2,4-dien-1-yl)-N,4-dimethylbenzenesulfonamide (20l)



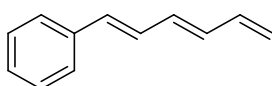
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.41 (d, 3H, $J = 7.2$ Hz), 2.44 (s, 3H), 2.67 (s, 3H), 3.34-3.42 (m, 1H), 3.67 (d, 2H, $J = 6.0$ Hz), 5.51-5.64 (m, 2H), 6.13 (dd, 1H, $J = 15.2$, 6.4 Hz), 6.31 (dd, 1H, $J = 15.2$, 6.4 Hz), 7.32 (d, 2H, $J = 8.0$ Hz), 7.67 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.7, 21.5, 27.9, 34.4, 51.9, 120.6, 127.4, 128.3, 129.0, 129.7, 131.3, 132.1, 134.3, 143.5; IR (ATR) v: 2934, 1598, 1452, 1335, 1157, 1089 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 327.1143, found 327.1154; Yellow oil (50%, 21.7 mg)

(1E,3E,5E)-1,6-diphenylhexa-1,3,5-triene (21p)



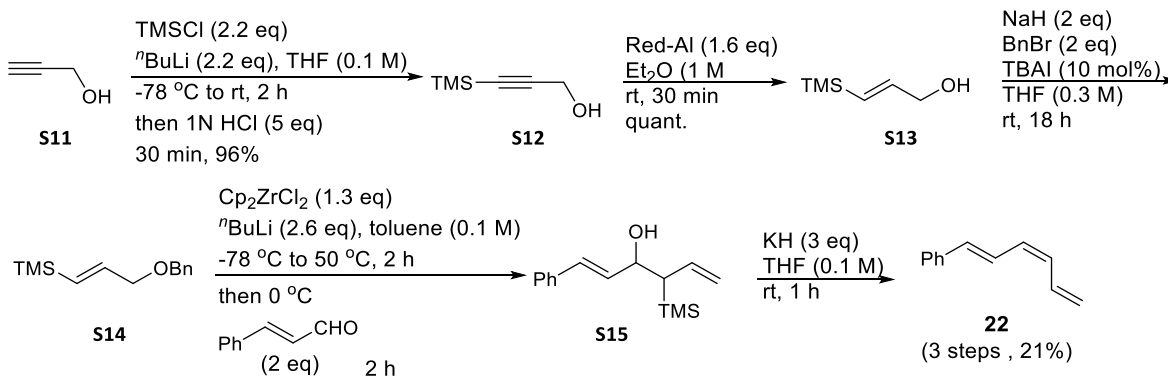
(CAS-Reg# 17329-15-6)
 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 6.52 (ddd, $J = 3.0$, 10.1, 15.1 Hz, 2H), 6.60 (d, $J = 15.6$ Hz, 2H), 6.87 (ddd, $J = 3.2$, 10.0, 15.1 Hz, 2H), 7.22 (t, $J = 7.3$ Hz, 2H), 7.32 (d, $J = 7.6$ Hz, 4H), 7.42 (d, $J = 7.3$ Hz, 4H)

(1E,3E)-hexa-1,3,5-trien-1-ylbenzene (21a) (CAS-Reg# 35008-84-5)



(10%, 3.3 mg)
 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 5.14 (d, 1H, $J = 9.6$ Hz), 5.27 (d, 1H, $J = 17.9$ Hz), 6.31-6.51 (m, 3 H), 6.58 (d, 1H, $J = 15.5$ Hz), 6.82 (dd, 1H, $J = 9.4$, 15.5 Hz), 7.20-7.45 (m, 5 H),

Synthesis of 5b



S11 to S122: To a solution of **S11** (0.62 mL, 10.5 mmol) in THF (80.8 mL) was added ⁿBuLi (14.2 mL of a 1.63 M solution in hexanes, 23.2 mmol) through a syringe at -78 °C (dry ice/MeOH bath). After addition was complete, the solution was allowed to warm to room temperature. After 1.5 h at the room temperature, the mixture was allowed to cool to -78 °C (dry ice/MeOH bath) and TMSCl (3.0 mL, 23.7 mmol) was added dropwise through a syringe. The solution was allowed to slowly warm to room temperature over 12 h, and the reaction was quenched by the addition of an aqueous solution of 1N HCl and diluted with Et₂O. The layers were separated and the aqueous layer was washed with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over Na₂SO₄, and the solvent was evaporated. The crude product was used for the next step without purification.

S12 to S13: To a solution of **S12** in Et₂O (10.1 mL) was slowly added Red-Al (4.5 mL of a 3.6 M solution in toluene, 16.2 mmol) at 0 °C (ice bath). The mixture was allowed to warm to room temperature over 2 h and then quenched by the addition of 2M HCl at 0 °C. The resulting solution was diluted with Et₂O. The layers were separated and the aqueous layer was washed with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over Na₂SO₄, filtered and concentrated in vacuo to afford desired product **S13** without purification as a pale yellow oil

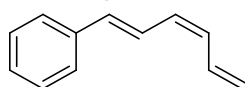
S13 to S14: To a solution of **S13** (1.69 g, 13 mmol) in THF (43 mL) was added NaH (1.04 g, 26 mmol, 60 % suspension in mineral oil) at 0 °C. After the evolution of gas, BnBr (3.1 mL, 26 mmol) and TBAI (480 mg, 1.3 mmol) were added and the solution was stirred for another 4 h at room temperature. The solution was dissolved in Et₂O (50 mL), water was added and the aqueous phase was extracted with Et₂O. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1).

S14 to S15: To a suspension of CP₂ZrCl₂ (730.8 mg, 2.50 mmol) in toluene (8 mL) was added a solution of n-butyllithium (1.63 M in hexane, 3.1 mL, 5.0 mmol) at -78 °C and the mixture was stirred at the same temperature for 1 h. A solution of **IV** (364.5 mg, 1.92 mmol) in toluene (12 mL) was added to the reaction mixture at -78 °C and the temperature was gradually raised to 50 °C. After being stirred at 50 °C for 2 h, a solution of cinnamaldehyde (0.48 mL, 3.84 mmol) was added at 0 °C and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous ammonium chloride, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue (957.3 mg) was used directly in the next step without further purification.

S15 to 22: To a solution of KH (1.56 g, 11.64 mmol) in THF (20 mL) was added **S15** in THF (20 mL) at 0 °C, and the solution was allowed to warm to room temperature over 1 h. The reaction was quenched with saturated aqueous NH₄Cl and extracted with Et₂O. The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was purified by column chromatography on silica gel (eluting with hexane) to afford pure **22** as a colorless solid (54.0 mg, 21%)

(1*E*,3*Z*)-hexa-1,3,5-trien-1-ylbenzene (**22**)

(CAS-Reg# 3864-19-5)

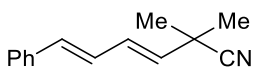


¹H-NMR (CDCl₃, 400 MHz) δ: 5.20 (d, 1H, *J* = 10.0 Hz), 5.28 (d, 1H, *J* = 17.2 Hz), 6.08 (dd, 1H, *J* = 10.8, 10.8 Hz), 6.18 (dd, 1H, *J* = 10.8, 10.8 Hz), 6.57 (d, 1H, *J* = 15.6 Hz), 6.93 (ddd, 1H, *J* = 17.2, 10.8, 10.8 Hz), 7.21-7.28 (m, 2H), 7.33 (dd, 2H, *J* = 8.0, 8.0 Hz), 7.42 (d, 2H, *J* = 8.0 Hz)

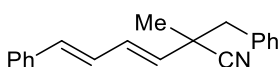
Synthesis of 22: To a THF (0.98 ml) solution of **20a** (39.1 mg, 0.21 mmol) was added LHMDs (0.24 ml, 1.0 M in THF, 0.24 mmol) at -78 °C under argon. The resulting solution was allowed to stir for an additional 30 min at same temperature. To this solution was added **MeI (0.13 ml, 2.13 mmol)** at -78 °C. The mixture was warmed to room temperature and stirred for a 1 h. The reaction was quenched with saturated aqueous ammonium chloride, and the products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (*n*-Hexane/AcOEt = 10/1) to afford **22b** as a colorless solid (82%, 34.6 mg).

22c-f were also synthesized by the same procedure using BnBr (for **22c**) or Allyl bromide (for **22d**) or MVK (for **22e**) or Methyl acrylate (for **22f**) instead of MeI.

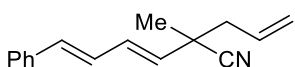
(3E,5E)-2,2-dimethyl-6-phenylhexa-3,5-dienitrile (22b)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 1.50 (s, 6H), 5.63 (d, 1H, *J* = 15.2 Hz), 6.55 (dd, 1H, *J* = 15.2, 10.4 Hz), 6.65 (d, 1H, *J* = 15.6 Hz), 6.73 (dd, 1H, *J* = 15.6, 10.4 Hz), 7.23-7.24 (m, 1H), 7.33 (dd, 2H, *J* = 7.2, 7.2 Hz), 7.39 (d, 2H, *J* = 7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 27.5, 34.6, 123.3, 126.4, 127.0, 127.8, 128.6, 130.2, 133.9, 133.9, 136.7; IR (ATR) ν: 2983, 2236, 1712, 1448, 1362, 1220 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₅NNa, [M+Na]⁺ 220.1102, found 220.1100; Colorless solid (mp : 69-72 °C, 82%, 34.6 mg)

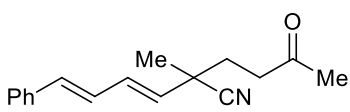
(3E,5E)-2-benzyl-2-methyl-6-phenylhexa-3,5-dienitrile (22c)

 (Benzyl bromide was used instead of MeI) ¹H-NMR (CDCl₃, 400 MHz) δ: 1.47 (s, 3H), 2.93 (d, 2H, *J* = 6.8 Hz), 5.59 (d, 1H, *J* = 15.2 Hz), 6.47 (dd, 1H, *J* = 15.2, 10.8 Hz), 6.56 (d, 1H, *J* = 15.6 Hz), 6.72 (dd, 1H, *J* = 15.6, 10.8 Hz), 7.24-7.40 (m, 10H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 25.4, 40.7, 46.5, 122.2, 126.5, 127.0, 127.4, 127.9, 128.3, 128.6, 130.4, 131.5, 132.4, 134.1, 134.8, 136.7; IR (ATR) ν: 3029, 1711, 1496, 1450, 1361, 1229 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₁₉N₁Na, [M+Na]⁺ 296.1415, found 296.1423; Colorless solid (46%, 17.5 mg)

(3E,5E)-2-allyl-2-methyl-6-phenylhexa-3,5-dienitrile (22d)

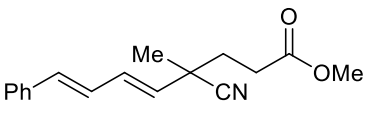
 (Allyl bromide was used instead of MeI) ¹H-NMR (CDCl₃, 400 MHz) δ: 1.47 (s, 3H), 2.40 (d, 2H, *J* = 7.6 Hz), 5.19-5.24 (m, 2H), 5.56 (d, 1H, *J* = 15.2 Hz), 5.77-5.87 (m, 1H), 6.56 (dd, 1H, *J* = 15.2, 10.0 Hz), 6.65 (d, 1H, *J* = 15.6 Hz), 6.73 (dd, 1H, *J* = 15.6, 10.0 Hz), 7.23-7.26 (m, 1H), 7.32 (dd, 2H, *J* = 7.6, 7.6 Hz), 7.39 (d, 2H, *J* = 7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 25.5, 39.6, 44.8, 120.3, 122.3, 126.6, 127.1, 128.0, 128.8, 131.5, 131.8, 132.6, 134.2, 136.9; IR (ATR) ν: 3025, 2980, 2932, 2235, 1641, 1490, 1448 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₁₇NNa, [M+Na]⁺ 246.1259, found 246.1251; Colorless oil (70%, 22.1 mg)

(3E,5E)-2-methyl-2-(3-oxobutyl)-6-phenylhexa-3,5-dienitrile (22e)

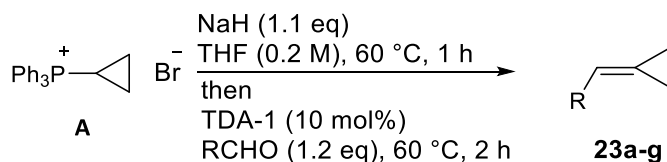
 (Methyl vinyl ketone was used instead of MeI) ¹H-NMR (CDCl₃, 400 MHz) δ: 1.50 (s, 3H), 1.87-2.04 (m, 2H), 2.16 (s, 3H), 2.52-2.70 (m, 2H), 5.43 (d, 1H, *J* = 15.2 Hz), 6.58 (dd, 1H, *J* = 15.2, 9.6 Hz), 6.62 (d,

1H, $J = 15.2$ Hz), 6.72 (dd, 1H, $J = 15.2, 9.6$ Hz), 7.23-7.27 (m, 1H), 7.33 (dd, 2H, $J = 8.0, 8.0$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz); ^{13}C -NMR (CDCl₃, 100 MHz) δ : 26.6, 30.1, 33.7, 39.4, 121.9, 126.4, 126.6, 128.0, 128.6, 131.7, 132.1, 134.3, 136.6, 206.8; IR (ATR) ν : 3025, 2932, 2236, 1714, 1448, 1364, 1172 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₁₉NNaO, [M+Na]⁺ 276.1364, found 276.1367; Colorless oil (40%, 29.5 mg)

(5E,7E)-methyl 4-cyano-4-methyl-8-phenylocta-5,7-dienoate (22f)

 (Methyl acrylate was used instead of MeI) ^1H -NMR (CDCl₃, 400 MHz) δ : 1.25 (s, 3H), 1.90-2.13 (m, 2H), 2.43-2.53 (m, 2H), 3.67 (s, 3H), 5.45 (d, 1H, $J = 14.4$ Hz), 6.57 (dd, 1H, $J = 14.4, 10.0$ Hz), 6.63 (d, 1H, $J = 14.8$ Hz), 6.72 (dd, 1H, $J = 14.8, 10.0$ Hz), 7.25-7.27 (m, 1H), 7.33 (dd, 2H, $J = 7.2$ Hz), 7.39 (d, 2H, $J = 7.2$ Hz); ^{13}C -NMR (CDCl₃, 100 MHz) δ : 26.5, 30.2, 35.1, 39.5, 51.9, 121.6, 126.5, 126.6, 128.0, 128.7, 131.6, 132.0, 134.4, 136.6, 172.8; IR (ATR) ν : 3410, 2927, 1735, 1437, 1362, 1200 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₁₉NNaO₂, [M+Na]⁺ 292.1314, found 292.1314; (28%, 10.9 mg)

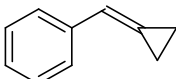
Synthesis of 23a-g



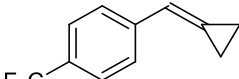
23a-g were synthesized from **I** according to the reported procedure³.

A suspension of NaH (626 mg, 13.1 mmol, 50% oil dispersion) and **A** (5.0 g, 13.1 mmol) in 50 ml THF was heated at 62 °C for 1 h. Benzaldehyde (1.0 ml, 10.0 mmol) and TDA-1 (0.32 ml, 1.0 mmol) was then added to the heated yellow suspension. The resulting mixture was stirred at 62 °C for 3 h. The reaction mixture was cooled to room temperature, and was filtered through a short silica gel column eluting with AcOEt. The solvent was removed in vacuum to leave a crude mixture, which was purified by column chromatography on silica gel (eluting with hexane) to afford pure **xxa** as a colorless oil (755 mg, 58%)

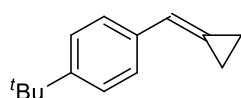
(cyclopropylidenemethyl)benzene (23a) (CAS-Reg# 7555-67-1)

 ^1H -NMR (CDCl₃, 400 MHz) δ : 1.17 (t, 2H, $J = 8.0$ Hz), 1.42 (t, 2H, $J = 8.0$ Hz), 6.75 (s, 1H), 7.20 (t, 1H, $J = 7.6$ Hz), 7.32 (dd, 2H, $J = 7.6, 7.6$ Hz), 7.52 (d, 2H, $J = 7.6$ Hz); (58%, 755.0 mg)

1-(cyclopropylidenemethyl)-4-(trifluoromethyl)benzene (23b)

 (CAS-Reg# 243449-23-2) ^1H -NMR (CDCl₃, 400 MHz) δ : 1.20-1.30 (m, 4H), 6.79 (s, 1H), 7.57 (d, 2H, $J = 8.4$ Hz), 7.60 (d, 2H, $J = 8.4$ Hz); (33%, 660 mg)

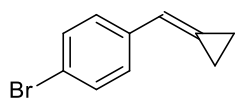
1-(tert-butyl)-4-(cyclopropylidenemethyl)benzene (23c) (CAS-Reg# 918831-65-9)



(75%, 1.49 g)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.16 (t, 2H, $J = 8.0$ Hz), 1.32 (s, 9H), 1.40 (t, 2H, $J = 8.0$ Hz), 6.73 (s, 1H), 7.34 (d, 2H, $J = 8.0$ Hz), 7.46 (d, 2H, $J = 8.0$ Hz)

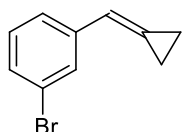
1-bromo-4-(cyclopropylidenemethyl)benzene (23d)



(CAS-Reg# 179251-27-5)

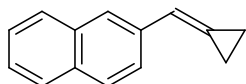
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.18 (t, 2H, $J = 7.6$ Hz), 1.40 (t, 2H, $J = 7.6$ Hz), 6.69 (s, 1H), 7.40 (d, 2H, $J = 8.8$ Hz), 7.43 (d, 2H, $J = 8.8$ Hz); (84%, 1.68 g)

1-bromo-3-(cyclopropylidenemethyl)benzene (23e) (CAS-Reg# 888505-25-7)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.19 (t, 2H, $J = 8.0$ Hz), 1.44 (t, 2H, $J = 8.0$ Hz), 6.67 (s, 1H), 7.18 (dd, 1H, $J = 7.6, 7.6$ Hz), 7.31 (d, 1H, $J = 7.6$ Hz), 7.41 (d, 1H, $J = 7.6$ Hz), 7.67 (s, 1H); (25%, 42.8 mg)

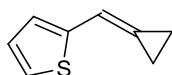
2-(cyclopropylidenemethyl)naphthalene (23f)



(CAS-Reg# 68854-50-2)

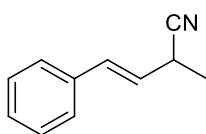
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.23 (t, 2H, $J = 7.6$ Hz), 1.52 (t, 2H, $J = 7.6$ Hz), 6.92 (s, 1H), 7.40-7.47 (m, 2H), 7.77-7.85 (m, 5H); (41%, 325.8 mg)

2-(cyclopropylidenemethyl)thiophene (23g)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.29-1.33 (m, 4H), 6.94 (dd, 1H, $J = 1.6, 1.6$ Hz), 6.98-7.00 (m, 2H), 7.15 (d, 1H, $J = 4.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 2.9, 4.4, 112.7, 123.9, 124.1, 124.4, 127.2, 144.1; IR (ATR) ν : 3069, 3046, 2975, 1786, 1660, 1523, 1411, 1215, 1040 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_8\text{H}_9\text{S}$, $[\text{M}+\text{H}]^+$ 137.0419, found 137.0418; Yellow oil (48%, 964.3 mg)

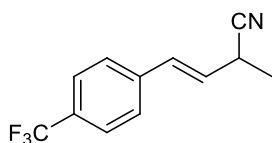
(E)-2-methyl-4-phenylbut-3-enitrile (24a)



(CAS-Reg# 112528-98-0)

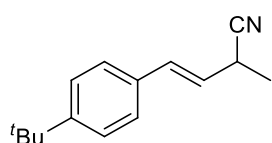
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.51 (d, 3H, $J = 6.8$ Hz), 3.51 (td, 1H, $J = 6.8, 6.0$ Hz), 6.06 (dd, 1H, $J = 15.6, 6.0$ Hz), 6.70 (d, 1H, $J = 15.6$ Hz), 7.26-7.39 (m, 5H); (63%, 28.4 mg)

(E)-2-methyl-4-(4-(trifluoromethyl)phenyl)but-3-enitrile (24b)



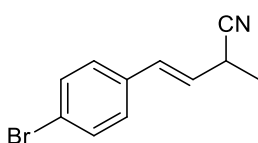
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.53 (d, 3H, $J = 7.2$ Hz), 3.54 (qd, $J = 7.2, 5.6$ Hz), 6.16 (dd, 1H, $J = 16.0, 5.6$ Hz), 6.75 (d, 1H, $J = 16.0$ Hz), 7.47 (d, 2H, $J = 8.0$ Hz), 7.59 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.8, 28.3, 120.4, 125.6, 125.6, 126.7, 126.9, 131.1, 139.1; IR (ATR) ν : 2991, 2245, 1617, 1416, 1263, 1164, 1119, 1107, 1065, 1016 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{12}\text{H}_{10}\text{NF}_3$, $[\text{M}]^+$ 225.0760, found 225.0755; Colorless oil (79%, 47.3 mg)

(E)-4-(4-(tert-butyl)phenyl)-2-methylbut-3-enitrile (24c)



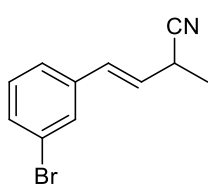
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.32 (s, 9H), 1.49 (d, 3H, $J = 7.2$ Hz), 3.49 (qd, 1H, $J = 7.2, 6.4$ Hz), 6.02 (dd, 1H, $J = 16.0, 6.4$ Hz), 6.67 (d, 1H, $J = 16.0$ Hz), 7.30 (d, 2H, $J = 8.0$ Hz), 7.35 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.1, 28.4, 31.2, 34.6, 121.0, 123.5, 125.6, 126.2, 132.2, 132.9, 151.4; IR (ATR) ν : 3734, 2962, 2242, 1783, 1509, 1456, 1363, 1269, 1109, 966, 814 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{15}\text{H}_{19}\text{N}$, $[\text{M}]^+ 213.1512$, found 213.1507; Colorless oil (67%, 28.8 mg)

(E)-4-(4-bromophenyl)-2-methylbut-3-enitrile (24d)



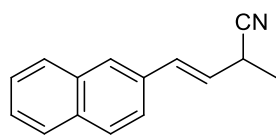
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.50 (d, 3H, $J = 7.2$ Hz), 3.50 (qd, 1H, $J = 7.2, 6.4$ Hz), 6.05 (dd, 1H, $J = 16.0, 6.4$ Hz), 6.64 (d, 1H, $J = 16.0$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 7.45 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.3, 120.6, 122.1, 125.0, 128.0, 131.3, 131.8, 134.5; IR (ATR) ν : 2991, 2939, 2243, 1487, 1072, 1008, 965, 807 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{11}\text{H}_{10}\text{NBr}$, $[\text{M}]^+ 234.9991$, found 234.9987; Colorless solid (mp: 36-40 $^\circ\text{C}$, 76%, 34.1 mg)

(E)-4-(3-bromophenyl)-2-methylbut-3-enitrile (24e)



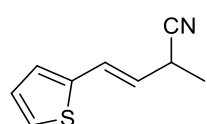
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.50 (d, 3H, $J = 6.8$ Hz), 3.47-3.54 (m, 1H), 6.03-6.10 (m, 1H), 6.64 (dd, 1H, $J = 15.6, 6.8$ Hz), 7.21 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.27 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.39 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.51 (d, 1H, $J = 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.3, 120.5, 122.8, 125.3, 125.8, 129.3, 130.2, 131.1, 137.7; IR (ATR) ν : 2985, 2242, 1561, 1473, 1072, 961, 883 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{11}\text{H}_{10}\text{NBr}$, $[\text{M}]^+ 234.9991$, found 234.9986; Colorless oil (72%, 31.2 mg)

(E)-2-methyl-4-(naphthalen-2-yl)but-3-enitrile (24f)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.53 (d, 3H, $J = 6.8$ Hz), 3.52-3.59 (qd, 1H, $J = 6.8, 6.0$ Hz), 6.16 (dd, 1H, $J = 15.6, 6.0$ Hz), 6.86 (d, 1H, $J = 15.6$ Hz), 7.44-7.50 (m, 2H), 7.55 (d, 1H, $J = 8.4$ Hz), 7.75 (s, 1H), 7.79-7.82 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.1, 28.5, 120.9, 123.2, 124.5, 126.2, 126.4, 126.9, 127.7, 128.0, 128.4, 132.6, 133.0, 133.2, 133.4; IR (ATR) ν : 2994, 2237, 1964, 1709, 1508, 1460 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_{15}\text{H}_{13}\text{N}$, $[\text{M}]^+ 207.1043$, found 207.1037; Colorless solid (mp: 85-88 $^\circ\text{C}$, 93%, 38.3 mg)

(E)-2-methyl-4-(thiophen-2-yl)but-3-enitrile (24g)



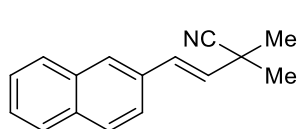
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.48 (d, 3H, $J = 7.2$ Hz), 3.44 (qd, 1H, $J = 7.2, 6.0$ Hz), 5.89 (d, 1H, $J = 16.0, 6.0$ Hz), 6.82 (d, 1H, $J = 16.0$ Hz), 6.96-7.00 (m, 2H), 7.19 (d, 1H, $J = 4.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.9, 28.1, 120.6, 123.5, 125.0, 125.6, 126.7, 127.5, 140.3; IR (ATR) ν : 2986, 2938, 2242, 1783, 1645, 1591, 1487, 1452, 1433, 1205, 1040 cm^{-1} ; HRMS (APPI) Calcd for $\text{C}_9\text{H}_9\text{NS}$, $[\text{M}]^+ 163.0450$, found 163.0445; Colorless oil (75%, 35.2 mg)

Synthesis of 25, 26, 27

To a THF (0.98 ml) solution of **24f** (40.6 mg, 0.20 mmol) was added LHMDS (0.24 ml, 1.0 M in THF, 0.24 mmol) at -78 °C under argon. The resulting solution was allowed to stir for an additional 30 min at same temperature. To this solution was added **MeI (0.12 ml, 2.00 mmol)** at -78 °C. The mixture was warmed to room temperature and stirred for a 1 h. The reaction was quenched with saturated aqueous ammonium chloride, and the products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (*n*-Hexane/AcOEt = 5/1) to afford **25** as a colorless solid.

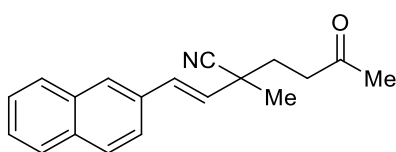
26 and **27** were also synthesized by the same procedure using MVK (methyl vinyl ketone) or paraformaldehyde instead of MeI.

(*E*)-2,2-dimethyl-4-(naphthalen-2-yl)but-3-enitrile (**25**)



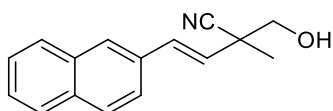
¹H-NMR (CDCl₃, 400 MHz) δ: 1.59 (s, 6H), 6.14 (d, 1H, *J* = 16.0 Hz), 6.91 (d, 1H, *J* = 16.0 Hz), 7.44-7.50 (m, 2H), 7.56 (d, 1H, *J* = 8.4 Hz), 7.77-7.82 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 27.7, 35.0, 123.3, 123.4, 126.2, 126.4, 126.9, 127.6, 128.0, 128.3, 129.9, 130.6, 133.1, 133.4; IR (ATR) ν: 3056, 2979, 2236, 1466, 1264, 963, 813 cm⁻¹; HRMS (APPI) Calcd for C₁₆H₁₃N, [M]⁺221.1199, found 221.1192; Colorless solid (mp: 64-69 °C, 56%, 23.1 mg)

(*E*)-2-methyl-2-(2-(naphthalen-2-yl)vinyl)-5-oxohexanenitrile (**26**)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.59 (s, 3H), 2.04-2.08 (m, 2H), 2.13 (s, 3H), 2.60-2.72 (m, 2H), 5.93 (d, 1H, *J* = 15.6 Hz), 6.93 (d, 1H, *J* = 15.6 Hz), 7.46-7.49 (m, 2H), 7.53 (d, 1H, *J* = 8.0 Hz), 7.77-7.81 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 26.8, 30.2, 33.8, 39.5, 39.9, 122.0, 123.2, 126.3, 126.5, 127.0, 127.7, 128.1, 128.5, 128.9, 131.4, 132.8, 133.2, 133.4, 206.9; IR (ATR) ν: 3017, 2931, 2236, 1714, 1363, 1171, 964, 812 cm⁻¹; HRMS (APPI) Calcd for C₁₉H₁₉ON, [M]⁺277.1461, found 277.1452; Colorless oil (35%, 17.6 mg)

(*E*)-2-(hydroxymethyl)-2-methyl-4-(naphthalen-2-yl)but-3-enitrile (**27**)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.58 (s, 3H), 3.76 (s, 2H), 6.07 (d, 1H, *J* = 16.0 Hz), 7.02 (d, 1H, *J* = 16.0 Hz), 7.45-7.52 (m, 2H), 7.57 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.79-7.83 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.9, 43.0, 68.6, 121.6, 123.2, 126.1, 126.3, 126.5, 127.2, 127.7, 128.1, 128.4, 132.8, 133.2, 133.3, 133.4; IR (ATR) ν: 3416, 2934, 2242, 1703, 1362, 1055, 963, 811 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₁₅NNaO, [M+Na]⁺260.1051, found 260.1062; Yellow solid (mp: 100-104 °C, 31%, 11.8 mg)

Synthesis of 11d

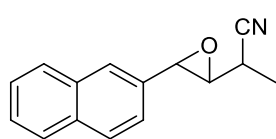
To a CH₂Cl₂ (0.79 ml) solution of **10e** (32.7 mg, 0.16 mmol) was added *m*CPBA (32.6 mg, 0.19 mmol) at 0 °C. The resulting mixture was stirred for 24 h, and then sat. NaHCO₃ was added, and the products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by flash

column chromatography (*n*-Hexane/AcOEt = 5/1) to afford **11d** as a colorless solid.

Synthesis of **28**

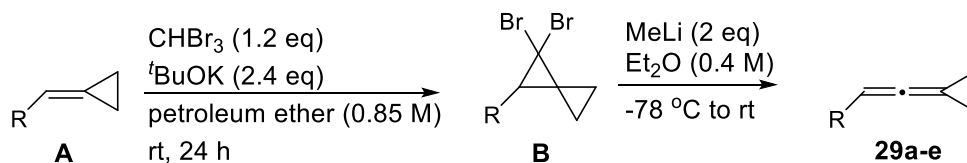
To a CH₂Cl₂ solution of **24f** (32.7 mg, 0.16 mmol, 0.79 mL) was added *m*CPBA (32.6 mg, 0.19 mmol) at 0 °C. The resulting mixture was stirred for 23 h, and then sat. NaHCO₃ was added, and the products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (*n*-Hexane/AcOEt = 5/1) to afford **28** as a colorless solid.

2-(3-(naphthalen-2-yl)oxiran-2-yl)propanenitrile (**28**)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.51 (d, 3H, *J* = 6.8 Hz), 2.92-3.05 (m, 1H), 3.20-3.23 (m, 1H), 4.09 (d, 1H, *J* = 1.2 Hz), 7.29 (dd, 1H, *J* = 8.8, 1.2 Hz), 7.47-7.52 (m, 2H), 7.79-7.84 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.6, 14.8, 28.2, 28.4, 57.6, 57.7, 61.3, 119.0, 119.2, 122.5, 125.5, 126.4, 126.6, 127.8, 127.8, 128.6, 132.8, 132.8, 133.0, 133.4; IR (ATR) ν: 3058, 2991, 2246, 1508, 1456, 1265, 895, 859 cm⁻¹; HRMS (APPI) Calcd for C₁₅H₁₃ON, [M]⁺223.0992, found 223.0983; Colorless solid (mp: 86-90 °C, 62%, 22.0 mg)

Synthesis of **29a-e**

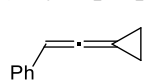


29a-e were synthesized from **I** according to the reported procedure⁴.

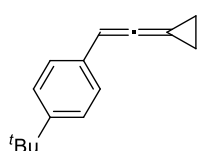
A to B: A solution of CHBr₃ (3.34 g, 1.16 mL, 13.2 mmol) in petroleum ether (3 ml) was added dropwise to a stirred mixture of the **A** (11.0 mmol) and *t*-BuOK (1.95 g, 26.4 mmol) in petroleum ether (10 ml) at 0 °C under an atmosphere of argon. After 20 min the resulting mixture was slowly warmed up to room temperature and then stirred for 48 h. Then it was quenched with cold water. The organic phase was separated, and the water phase was extracted with Et₂O. The combined organic layers were dried with anhydrous MgSO₄. The solvent was evaporated in vacuo to leave a crude mixture, which was purified by column chromatography (eluting with hexane).

B to 29: To a solution of **B** (1.2 mmol) in Et₂O (3 mL) was added MeLi (1.5 M in Et₂O, 1.6 mL, 2.4 mmol) at -78 °C. Then the reaction was allowed to warm up to 0 °C and stirred for 2 h. Sat. NH₄Cl was added to quench the reaction. The reaction mixtures were extracted with AcOEt, dried over anhydrous Na₂SO₄ and the solid was filtered. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-Hexane) to afford pure **29**.

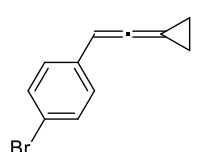
(2-cyclopropylidenevinyl)benzene (29a)

(CAS-Reg# 42311-14-8)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.65-1.77 (m, 4H), 6.27-6.30 (m, 1H), 7.14-7.29 (m, 5H)
 (12%, 16.4 mg)

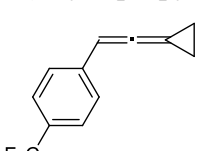
1-(tert-butyl)-4-(2-cyclopropylidenevinyl)benzene (29b)


¹H-NMR (CDCl₃, 400 MHz) δ: 1.30 (s, 9H), 1.61-1.74 (m, 4H), 6.23 (ddd, 1H, *J* = 6.8, 3.6, 3.6 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 8.7, 31.4, 34.6, 80.0, 96.4, 125.6, 126.3, 133.0, 149.6, 189.9; IR (ATR) ν: 2961, 2009, 1699, 1514, 1362, 1268, 841 cm⁻¹; HRMS (ESI) Calcd for C₁₅H₁₈Cs, [M+Cs]⁺331.0463, found 331.0466; Yellow oil (5%, 9.5 mg)

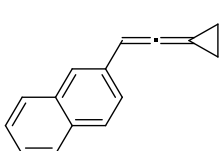
1-bromo-4-(2-cyclopropylidenevinyl)benzene (29c)

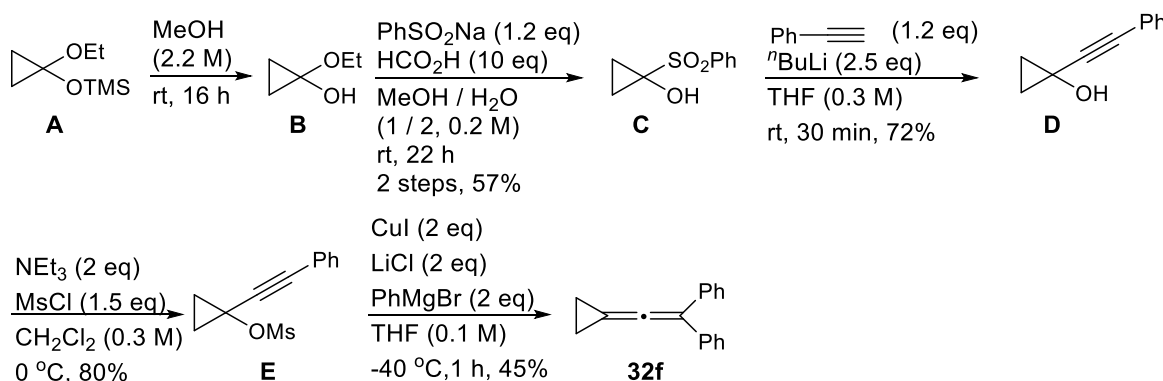

¹H-NMR (CDCl₃, 400 MHz) δ: 1.66-1.78 (m, 4H), 6.22 (ddd, 1H, *J* = 6.8, 3.6, 3.6 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 8.9, 80.3, 95.7, 119.8, 128.0, 131.5, 133.0, 189.9; IR (ATR) ν: 2985, 2008, 1475, 1008, 831 cm⁻¹; HRMS (ESI) Calcd for C₁₁H₉BrCs, [M+Cs]⁺352.8942, found 352.8947; yellow oil (5%, 25.6 mg)

1-(2-cyclopropylidenevinyl)-4-(trifluoromethyl)benzene (29d)


¹H-NMR (CDCl₃, 400 MHz) δ: 1.70-1.82 (m, 4H), 6.29 (ddd, 1H, *J* = 6.8, 3.6, 3.6 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 9.3, 80.2, 95.6, 125.4, 125.4, 126.5, 131.7, 140.0, 190.7; IR (ATR) ν: 2993, 2009, 1613, 1320, 1161, 1104, 1064, 846 cm⁻¹; HRMS (ESI) Calcd for C₁₂H₉CsF₃, [M+Cs]⁺342.9711, found 342.9700; Colorless oil (25%, 89.0 mg)

2-(2-cyclopropylidenevinyl)naphthalene (29e)


¹H-NMR (CDCl₃, 400 MHz) δ: 1.69-1.82 (m, 4H), 6.46 (ddd, 1H, *J* = 7.2, 3.6, 3.6 Hz), 7.38-7.48 (m, 3H), 7.76 (s, 1H), 7.73-7.82 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 8.9, 80.2, 96.9, 124.8, 124.9, 125.3, 126.1, 127.6, 127.7, 128.0, 132.4, 133.4, 133.7, 190.3; IR (ATR) ν: 3045, 2006, 1597, 1508, 902, 822 cm⁻¹; HRMS (ESI) Calcd for C₁₅H₁₂Cs, [M+Cs]⁺324.9994, found 324.9981; Colorless solid (mp: 63-65 °C, 13%, 124.1 mg)

Synthesis of 32f

32f was synthesized according to the reported procedure⁵⁻⁷.

A to B: **A** (2.31 mL, 11.5 mmol) was dissolved in MeOH (5.2 mL) and stirred for 17 h at room temperature. Then, the solvent was removed under reduced pressure. Crude **B** was used in the next step without further purification.

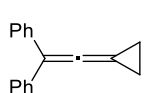
B to C: To a solution of **B** (2.0g, 11.5 mmol), PhSO₂Na (2.27 g, 13.8 mmol) in a mixture of solvent (MeOH/H₂O = 1/2, 58 ml) was added HCO₂H (6.0 g, 115 mmol) at 0 °C. The mixture was warmed up to room temperature and stirred overnight. The reaction was quenched with H₂O and extracted with CH₂Cl₂. The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated. The crude product was purified by recrystallization to afford **C** as a colorless solid (2 steps, 57%, 700 mg).

C to D: To a solution of phenylacetylene (0.41 ml, 3.72 mmol) in THF (7 ml) was added *n*-BuLi (1.63 M, 4.8 ml, 7.75 mmol) within 20 minutes at -78 °C. The resulting solution was stirred at -78 °C for 2 h before a solution of **C** (610.5 mg, 3.10 mmol) in THF (3 ml) was added dropwise. Then, the reaction mixture was allowed warm up to room temperature and stirred for 4 h. Saturated NH₄Cl solution was added to quench the reaction. The reaction mixtures were extracted with AcOEt, dried over anhydrous Na₂SO₄ and the solid was filtered. The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (Hexane/AcOEt: 10/1) to afford pure **D** as a yellow oil. (72%, 355.3 mg)

D to E: To a solution of **D** (355.3 mg, 2.25 mmol) and NEt₃ (0.63 ml, 4.5 mmol) in CH₂Cl₂ (7.5 ml) was added MsCl (0.26 ml, 3.38 mmol) within 5 minutes at 0 °C. The resulting solution was stirred at 0 °C for 30 min before H₂O was added to quench the reaction. The reaction mixtures were extracted with CH₂Cl₂, dried with anhydrous Na₂SO₄ and the solid was filtered. The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/AcOEt: 10/1) to afford **E** as a colorless solid (80%, 425.6 mg).

E to 32f: To a solution of CuI (819 mg, 4.3 mmol) and LiCl (182 mg, 4.3 mmol) in anhydrous THF (17 ml) was added PhMgBr (1.0 M in THF, 4.3 ml, 4.3 mmol) within 5 minutes at -10 °C. The resulting solution was stirred at -10 °C for 5 min and then the solution was cooled to -40 °C before a solution of **E** (508.7 mg, 2.15 mmol) in THF (4 ml) was added dropwise. The reaction mixture was stirred at -40 °C for at least 8 h. Saturated NH₄Cl solution was added to quench the reaction. Extracted with Et₂O, dried with anhydrous Na₂SO₄ and the solid was filtered. The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluting with hexane) to afford **32f** as a colorless solid (40%, 187.6 mg).

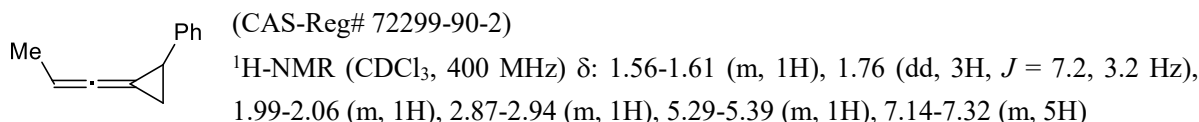
(2-cyclopropylideneethene-1,1-diyl)dibenzene (**32f**)



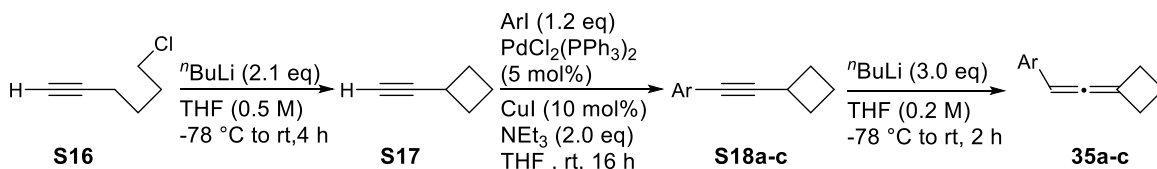
(CAS-Reg# 1403484-23-0)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.74 (s, 4H), 7.20-7.45 (m, 10H); (40%, 187.6 mg)

(2-(prop-1-en-1-ylidene)cyclopropyl)benzene (29g)



Synthesis 35a-c



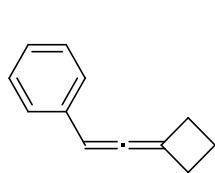
| entry | Ar | S16 to S18 (%) | S18 to 35 (%) |
|-------|---------|------------------------------|-----------------------------|
| 1 | Ph | S18a (79) | 35a (71) |
| 2 | 4-MePh | S18b (37) | 35b (69) |
| 3 | 4-MeOph | S18c (32) | 35c (73) |

S16 to **S17**: *n*-BuLi (46.5 mL, 7.20 mmol, 1.55 M in hexanes) was added to a solution of **S16** (4.0 g, 34.3 mmol) in THF (69 mL) dropwise at -78°C . After being stirred for 20 min at -78°C , it was allowed to warm up naturally to rt and stirred 4 h. When the reaction was complete, it was quenched with saturated aqueous solution of NH₄Cl and extracted with THF. Drying over anhydrous MgSO₄, afforded a solution of the **S17** in THF, which was submitted to next step directly.

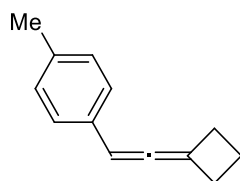
S17 to **S18**: To a THF solution of **S17** (40 mL, 6.86 mmol, 0.17 M in THF) was added aryl iodide (Arl, 8.23 mmol), PdCl₂(PPh)₃ (241 mg, 0.34 mmol), CuI (131 mg, 0.69 mmol), NEt₃ (1.9 mL, 13.72 mmol) at room temperature under argon, and stirred for 16 h at the same temperature. The reaction mixture was pored into silica gel to be purified by column chromatography (*n*-Hexane), and the desired product was given.

S18 to **35**: *n*-BuLi (3.0 eq, 1.55 M in hexanes) was added to a solution of **S18** (1.0 eq) in THF (0.2 M) dropwise at -78°C . After being stirred for 20 min at -78°C , it was allowed to warm up naturally to rt and stirred 2 h. When the reaction was complete, it was quenched with saturated aqueous solution of NH₄Cl and extracted with AcOEt. The solvent was removed in vacuum to leave a crude mixture, which was purified by column chromatography on silica gel (eluting with *n*-Hexane) to afford pure **35**.

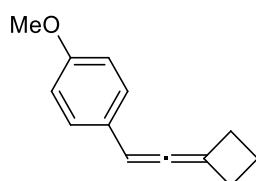
(2-cyclobutylidenevinyl)benzene (35a)



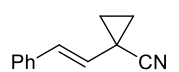
¹H-NMR (CDCl₃, 400 MHz) δ: 1.95-2.08 (m, 2H), 2.89-3.08 (m, 4H), 6.10-6.14 (m, 1H), 7.14-7.18 (m, 1H), 7.26-7.32 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 17.6, 29.8, 96.5, 104.6, 126.7, 126.8, 128.5, 135.7, 196.4; IR (ATR) ν: 2951, 1948, 1705, 1599, 1495, 1452, 824, 758, 691 cm⁻¹; HRMS (ESI) Calcd for C₁₂H₁₂Na, [M+Na]⁺ 179.0837, found 179.0840; Yellow oil (71%, 275.1 mg)

1-(2-cyclobutylidenevinyl)-4-methylbenzene (35b)

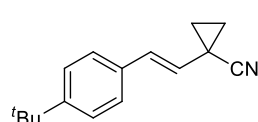
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.94-2.08 (m, 2H), 2.31 (s, 3H), 2.88-3.07 (m, 4H), 6.09 (dt, 1H, $J = 8.0, 4.0$ Hz), 7.07 (d, 2H, $J = 8.0$ Hz), 7.18 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.7, 21.3, 30.1, 96.5, 104.6, 126.8, 129.4, 132.9, 136.6, 196.2; IR (ATR) ν : 2954, 1705, 1515, 849, 607 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{Na}$, $[\text{M}+\text{Na}]^+$ 193.0993, found 193.0993; Yellow oil (69%, 261.7 mg)

1-(2-cyclobutylidenevinyl)-4-methoxybenzene (35c)

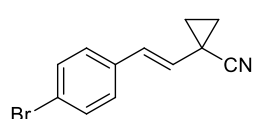
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.95-2.06 (m, 2H), 2.88-3.06 (m, 4H), 3.76 (s, 3H), 6.08 (dt, 1H, $J = 8.0, 4.0$ Hz), 6.81 (d, 2H, $J = 8.4$ Hz), 7.21 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.5, 29.9, 55.2, 95.9, 104.4, 113.9, 127.8, 132.7, 158.5, 195.6; IR (ATR) ν : 2953, 1699, 1607, 1511, 1251, 1036, 834, 540 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{NaO}$, $[\text{M}+\text{Na}]^+$ 209.0942, found 209.0944; Yellow oil (73%, 340.8 mg)

(E)-1-styrylcyclopropanecarbonitrile (32a)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.15-1.25 (m, 2H), 1.55-1.65 (m, 2H), 5.51 (d, 1H, $J = 15.6$ Hz), 6.80 (d, 1H, $J = 15.6$ Hz), 7.25-7.33 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.5, 16.8, 121.3, 126.1, 126.2, 127.9, 128.7, 130.8, 135.8; IR (ATR) ν : 3025, 2234, 1448, 1071, 963, 806 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{11}\text{CsN}$, $[\text{M}+\text{Cs}]^+$ 301.9946, found 301.9939; Colorless oil (63%, 12.2 mg)

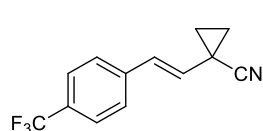
(E)-1-(4-(tert-butyl)styryl)cyclopropanecarbonitrile (32b)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.15-1.21 (m, 2H), 1.31 (s, 9H), 1.58-1.62 (m, 2H), 5.48 (d, 1H, $J = 16.0$ Hz), 6.78 (d, 1H, $J = 16.0$ Hz), 7.26 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.5, 16.8, 31.2, 34.6, 121.5, 125.4, 125.6, 125.8, 129.7, 130.6, 133.0; IR (ATR) ν : 2961, 2235, 963, 828 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{19}\text{CsN}$, $[\text{M}+\text{Cs}]^+$ 358.0572, found 358.0562; Colorless solid (mp: 65-69 $^{\circ}\text{C}$, 65%, 4.6 mg)

(E)-1-(4-bromostyryl)cyclopropanecarbonitrile (32c)

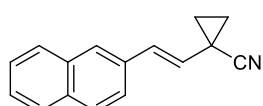
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.20-1.23 (m, 2H), 1.61-1.65 (m, 2H), 5.50 (d, 1H, $J = 16.0$ Hz), 6.74 (d, 1H, $J = 16.0$ Hz), 7.19 (d, 2H, $J = 8.0$ Hz), 7.43 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.6, 16.9, 121.1, 121.7, 127.1, 127.6, 129.7, 131.8, 134.8; IR (ATR) ν : 3016, 2237, 1488, 1068, 957 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{10}\text{BrCsN}$, $[\text{M}+\text{Cs}]^+$ 379.9051, found 379.9043; Colorless solid (mp: 105-107 $^{\circ}\text{C}$, 82%, 23.6 mg)

(E)-1-(4-(trifluoromethyl)styryl)cyclopropanecarbonitrile (32d)



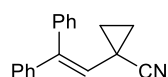
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.26 (dd, 2H, $J = 7.2, 5.6$ Hz), 1.66 (dd, 2H, $J = 7.2, 5.6$ Hz), 5.59 (d, 1H, $J = 15.6$ Hz), 6.84 (d, 1H, $J = 15.6$ Hz), 7.42 (d, 2H, $J = 8.4$ Hz), 7.56 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.7, 17.1, 120.9, 125.6, 125.7, 126.3, 129.1, 129.4, 139.2; IR (ATR) ν : 3016, 2240, 1326, 1103, 1067, 967 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}$, $[\text{M}+\text{Cs}]^+ 369.9820$, found 369.9826; Colorless solid (mp: 91-93 $^\circ\text{C}$, 76%, 35.9 mg)

(E)-1-(2-(naphthalen-2-yl)vinyl)cyclopropanecarbonitrile (32e)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.24 (dd, 2H, $J = 6.8, 5.2$ Hz), 1.63 (dd, 2H, $J = 6.8, 5.2$ Hz), 5.63 (d, 1H, $J = 15.6$ Hz), 6.96 (d, 1H, $J = 15.6$ Hz), 7.43-7.50 (m, 3H), 7.72-7.80 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.7, 16.9, 121.3, 123.0, 126.0, 126.2, 126.4, 126.5, 127.6, 128.0, 128.3, 130.8, 133.0, 133.2, 133.5; IR (ATR) ν : 3054, 2236, 969, 954, 818 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{13}\text{N}$, $[\text{M}+\text{Cs}]^+ 352.0102$, found 352.0092; Colorless solid (mp: 93-95 $^\circ\text{C}$, quant, 31.6 mg)

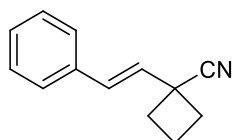
1-(2,2-diphenylvinyl)cyclopropanecarbonitrile (32f)



(CAS-Reg# 260261-08-3)

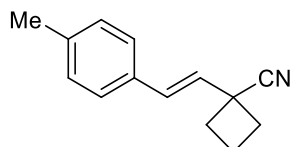
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.51 (d, 3H, $J = 6.8$ Hz), 3.51 (qd, 1H, $J = 6.8, 6.0$ Hz), 6.04 (dd, 1H, $J = 15.6, 6.0$ Hz), 6.70 (d, 1H), 7.26-7.39 (m, 5H); (17%, mg)

(E)-1-styrylcyclobutanecarbonitrile (9a)



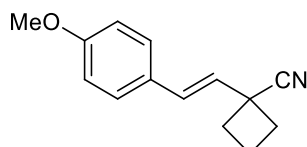
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.05-2.15 (m, 1H), 2.23-2.32 (m, 1H), 2.34-2.45 (m, 2H), 2.67-2.74 (m, 2H), 6.26 (d, 1H, $J = 16.0$ Hz), 6.70 (d, 1H, $J = 16.0$ Hz), 7.28-7.30 (m, 1H), 7.34 (dd, 2H, $J = 8.0, 8.0$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.1, 33.9, 38.2, 123.0, 126.5, 127.9, 128.1, 128.7, 130.5, 135.7; IR (ATR) ν : 2948, 2231, 1448, 963, 749, 694 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NNa}$, $[\text{M}+\text{Na}]^+ 206.0946$, found 206.0952; Colorless oil (72%, 35.1 mg)

(E)-1-(4-methylstyryl)cyclobutanecarbonitrile (9b)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.03-2.15 (m, 1H), 2.21-2.41 (m, 6H), 2.66-2.72 (m, 2H), 6.20 (d, 1H, $J = 16.0$ Hz), 6.66 (d, 1H, $J = 16.0$ Hz), 7.13 (d, 2H, $J = 8.0$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.1, 21.2, 33.9, 38.2, 123.1, 126.4, 126.9, 129.4, 130.3, 132.9, 138.1; IR (ATR) ν : 2948, 2231, 1514, 1445, 964, 803 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{15}\text{NNa}$, $[\text{M}+\text{Na}]^+ 220.1102$, found 220.1109; Colorless oil (64%, 33.2 mg)

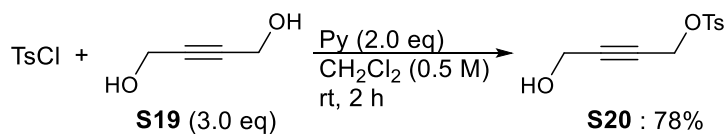
(E)-1-(4-methoxystyryl)cyclobutanecarbonitrile (9c)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.02-2.13 (m, 1H), 2.21-2.30 (m, 1H), 2.32-2.40 (m, 2H), 2.65-2.71 (m, 2H), 3.81 (s, 3H), 6.11 (d, 1H, $J = 15.6$ Hz), 6.63 (d, 1H, $J = 15.6$ Hz), 6.86 (d, 2H, $J = 8.8$ Hz), 7.32 (d, 2H, $J = 8.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.0, 33.9, 38.2, 55.3, 114.0, 123.2,

125.7, 127.7, 128.4, 129.9, 159.5; IR (ATR) ν : 2950, 2232, 1607, 1513, 1251, 1176, 1034, 740 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{15}\text{NNaO}$, $[\text{M}+\text{Na}]^+$ 236.1051, found 236.1060; Colorless solid (mp: 58-61 $^{\circ}\text{C}$, 64%, 33.2 mg)

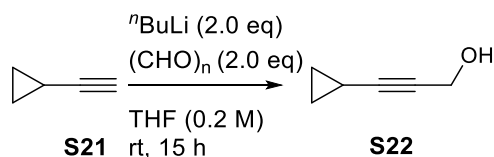
Synthesis of 38



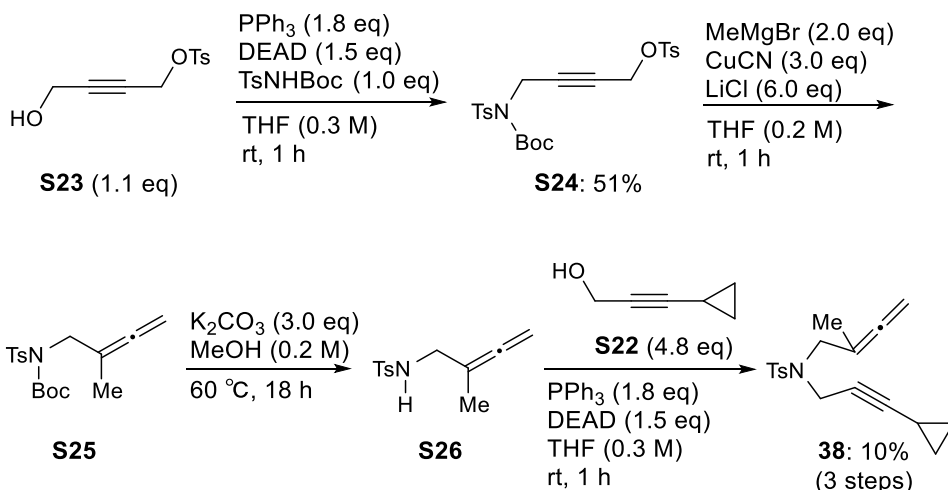
S19 to S20 : To a stirring 0 $^{\circ}\text{C}$. solution of **S19** (20.3 g, 236.1 mmol) in anhydrous CH_2Cl_2 (157 mL) was added pyridine (12.5 g, 157.4 mmol). TsCl (15.6 g, 78.7 mmol) was then added portionwise over a period of 15 min. After stirring for another 2 h at 0 $^{\circ}\text{C}$, 1N HCl was added to quench the reaction. The CH_2Cl_2 layer was washed with H_2O , then finally dried over anhydrous Na_2SO_4 . After evaporation of the solvent, the crude product was purified by column chromatography (n -Hexane/AcOEt = 3/1) to afford **S20**.



TsNH₂ to TsNHBoc : To a stirred suspension of TsNH_2 (10 g, 58.4 mmol) in dry CH_2Cl_2 (70 mL) was added NEt_3 (8.95 mL, 64 mmol) followed by DMAP (713 mg, 0.584 mmol). To this suspension, a solution of Boc_2O (14.7 g, 67.16 mmol) in anhydrous CH_2Cl_2 (110 mL) was added dropwise via an addition funnel over 10 min. The mixture was stirred at room temperature for 2 h. The solvent was evaporated and AcOEt was added. The organic layer was washed with 1N HCl, water and brine. The organic layer was dried over Na_2SO_4 . Filtered and evaporated all solvent. The crude product was used for next step without purification.



S21 to S22: At -78 $^{\circ}\text{C}$, n -BuLi (3.9 mL, 1.55 M in hexane, 6.0 mmol) was added to **S21** (0.42 mL, 5.0 mmol) in THF (25 mL). The reaction mixture was stirred at 0 $^{\circ}\text{C}$ for 1 h, then cooled to -78 $^{\circ}\text{C}$. Paraformaldehyde (300 mg, 10 mmol) was added. The reaction mixture was then stirred at -78 $^{\circ}\text{C}$ and warmed to room temperature overnight. The reaction mixture was then concentrated, AcOEt was added, and the organic layer was washed with brine. The organic layer was concentrated carefully, and the crude **S22** was used for next step without purification.



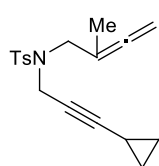
S23 to S24: To a solution of **S23** (2.91 g, 12.1 mmol), PPh₃ (5.19 g, 19.8 mmol), TsNHBoc (2.98 g, 11.0 mmol) in THF (36.7 mL) was added DEAD (7.5 mL, 16.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (*n*-Hexane/AcOEt = 5 / 1), to afford **S24** (52%, 2.85 g).

S24 to S25: To a stirred suspension of LiCl (1.55 g, 36.5 mmol) and CuCN (1.63 g, 18.2 mmol) in THF (20.0 mL) at 0 °C was slowly added a solution of MeMgBr (4.1 mL, 3.0 M in Et₂O, 12.4 mmol). After the mixture was stirred for 15 min, a solution of **S24** (3.0 g, 6.1 mmol) in THF (10.0 mL) was added. The reaction mixture was allowed to warm to rt over 1 h, and then a saturated solution of NH₄Cl was added and the reaction was extracted with AcOEt. After drying (Na₂SO₄), concentration, and flash column chromatography (*n*-Hexane/AcOEt = 5/1), crude **S25** was obtained.

S25 to S26: To the solution of crude **S25** (1.62 g, 4.81 mmol) in MeOH (48 mL) was added K₂CO₃ (3.98 g, 28.8 mmol) and stirred for 18 h at 60 °C. The reaction was quenched by H₂O and aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄ and filtrated off, the resulting residue was concentrated, and the crude **S26** was used for next step without purification.

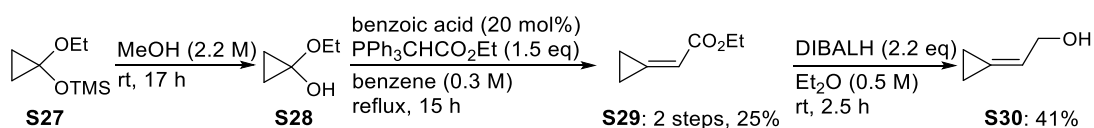
S26 to 38: Same as **S23 to S24**.

N-(3-cyclopropylprop-2-yn-1-yl)-4-methyl-N-(2-methylbuta-2,3-dien-1-yl)benzenesulfonamide (**38**)



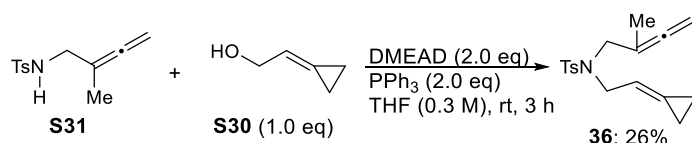
¹H-NMR (CDCl₃, 400 MHz) δ: 0.27-0.31 (m, 2H), 0.56-0.61 (m, 2H), 0.87-0.97 (m, 1H), 1.71 (t, 3H, *J* = 3.2 Hz), 2.43 (s, 3H), 3.74 (s, 2H), 4.03 (s, 2H), 4.66 (brs, 2H), 7.29 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 400 MHz): 8.8, 16.8, 22.5, 37.1, 50.7, 68.3, 75.9, 90.2, 94.4, 128.7, 130.3, 137.2, 144.2, 208.6; IR (ATR) ν: 2922, 2250, 1962, 1728, 1346, 1158, 1092, 900 cm⁻¹; HRMS (ESI) Calcd for C₁₈H₂₁NNaO₂S, [M+Na]⁺ 338.1191, found 338.1190; Yellow oil (10%, 39.1 mg)

Synthesis of 36



S27 to **S28** : **S27** (2.15 mL, 10.7 mmol) was dissolved in MeOH (4.9 mL) and stirred for 17 h at room temperature. Then, the solvent was removed under reduced pressure. The residue **S28** was dissolved in benzene (20 mL) and added benzoic acid (261 mg, 2.14 mmol). This flask was brought to gentle reflux. To a refluxing solution was added ylide (5.6 g, 16.1 mmol) dissolved in benzene (16 mL) at a rate so as to maintain reflux. After complete addition, the mixture was allowed to reflux for 15 h. After cooling to room temperature, benzene was removed under reduced pressure and the residue was purified by flash column chromatography (*n*-Hexane/AcOEt = 3 / 1) to afford **S29** (334 mg, 2 steps, 25%) as a colorless oil.

S29 to **S30** : To a solution of **S29** (334 mg, 2.65 mmol) in Et₂O (5.3 mL) was added DIBALH (5.8 mL, 1.0 M solution in toluene, 5.83 mmol) at -78 °C and the reaction was warmed to 0 °C for 3 h, then quenched by MeOH and saturated solution of Rochell salt at 0 °C. After being stirred for 1 h, the precipitate was filtrated through a Celite pad and the organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-Hexane/Et₂O = 1 / 4), to afford **S22** (41%, 90.7 mg) as a colorless oil.



S31 to **36**: Same as **S23** to **S24** (DMEAD was used instead of DEAD)

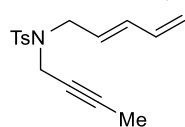
N-(2-cyclopropylideneethyl)-4-methyl-*N*-(2-methylbuta-2,3-dien-1-yl)benzenesulfonamide (**36**)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.98-1.06 (m, 4H), 1.66 (d, 3H, *J* = 3.2 Hz), 2.42 (s, 3H), 3.76 (brs, 2H), 3.94 (d, 2H, *J* = 6.8 Hz), 4.57 (q, 2H, *J* = 3.2 Hz), 5.50-5.57 (m, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 1.7, 2.5, 15.9, 21.4, 48.0, 50.1, 74.8, 94.5, 112.3, 127.1, 127.2, 129.5, 137.7, 143.0, 207.3; IR (ATR) ν: 2982, 2923, 1961, 1335, 1155, 1092 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₂₁NNaO₂S, [M+Na]⁺ 326.1191, found 326.1182; Orange oil (26%, 121 mg)

N-(but-2-yn-1-yl)-*N*-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (**40**)

(CAS-Reg# 1262899-40-0)
¹H-NMR (CDCl₃, 400 MHz) δ: 1.01-1.14 (m, 4H), 1.54 (s, 3H), 2.43 (s, 3H), 3.94 (d, 2H, *J* = 6.8 Hz), 4.00 (d, 2H, *J* = 1.6 Hz), 5.65-5.75 (m, 1H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 2H, *J* = 8.0 Hz)

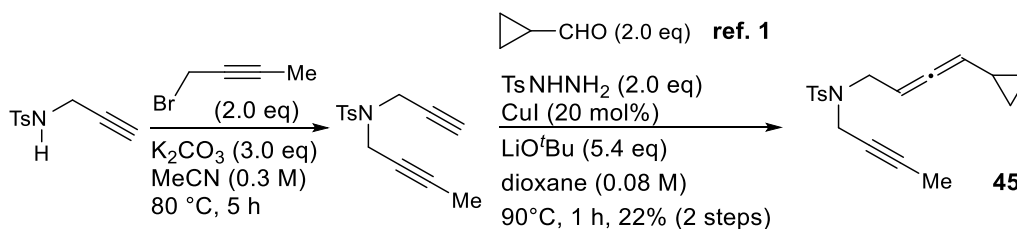
(E)-N-(but-2-yn-1-yl)-4-methyl-N-(penta-2,4-dien-1-yl)benzenesulfonamide (44)



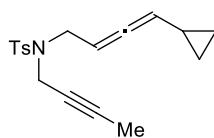
(CAS-Reg# 478176-01-1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.56 (t, 3H, $J = 2.0$ Hz), 2.42 (s, 3H), 3.83 (d, 2H, $J = 8.0$ Hz), 4.00 (q, 2H, $J = 2.0$ Hz), 5.11 (d, 1H, $J = 10.0$ Hz), 5.20 (d, 1H, $J = 16.4$ Hz), 5.58 (dt, 1H, $J = 15.6, 8.0$ Hz), 6.22 (dd, 1H, $J = 15.6, 10.0$ Hz), 6.33 (dt, 1H, $J = 16.4, 10.0$ Hz), 7.31 (d, 2H, $J = 8.4$ Hz), 7.72 (d, 2H, $J = 8.4$ Hz)

Synthesis of 45

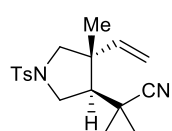


N-(but-2-yn-1-yl)-N-(4-cyclopropylbuta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (45)



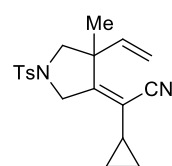
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.34-0.36 (m, 2H), 0.68-0.72 (m, 2H), 1.18-1.28 (m, 1H), 1.55-1.57 (m, 3H), 2.42 (s, 3H), 3.73-3.88 (m, 2H), 4.07-4.12 (m, 2H), 5.03-5.11 (m, 1H), 7.28 (d, 2H, $J = 8.4$ Hz), 7.72 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 3.2, 6.8, 9.1, 21.4, 36.3, 46.1, 71.5, 81.4, 87.9, 97.1, 127.7, 129.2, 136.2, 143.2, 204.9; IR (ATR) ν : 2921, 1726, 1597, 1345, 1157, 1092 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{S}$, $[\text{M}+\text{H}]^+$ 316.1371, found 316.1382; Yellow oil (22%, 54 .1 mg)

1-((3S,4R)-4-methyl-1-tosyl-4-vinylpyrrolidin-3-yl)cyclopropanecarbonitrile (37)



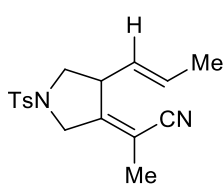
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.72-0.77 (m, 1H), 0.87-0.92 (m, 1H), 1.13-1.16 (m, 1H), 1.18 (s, 3H), 1.25-1.33 (m, 2H), 2.44 (s, 3H), 3.11 (d, 1H, $J = 10.0$ Hz), 3.30 (dd, 1H, $J = 9.6, 9.6$ Hz), 3.39 (d, 1H, $J = 10.0$ Hz), 3.66 (dd, 1H, $J = 9.6, 9.6$ Hz), 5.08 (d, 1H, $J = 17.2$ Hz), 5.15 (d, 1H, $J = 10.4$ Hz), 5.89 (dd, 1H, $J = 17.2, 10.4$ Hz), 7.34 (d, 2H, $J = 7.6$ Hz), 7.73 (d, 2H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 8.9, 13.7, 14.1, 21.7, 23.9, 47.2, 50.0, 53.4, 58.4, 115.8, 121.9, 127.5, 129.9, 133.8, 138.4, 143.9; IR (ATR) ν : 3018, 2229, 1598, 1342, 1154, 1093 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 353.1300, found 353.1308; Colorless solid (mp: 103-107 °C, 34%, 19.8 mg)

(E)-2-cyclopropyl-2-(4-methyl-1-tosyl-4-vinylpyrrolidin-3-ylidene)acetonitrile (39)



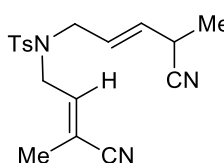
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.71-0.77 (m, 2H), 0.83-0.89 (m, 2H), 1.23-1.30 (m, 1H), 1.45 (s, 3H), 2.46 (s, 3H), 3.08 (d, 1H, $J = 9.6$ Hz), 3.15 (d, 1H, $J = 9.6$ Hz), 3.95 (d, 1H, $J = 16.0$ Hz), 4.09 (d, 1H, $J = 16.0$ Hz), 5.19 (d, 1H, $J = 17.2$ Hz), 5.21 (d, 1H, $J = 10.4$ Hz), 5.78 (dd, 1H, $J = 17.2, 10.4$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 7.71 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 6.3, 6.4, 7.8, 12.2, 21.6, 49.1, 52.2, 60.4, 110.4, 113.9, 115.8, 128.0, 129.9, 131.5, 138.4, 144.3, 157.9; IR (ATR) ν : 2929, 2215, 1597, 1486, 1347, 1161 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 365.1300, found 365.1317; Colorless solid (mp : 97-100 °C, 72%, 29.7 mg)

(E)-2-(4-((E)-prop-1-en-1-yl)-1-tosylpyrrolidin-3-ylidene)propanenitrile (43)



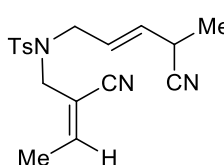
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.65 (d, 3H, $J = 7.2$ Hz), 1.81 (s, 3H), 2.46 (s, 3H), 3.21 (dd, 1H, $J = 9.6, 6.4$ Hz), 3.32 (dd, 1H, $J = 9.6, 3.2$ Hz), 3.49-3.52 (m, 1H), 3.70 (d, 1H, $J = 16.4$ Hz), 3.98 (d, 1H, $J = 16.4$ Hz), 5.24 (dq, 1H, $J = 15.2, 7.2$ Hz), 5.64 (dd, $J = 15.2, 6.4$ Hz), 7.36 (d, 2H, $J = 8.0$ Hz), 7.70 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 17.3, 17.7, 21.5, 46.9, 50.6, 53.5, 103.2, 117.5, 127.1, 127.8, 129.2, 129.9, 131.8, 144.2, 156.7; IR (ATR) ν : 3649, 2922, 2215, 1712, 1341, 1158 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 339.1143, found 339.1144; Colorless solid (mp : 109-112 $^\circ\text{C}$, 27%, 16.3 mg)

N-((E)-3-cyanobut-2-en-1-yl)-N-((E)-4-cyanopent-2-en-1-yl)-4-methylbenzenesulfonamide (41)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.38 (d, 3H, $J = 6.8$ Hz), 1.88 (s, 3H), 2.45 (s, 3H), 3.28-3.32 (m, 1H), 3.80 (d, 2H, $J = 5.6$ Hz), 3.91 (d, 2H, $J = 6.8$ Hz), 5.53 (dd, 15.6, 5.6 Hz), 5.64-5.71 (m, 1H), 6.10 (dd, 1H, $J = 6.8, 6.8$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 7.67 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 15.3, 18.5, 21.6, 27.7, 44.2, 48.9, 112.8, 120.2, 127.1, 127.5, 130.0, 130.1, 136.3, 141.6, 144.3; IR (ATR) ν : 3649, 2928, 2220, 1339, 1156 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 366.1252, found 366.1238; Colorless oil (38%, 24.5 mg)

N-((E)-2-cyanobut-2-en-1-yl)-N-((E)-4-cyanopent-2-en-1-yl)-4-methylbenzenesulfonamide (42)



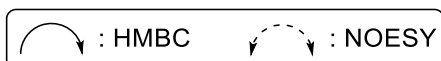
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.38 (d, 3H, $J = 7.2$ Hz), 1.94 (d, 3H, $J = 7.2$ Hz), 2.44 (s, 3H), 3.27-3.38 (m, 1H), 3.89 (d, 2H, $J = 5.6$ Hz), 3.97 (s, 2H), 5.59 (dd, 1H, $J = 15.6, 5.6$ Hz), 5.65 (dt, 1H, $J = 15.6, 5.6$ Hz), 6.59 (q, 1H, $J = 7.2$ Hz), 7.33 (d, $J = 8.4$ Hz), 7.72 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 14.9, 18.4, 21.6, 27.7, 43.5, 49.0, 111.5, 118.8, 118.9, 120.3, 127.3, 129.9, 130.4, 136.0, 144.2, 148.0; IR (ATR) ν : 3628, 2928, 2238, 1456, 1339, 1156, 1091 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 366.1252, found 366.1238; Colorless oil (10%, 6.9 mg)

References

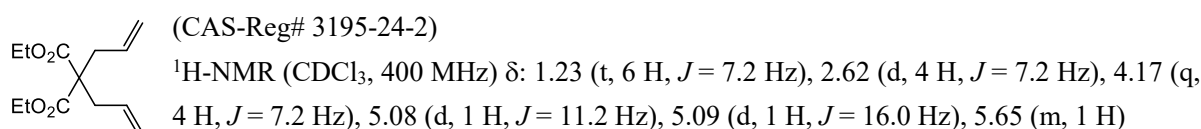
- (1) Mohammad Lokman Hossain, Fei Ye, Yan Zhang, and Jianbo Wang, *J. Org. Chem.* **2013**, 78, 1236.
- (2) Pierre Garcia, Youssef Harrak, Lisa Diab, Pierre Cordier, Cyril Ollivier, Vincent Gandon, Max Malacria, Louis Fensterbank, and Corinne Aubert. *Org. Lett.* **2011**, 13, 2952.
- (3) Jeffrey A. Stafford and John E. McMurry, *Tetrahedron Lett.* **1988**, 29, 2531.
- (4) Kseniya N. Sedenkova, Elena B. Averina, Yuri K. Grishin, Victor B. Rybakov, Tamara S. Kuznetzova, and Nikolay S. Zefirov, *Eur. J. Org. Chem.* **2010**, 4145.
- (5) Fedor Romanov-Michailidis, Laure Guénée, and Alexandre Alexakis, *Angew. Chem. Int. Ed.* **2013**, 52, 9266.
- (6) Jie Liu, Yan An, Hai-Ying Jiang, Zili Chen, *Tetrahedron Lett.* **2008**, 49, 490.
- (7) Wei Yuan, Xiang Dong, Yin Wei, and Min Shi, *Chem. Eur. J.* **2012**, 18, 10501.

第二章の実験

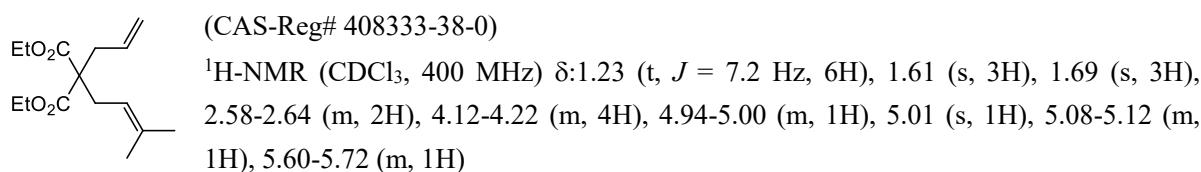
General procedure for hydrocyanative cyclization: EtOH (0.2 M for diene) was added to the mixture of diene (1.0 eq.), Co A (2 mol%), TsCN (1.2 eq.) under an argon atmosphere at rt, then PhSiH₃ (1.2 eq.) was added at rt and the solution was stirred at room temperature. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography.



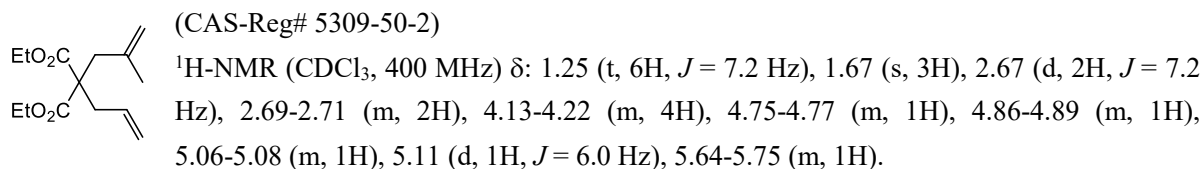
diethyl 2,2-diallylmalonate (61a)



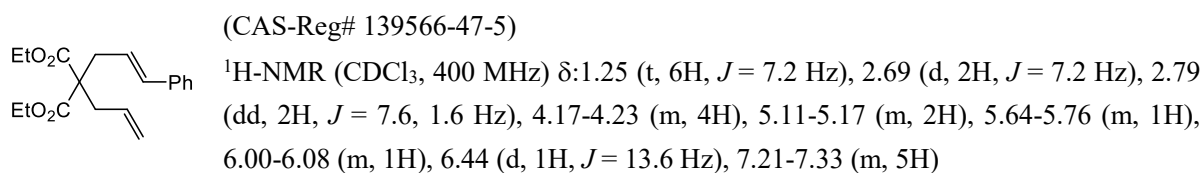
diethyl 2-allyl-2-(3-methylbut-2-en-1-yl)malonate (61b)



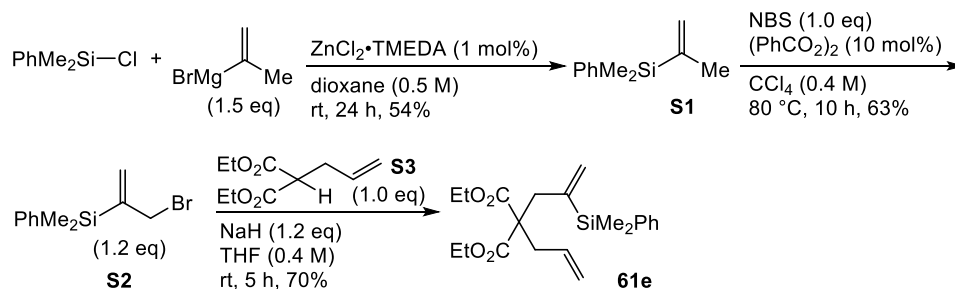
diethyl 2-allyl-2-(2-methylallyl)malonate (61c)



diethyl 2-allyl-2-cinnamylmalonate (61d)



Synthesis of 61e

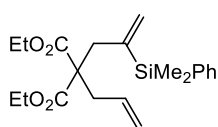


Synthesis of S1¹: ZnCl₂·TMEDA (25.2 mg, 0.1 mmol) was placed in a 50-mL reaction flask under argon. Chlorodimethylphenylsilane (1.66 mL, 10 mmol) in 1,4-dioxane (20 mL) was added to the flask. Then, *p*-methylphenylmagnesium bromide (0.5 M in THF solution, 30 mL, 15 mmol) was added. The mixture was stirred at 20°C for 1 h. A saturated aqueous solution of NH₄Cl was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na₂SO₄ and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded **S1** (947 mg, 54%)

S1 to S2²: **S1** (947 mg, 5.37 mmol) and NBS (672 mg, 3.78 mmol) were refluxed in CCl₄ (9.5 ml) for 10 h with a catalytic quantity of benzoyl peroxide (92 mg, 0.378 mmol). Filtration, evaporation, and chromatography (SiO₂, *n*-hexane) gave **S2** (612 mg, 63%)

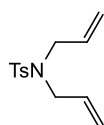
S2 to 61e: To a stirred solution of **S3** (131 mg, 0.65 mmol) in THF (0.6 mL) at 0°C was added NaH (38 mg, 0.78 mmol) slowly, and the reaction mixture was stirred for 30 min. Then **S2** (200 mg, 0.78 mmol) was added at 0 °C, and the solution was warmed up to rt stirred for another 5h. The reaction was quenched with saturated aqueous ammonium chloride, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO₂, *n*-hexane/AcOEt = 4/1) afforded **61e** (170.9 mg, 70%)

diethyl 2-allyl-2-(2-(dimethyl(phenyl)silyl)allyl)malonate (61e)



¹H-NMR (CDCl₃, 400 MHz) δ: 0.37 (s, 6H), 1.20 (t, 6H, *J* = 6.8 Hz), 2.66 (d, 2H, *J* = 7.6 Hz), 2.76 (s, 2H), 4.11 (q, 4H, *J* = 6.8 Hz), 4.95 (s, 1H), 4.97 (d, 1H, *J* = 9.2 Hz), 5.48-5.59 (m, 2H), 5.70 (d, 1H, *J* = 1.6 Hz), 7.31-7.36 (m, 3H), 7.48-7.51 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ: -3.0, 13.9, 35.7, 36.8, 57.3, 61.1, 118.5, 127.7, 128.1, 129.0, 132.6, 133.9, 137.6, 145.0, 171.1; IR (ATR) ν: 2980, 1729, 1217, 817 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₃₀NaO₄Si, [M+Na]⁺ 397.1811, found 397.1814; colorless oil

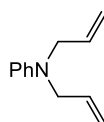
N,N-diallyl-4-methylbenzenesulfonamide (61f)



(CAS-Reg# 50487-72-4)

¹H-NMR (CDCl₃, 400 MHz) δ: 2.39 (s, 3H), 3.77 (d, 4H, *J* = 6.4 Hz), 5.08-5.51 (m, 4H), 5.56 (ddt, 2H, *J* = 16.4 Hz, 10.0 Hz, 6.4 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 8.4 Hz)

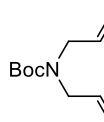
N,N-diallylaniline (61g)



(CAS-Reg# 6247-00-3)

¹H-NMR (CDCl₃, 400 MHz) δ: 3.79 (d, 2H, *J* = 4.8 Hz, 2 H), 5.17-5.33 (m, 2 H), 5.98 (m, 1 H), 6.63-6.65 (m, 2 H), 6.71-6.75 (m, 1 H), 7.18-7.22 (m, 2 H)

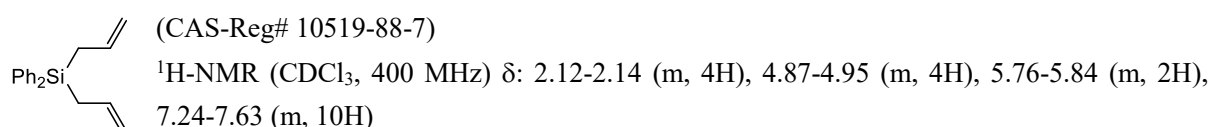
tert-butyl diallylcarbamate (61h)



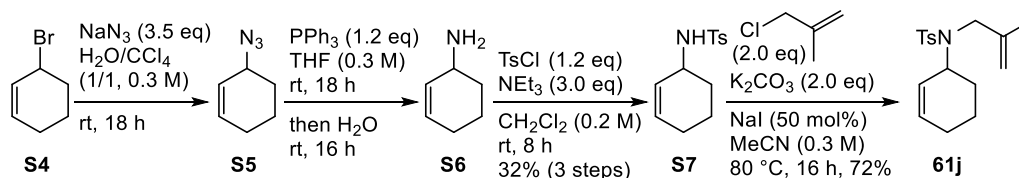
(CAS-Reg# 151259-38-0)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.45 (s, 9H), 3.80 (s, 4H), 5.08-5.13 (m, 4H), 5.70-5.82 (m, 2H)

Diallyldiphenylsilane (61i)



Synthesis of 61j



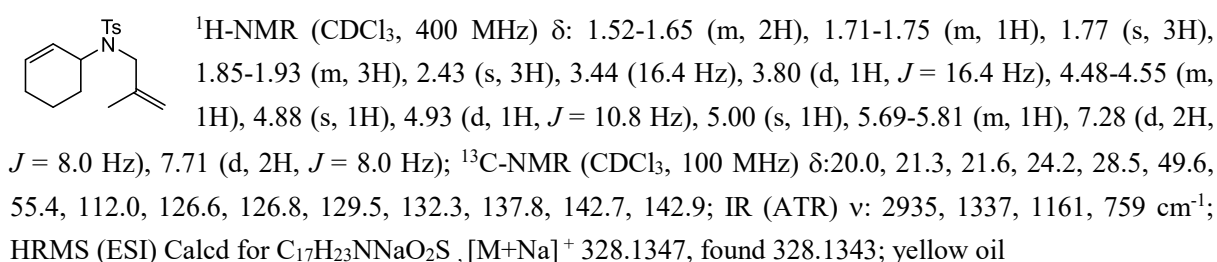
S4 to S5: To a stirred solution of **S4** (1.0 mL, 8.6 mmol) in CCl_4 (15 mL) at rt was added NaN_3 (1.95 g, 30 mmol) in H_2O (15 mL), and the reaction mixture was stirred for 18 h at rt. The reaction mixture was extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo gave crude **S5** which was used in the next step without further purification.

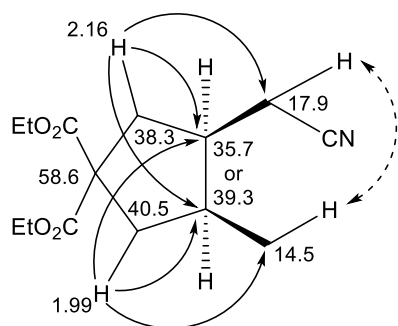
S5 to S6: A mixture of the crude **S5** (approximately 8.6 mmol), PPh_3 (2.7 g, 10.32 mmol), THF (29 mL) was stirred for 16 h. The mixture was extracted with 1 N HCl (3 times). The combined aqueous phases were made basic with NaOH. The aqueous solution was extracted with CH_2Cl_2 . The organic phases were combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield crude **S6** (444 mg) which was used in the next step without further purification.

S6 to S7: To a stirred solution of crude **S6** (444 mg) in CH_2Cl_2 (23 mL) was added NEt_3 (1.9 mL, 13.71 mmol), and TsCl (1.05 g, 5.48 mmol) at 0 °C, and the reaction mixture was stirred for 8 h at rt. The reaction was quenched with 1 N HCl, extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2 , *n*-hexane/ AcOEt = 5/1) afforded **S7** (686 mg, 32%, 3 steps)

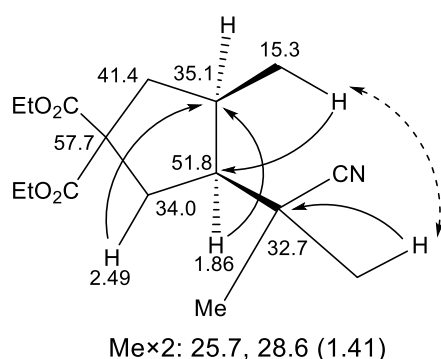
S7 to 61j: A solution of crude **S7** (234 mg), K_2CO_3 (259 mg, 1.88 mmol), 4-chloro-2-methyl-1-butene (0.18 mL, 1.88 mmol), NaI (71 mg, 0.47 mmol) in MeCN (3.1 mL) was stirred for 8 h at 80 °C. The reaction was quenched with aqueous sodium thiosulfate, extracted with AcOEt , dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2 , *n*-hexane/ AcOEt = 10/1) afforded **61j** (219.9 mg, 72%)

N-(cyclohex-2-en-1-yl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (61j)

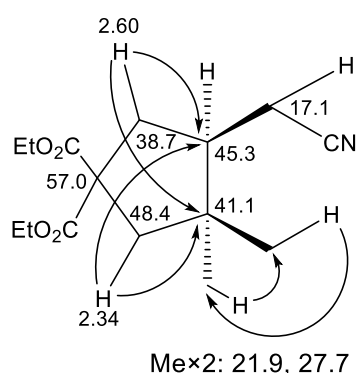


diethyl-3-(cyanomethyl)-4-methylcyclopentane-1,1-dicarboxylate (62a)

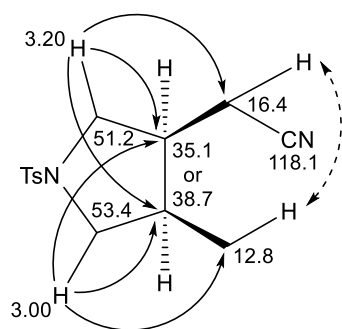
¹H-NMR (CDCl₃, 400 MHz) δ: 0.94 (dd, 3H, *J* = 7.2, 2.4 Hz), 1.25 (t, 6H, *J* = 7.2 Hz), 1.99 (ddd, 1H, *J* = 14.0, 7.2, 2.0 Hz), 2.16 (ddd, 1H, *J* = 14.0, 7.2, 2.0 Hz), 2.25-2.65 (m, 6H), 4.19 (q, 4H, *J* = 7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.9, 14.5, 17.9, 35.7, 38.3, 39.3, 40.5, 58.6, 61.6, 119.1172.1, 172.2; IR (ATR) ν: 2984, 1711, 1360, 1219 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₂₁NNaO₄, [M+Na]⁺ 290.1368, found 290.1372; colorless oil (60.3 mg, 82%).

diethyl-3-(2-cyanopropan-2-yl)-4-methylcyclopentane-1,1-dicarboxylate (62b)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.06 (d, 3H, *J* = 6.8 Hz), 1.24 (t, 3H, *J* = 7.6 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 1.41 (d, 6H, *J* = 4.8 Hz), 1.86 (ddd, 1H, *J* = 13.6, 6.8, 6.8 Hz), 2.24-2.41 (m, 4H), 2.49 (dd, 1H, *J* = 13.6, 6.8 Hz), 4.14-4.26 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.0, 15.3, 25.7, 28.6, 32.7, 34.0, 35.1, 41.4, 51.8, 57.7, 61.6, 124.2, 172.0, 172.9; IR (ATR) ν: 2980, 1728, 1253 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₂₅NNaO₄, [M+Na]⁺ 318.1681, found 318.1684; colorless oil (22.6 mg, 62%).

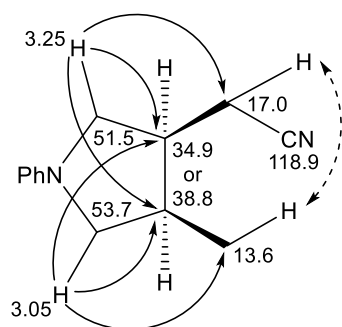
diethyl-4-(cyanomethyl)-3,3-dimethylcyclopentane-1,1-dicarboxylate (62c)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.85 (d, 3H, *J* = 2.0 Hz), 1.10 (d, 3H, *J* = 2.0 Hz), 1.25 (t, 3H, *J* = 7.2 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 1.90-2.08 (m, 1H), 2.12-2.29 (m, 4H), 2.34 (ddd, 1H, *J* = 16.4, 5.6, 2.0 Hz), 2.60 (ddd, 1H, *J* = 13.6, 6.8, 2.0 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 4.19 (q, 2H, *J* = 7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.9, 17.1, 21.9, 27.7, 38.7, 41.1, 45.3, 48.4, 57.0, 61.6, 61.7, 119.0, 172.1, 172.4; IR (ATR) ν: 2981, 1716, 1239 cm⁻¹; HRMS (ESI) Calcd for C₁₅H₂₃NNaO₄, [M+Na]⁺ 304.1525, found 304.1520; colorless oil (24.4 mg, 72%).

2-(4-methyl-1-tosylpyrrolidin-3-yl)acetonitrile (62f)

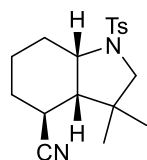
¹H-NMR (CDCl₃, 400 MHz) δ: 0.87 (d, 2.1H, *J* = 6.4 Hz), 0.98 (d, 0.9H, *J* = 6.4 Hz), 1.86-2.48 (m, 7H), 2.85 (dd, 0.3H, *J* = 10.4, 8.0 Hz), 3.00 (dd, 0.7H, *J* = 10.4, 5.6 Hz), 3.06 (dd, 0.3H, *J* = 10.4, 8.0 Hz), 3.20 (dd, 0.7H, *J* = 10.4, 5.6 Hz), 3.41-3.58 (m, 2H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz)* δ: 12.8, (16.2), 16.4, (19.1), 21.5, 35.1, (38.1), 38.7, (41.7), 51.2, (52.0), 53.4, (54.3), 118.1, 127.4, 129.8, 133.4, 143.8; IR (ATR) ν: 2970, 1736, 1345, 1167 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₈N₂NaO₂S, [M+Na]⁺ 301.0987, found 301.0998; yellow oil (35.2 mg, 68%); *() in ¹³C NMR is peak of *trans*-62f

2-4-methyl-1-phenylpyrrolidin-3-yl)acetonitrile (62g)



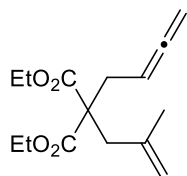
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.05 (dd, 2.1H, $J = 6.8, 1.6$ Hz), 1.16 (d, 0.9H, $J = 4.4$ Hz), 2.10-2.72 (m, 4H), 2.97 (dd, 0.3H, $J = 7.6, 7.6$ Hz), 3.05 (dd, 0.7H, $J = 7.2, 7.2$ Hz), 3.17 (dd, 0.3 H, $J = 7.2, 7.2$ Hz), 3.25 (dd, 0.7H, $J = 8.4, 5.6$ Hz), 3.49 (ddd, 1.4 H, $J = 14.4, 7.2, 7.2$ Hz), 3.58 (ddd, 0.6H, $J = 14.4, 7.2, 7.2$ Hz), 6.52 (d, 2H, $J = 7.6$ Hz), 6.69 (dd, 1H, $J = 7.6, 7.6$ Hz), 7.23 (dd, 2H, $J = 7.6, 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 13.6, (16.8), 17.0, (19.6), 34.9, (38.0), 38.8, (41.8), 51.5, (52.4), 53.7, (54.7), 111.4, 116.0, 118.9, 129.2, 147.2; IR (ATR) ν : 2974, 1736, 1345 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{Na}$, $[\text{M}+\text{Na}]^+$ 223.1211, found 223.1203; yellow oil (28.9 mg, 47%); *() in ^{13}C NMR is peak of *trans*-62g

3,3-dimethyl-1-tosyloctahydro-1H-indole-4-carbonitrile (62j)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.62 (s, 3H), 1.15 (s, 3H), 1.56-1.68 (m, 4H), 1.76 (dd, 1H, $J = 9.6, 6.0$ Hz), 2.05-2.14 (m, 1H), 2.44 (s, 3H), 2.41-2.48 (m, 2H), 3.06 (d, 1H, $J = 10.8$ Hz), 3.27 (d, 1H, $J = 10.8$ Hz), 3.61 (brs, 1H), 7.33 (d, 2H, $J = 7.6$ Hz), 7.68 (d, 2H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.2, 21.5, 23.0, 26.6, 27.1, 27.9, 28.8, 39.6, 49.6, 57.8, 60.2, 122.8, 127.5, 129.7, 133.1, 143.8; IR (ATR) ν : 2938, 1337, 1159, 669 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 355.1456, found 355.1450; colorless solid (30.7 mg, 70%, mp: 115-118 $^\circ\text{C}$).

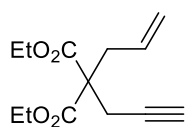
diethyl 2-(buta-2,3-dien-1-yl)-2-(2-methylallyl)malonate (65)



(CAS-Reg# 1320363-33-4)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.26 (t, 6H, $J = 7.6$ Hz), 1.67 (s, 3H), 2.62-2.66 (m, 2H), 2.74 (s, 2H), 4.18 (q, 4H, $J = 7.6$ Hz), 4.63-4.66 (m, 2H), 4.77 (s, 1H), 4.88 (s, 1H), 4.93-5.00 (m, 1H)

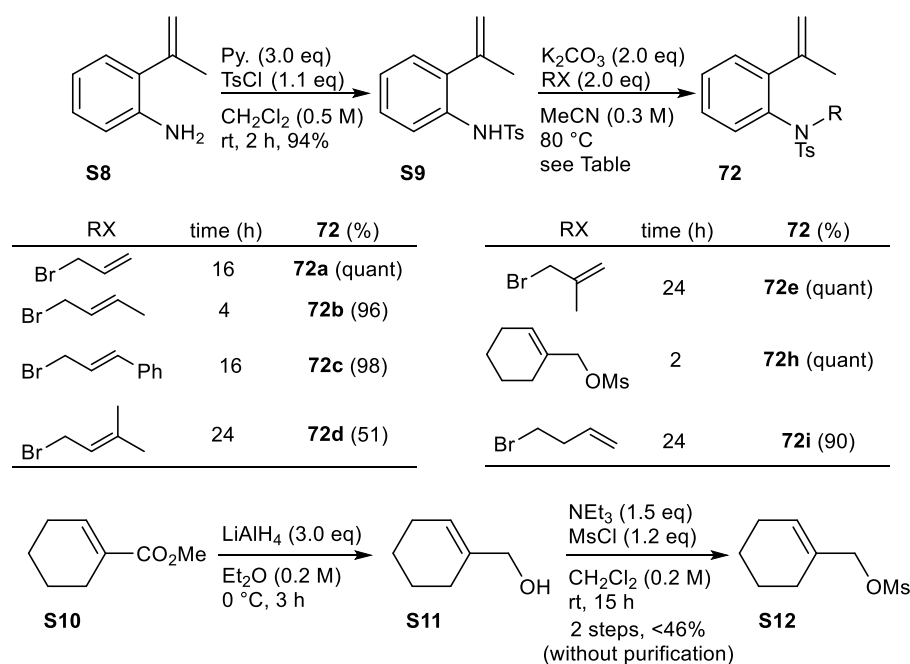
diethyl 2-allyl-2-(prop-2-yn-1-yl)malonate (69)



(CAS-Reg# 101268-55-7)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.26 (t, 6H, $J = 7.2$ Hz), 2.01 (t, 1H, $J = 2.8$ Hz), 2.80 (d, 2H, $J = 2.8$ Hz), 2.81 (d, 1H, $J = 7.6$ Hz), 4.21 (q, 4H, $J = 7.2$ Hz), 5.14 (dq, 1H, $J = 10.8, 1.2$ Hz), 5.19 (dq, 1H, $J = 17.2, 1.2$ Hz), 5.63 (ddt, 1H, $J = 17.2, 10.8, 7.2$ Hz).

Synthesis of 72a-e,h,i



S8 to S9: To a stirred solution of **S8** (2 mL, 14.7 mmol) in CH₂Cl₂ (29 mL) was added pyridine (3.6 mL, 44.1 mmol), and TsCl (3.1 g, 16.2 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at rt. The reaction was quenched with 1 N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO₂, n-hexane/AcOEt = 2/1) afforded **S9** (3.96 g, 94%)

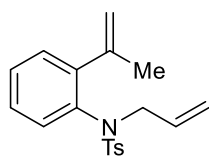
S9 to 72: To a stirred solution of **S9** (1.0 eq.) in MeCN (0.3 M for **S9**) was added K₂CO₃ (2.0 eq.), and RX (2.0 eq.), and the reaction mixture was stirred at 80 °C. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **72**.

S10 to S11: A solution of **S10** (2 mL, 14.7 mmol) was added dropwise to a suspension of LiAlH₄ (1.67 g, 44.1 mmol) in Et₂O (74 mL) at 0 °C under argon atmosphere. After addition, the mixture was warmed to rt, and the mixture was stirred for 3 h. Then, worked up by precipitation with 1.7 mL of water and 1.7 mL of 15% NaOH and 5.1 mL of water at 0 °C, and filtration through celite and washed thoroughly with ethyl acetate. The solvent was reduced under vacuum gave crude **S11** which was used in the next step without further purification.

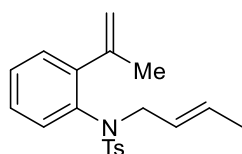
S11 to S12: To a stirred solution of crude **S11** in CH₂Cl₂ (74 mL) was added NEt₃ (3.1 mL, 22.1 mmol), and MsCl (1.4 mL, 17.6 mmol) at 0 °C, and the reaction mixture was stirred for 15 h at rt. The reaction was quenched with 1 N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Crude **S12** (1.3 g) was used in the next step without further purification.

N-allyl-4-methyl-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72a)

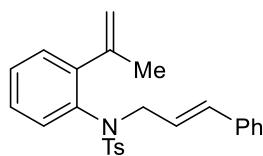
(CAS-Reg# 402822-74-6)



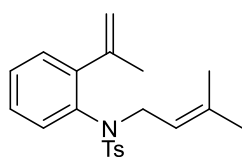
¹H-NMR (CDCl₃, 400 MHz) δ: 2.18 (s, 3H), 2.44 (s, 3H), 4.12 (d, 2H, *J* = 6.8 Hz), 4.94 (dd, 1H, *J* = 11.2, 1.6 Hz), 4.98 (d, 1H, *J* = 3.2 Hz), 5.05 (dd, 1H, *J* = 1.2, 0.8 Hz), 5.22 (dd, 1H, *J* = 1.6, 1.2 Hz), 5.69 (dddd, 1H, *J* = 17.2, 11.2, 6.8, 6.8 Hz), 6.74 (d, 1H, *J* = 8.0 Hz), 7.12 (ddd, 1H, *J* = 7.8, 6.4, 2.4 Hz), 7.27-7.31 (m, 4H), 7.67 (d, 2H, *J* = 8.4 Hz); (675 mg, quant.)

(E)-N-(but-2-en-1-yl)-4-methyl-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72b)

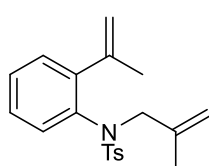
¹H-NMR (CDCl₃, 400 MHz) δ: 1.49 (d, 3H, *J* = 5.6 Hz), 2.17 (s, 3H), 2.43 (s, 3H), 4.05 (brs, 2H), 5.05 (s, 1H), 5.21 (s, 1H), 5.26-5.42 (m, 2H), 6.71 (d, 1H, *J* = 8.4 Hz), 7.11 (dd, 1H, *J* = 7.6, 2.0 Hz), 7.21-7.29 (m, 4H), 7.65 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 17.5, 21.4, 24.1, 24.2, 54.0, 116.3, 125.0, 127.1, 127.9, 128.0, 128.5, 129.3, 129.8, 130.6, 136.4, 136.8, 143.2, 143.6, 144.9; IR (ATR) ν: 2982, 1736, 1237, 1044 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₃NNaO₂S, [M+Na]⁺ 364.1347, found; 364.1360; yellow oil (126.2 mg, 96%).

N-cinnamyl-4-methyl-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72c)

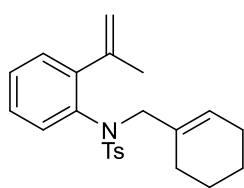
¹H-NMR (CDCl₃, 400 MHz) δ: 2.18 (s, 3H), 2.40 (s, 3H), 4.27 (brs, 2H), 5.05 (s, 1H), 5.23 (s, 1H), 6.05 (dd, 1H, *J* = 16.0, 6.8 Hz), 6.22 (d, 1H, *J* = 16.0 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 7.09-7.36 (m, 10H), 7.68 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.7, 24.5, 54.6, 116.8, 123.9, 126.5, 127.5, 128.0, 128.4, 128.4, 128.6, 128.8, 129.6, 130.3, 134.2, 136.4, 136.8, 137.1, 143.6, 143.9, 145.2; IR (ATR) ν: 2983, 1712, 1239, 1044 cm⁻¹; HRMS (ESI) Calcd for C₂₅H₂₅NNaO₂S, [M+Na]⁺ 426.1504, found 426.1496; yellow solid (157.2 mg, 98%).

4-methyl-N-(3-methylbut-2-en-1-yl)-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72d)

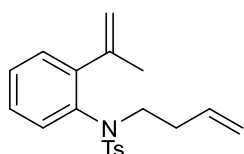
¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (s, 3H), 1.54 (s, 3H), 2.18 (s, 3H), 2.43 (s, 3H), 4.12 (brs, 2H), 5.03 (t, 1H, *J* = 7.2 Hz), 5.06 (s, 1H), 5.22 (s, 1H), 6.74 (d, 1H, *J* = 7.6 Hz), 7.09-7.29 (m, 5H), 7.66 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 17.7, 21.7, 24.3, 25.8, 49.6, 116.5, 118.4, 127.3, 128.2, 128.3, 128.6, 129.5, 130.0, 136.8, 137.1, 137.3, 143.4, 143.9, 145.1; IR (ATR) ν: 2969, 1737, 1347, 756 cm⁻¹; HRMS (ESI) Calcd for C₁₀H₂₅NNaO₂S, [M+Na]⁺ 378.1504, found 378.1515; orange solid (133.7 mg, 51%).

4-methyl-N-(2-methylallyl)-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72e)

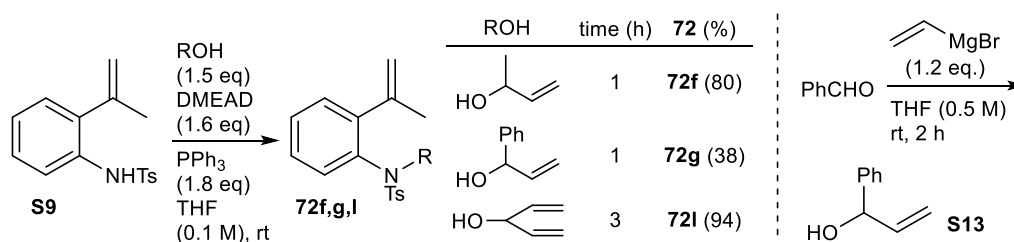
¹H-NMR (CDCl₃, 400 MHz) δ: 1.61 (s, 3H), 2.13 (s, 3H), 2.44 (s, 3H), 4.05 (s, 2H), 4.55 (brs, 1H), 4.68 (brs, 1H), 5.07 (brs, 1H), 5.21 (brs, 1H), 6.88 (d, 1H, *J* = 8.4 Hz), 7.12-7.17 (m, 1H), 7.22-7.26 (m, 2H), 7.29 (d, 2H, *J* = 7.6 Hz), 7.69 (d, 2H, *J* = 7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 20.6, 21.5, 24.4, 58.0, 116.0, 116.8, 127.2, 127.9, 128.1, 128.6, 129.4, 130.0, 136.9, 137.2, 140.1, 143.1, 143.4, 144.5; IR (ATR) ν: 2983, 1737, 1239, 1045, 758 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₃NNaO₂S, [M+Na]⁺ 364.1347, found 364.1355; colorless solid (305.8 mg, quant.).

N-(cyclohex-1-en-1-ylmethyl)-4-methyl-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72h)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.88 (t, 1H, *J* = 6.8 Hz), 1.23-1.33 (m, 1H), 1.43 (brs, 3H), 1.81 (brs, 3H), 2.16 (s, 3H), 2.43 (s, 3H), 3.98 (brs, 2H), 5.06 (s, 1H), 5.21 (s, 1H), 5.30 (brs, 1H), 6.84 (d, 1H, *J* = 8.0 Hz), 7.10-7.29 (m, 5H), 7.68 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.4, 21.7, 22.2, 24.4, 25.0, 26.7, 58.7, 116.6, 127.1, 127.8, 128.1, 128.6, 129.2, 129.9, 132.6, 137.3, 137.4, 143.1, 143.3, 144.5; IR (ATR) ν: 2968, 2147, 1364, 1216 cm⁻¹; HRMS (ESI) Calcd for C₂₃H₂₇NNaO₂S, [M+Na]⁺ 404.1660, found 404.1648; colorless solid (354 mg, quant.).

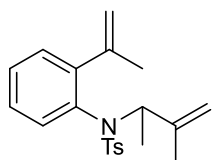
N-(but-3-en-1-yl)-4-methyl-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72i)

(CAS-Reg# 402822-86-0)
¹H-NMR (CDCl₃, 400 MHz) δ: 2.08 (br, 2H), 2.18 (s, 3H), 2.44 (s, 3H), 3.53 (br, 2H), 4.91-4.96 (m, 2H), 5.05 (s, 1H), 5.22 (s, 1H), 5.54-5.64 (m, 1H), 6.80 (d, 1H, *J* = 7.6 Hz), 7.16 (dd, 1H, *J* = 8.0, 2.8 Hz), 7.27-7.31 (m, 4H), 7.66 (d, 2H, *J* = 8.4 Hz); (354 mg, 90%)

Synthesis of 72f,g,l

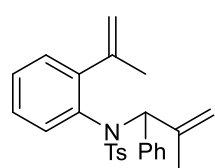
S9 to 72f,g,l: To a stirred solution of **S9** (1.0 eq.), ROH (1.5 eq.), PPh₃ (1.8 eq.) in THF (0.1 M for **S9**) was added DMEAD (1.6 eq.) at 0 °C, and the reaction mixture was stirred for 1-3 h at rt. Then, the reaction mixture was concentrated in vacuo. Purification by flash column chromatography gave **72f,g,l**.

PhCHO to S13: To a stirred solution of vinyl magnesium bromide (6.0 mL, 1.0 M in THF, 6.0 mmol) in THF (10 mL) was added PhCHO (0.51 mL, 5.0 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at rt. The reaction was quenched with sat. NH₄Cl aq., extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude **S13** (1.1 g) was used in the next step without further purification.

4-methyl-N-(3-methylbut-3-en-2-yl)-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72f)

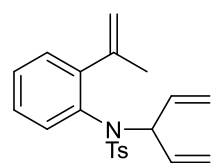
¹H-NMR (CDCl₃, 400 MHz) δ: 1.22 (d, 3H, *J* = 7.2 Hz), 2.16 (s, 3H), 2.43 (s, 3H), 4.54-4.74 (m, 1H), 4.85-5.05 (m, 2H), 5.22-5.49 (m, 3H), 6.79 (d, 1H, *J* = 7.6 Hz), 7.13-7.30 (m, 5H), 7.74 (dd, 2H, *J* = 8.0, 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 17.5, 19.6, 21.5, 24.2, 24.9, 54.0, 58.6, 58.9, 115.2, 116.4, 116.6, 117.7, 115.0, 126.7, 127.1, 128.0, 128.1, 128.4, 128.5, 129.2, 129.4, 129.9, 130.2, 130.6, 130.9, 131.4, 133.8, 136.4, 136.8, 137.2, 138.1, 139.0, 143.2, 143.6, 146.1; IR (ATR) ν: 2970, 1712, 1340, 1159 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₃NNaO₂S, [M+Na]⁺ 364.1347, found 364.1345; yellow solid (142 mg, 80%).

4-methyl-N-(2-methyl-1-phenylallyl)-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72g)



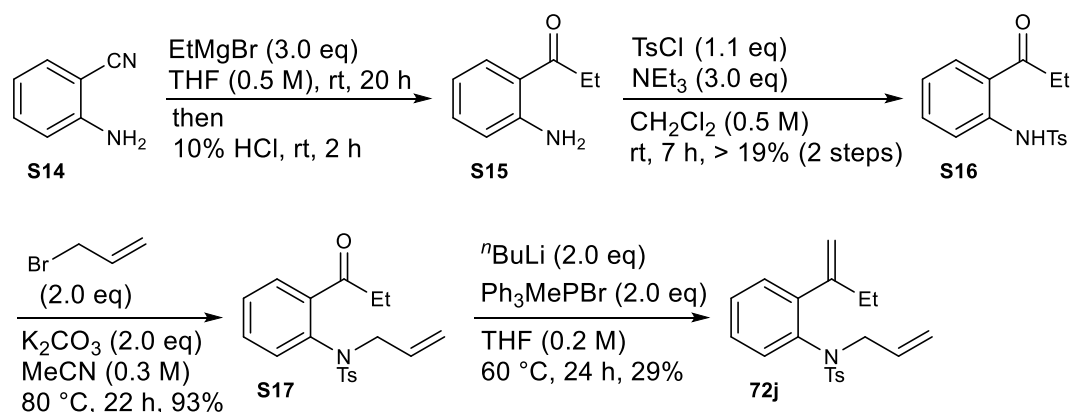
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.18 (s, 3H), 2.42 (s, 3H), 4.28 (brs, 1H), 5.05 (s, 1H), 5.23 (s, 1H), 6.02 (ddd, 1H, $J = 15.6, 7.6, 6.8$ Hz), 6.23 (d, 1H, $J = 15.6$ Hz), 6.77 (d, 1H, $J = 8.4$ Hz), 7.10-7.29 (m, 11H), 7.69 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 24.3, 54.4, 116.6, 123.6, 126.3, 126.6, 127.3, 127.7, 128.0, 128.2, 128.4, 128.5, 129.1, 129.2, 129.4, 130.0, 134.0, 136.2, 136.6, 136.8, 143.4, 143.7, 145.0; IR (ATR) ν : 2982, 1735, 1235, 1043 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{25}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 426.1504, found 426.1496; yellow oil (80 mg, 38%).

4-methyl-N-(penta-1,4-dien-3-yl)-N-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (72l)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.17 (s, 3H), 2.45 (s, 3H), 4.09-4.21 (m, 1H), 4.92-5.10 (m, 4H), 5.21-5.29 (m, 1.5H), 5.49-5.71 (m, 1H), 5.88-6.04 (m, 1H), 6.09-6.19 (m, 0.5H), 6.73 (d, 1H, $J = 8.4$ Hz), 7.11-7.31 (m, 5H), 7.68 (dd, 2H, $J = 8.4, 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 24.3, 24.9, 53.9, 66.8, 116.6, 117.6, 118.0, 118.4, 126.8, 127.3, 127.5, 128.2, 128.6, 129.2, 129.4, 130.0, 130.1, 131.3, 134.8, 135.8, 136.3, 136.5, 136.8, 137.9, 143.3, 143.4, 143.6, 144.9, 145.8; IR (ATR) ν : 2983, 1736, 1372, 1234, 1043 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{23}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 376.1347, found 376.1346; yellow solid (399.1 mg, 94%).

Synthesis of 72j



S14 to S15: Ethylmagnesium bromide (10 mL, 3.0 M in Et_2O , 30 mmol) was added to a solution of **S14** (1.18 g, 10 mmol) in THF (20 mL) at 0 °C. Then the reaction was allowed to warm to ambient temperature and allowed to stir at this temperature for 20 h. The reaction was quenched by slow addition of 10% HCl and made basic by the addition of NaOH at 0 °C. The organic layer was separated and the remaining aqueous layer was extracted with AcOEt for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude **S15** (1.68 g) was used in the next step without further purification.

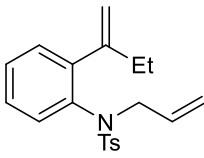
S15 to S16: To a stirred solution of crude **S15** (1.68 g) in CH_2Cl_2 (20 mL) was added NEt_3 (4.2 mL, 30 mmol), and TsCl (1.9 g, 10 mmol) at 0 °C, and the reaction mixture was stirred for 7 h at rt. The reaction was quenched with 1 N HCl, extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in

vacuo. Purification by flash column chromatography (SiO₂, n-hexane/AcOEt = 4/1) afforded **S16** (573 mg, 19%, 2 steps)

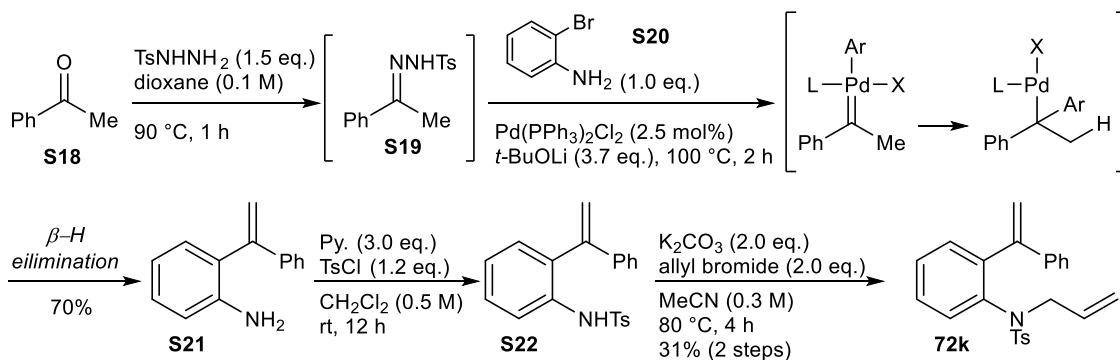
S16 to S17: To a stirred solution of **S16** (150 mg, 0.49 mmol) in MeCN (1.6 mL) was added K₂CO₃ (136 mg, 0.99 mmol), and allyl bromide (0.08 mL, 0.99 mmol), and the reaction mixture was stirred at 80 °C for 22 h. The reaction was quenched with 1N HCl, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S17** (158 mg, 93%).

S17 to 72j: To a stirred solution of Ph₃PMeBr (357 mg, 1.0 mmol) in THF (2.5 mL) was added *n*-BuLi (0.63 mL, 1.6 M in hexane, 1.0 mmol) at 0 °C, and the reaction mixture was stirred at rt for 1 h. Then, **S17** (158 mg, 0.46 mmol) in THF (1.0 mL) was added at 0 °C, and the reaction mixture was stirred at 60 °C for 24 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **72j** (45.6 mg, 29%).

N-allyl-N-(2-(but-1-en-2-yl)phenyl)-4-methylbenzenesulfonamide (**72j**)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 1.07 (t, 3H, *J* = 7.2 Hz), 2.45 (s, 3H), 2.50 (q, 2H, *J* = 7.2 Hz), 4.11 (d, 2H, *J* = 6.8 Hz), 4.92-4.98 (m, 2H), 5.04 (s, 1H), 5.21 (d, 1H, *J* = 6.0 Hz), 5.66 (ddd, 1H, *J* = 16.8, 10.4, 6.8 Hz), 6.79 (d, 1H, *J* = 8.0 Hz), 7.14 (ddd, 1H, *J* = 7.6, 7.6, 2.0 Hz), 7.20-7.27 (m, 2H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 12.5, 21.5, 29.7, 54.6, 114.2, 119.1, 127.2, 128.0, 128.2, 128.8, 129.5, 130.7, 132.6, 136.5, 137.1, 143.4, 144.6, 149.8; IR (ATR) ν: 2965, 1349, 1165, 1091 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₃NNaO₂S, [M+Na]⁺ 364.1347, found 364.1356; yellow oil

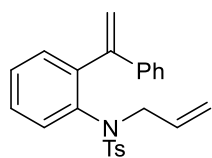
Synthesis of **72k**



S18 to S21³: A well stirred mixture of **S18** (0.51 mL, 4.4 mmol), TsNHNH₂ (819 mg, 4.4 mmol), in dioxane (33 mL) was heated at 90 °C for 2 h gave intermediate **S19**. To this reaction mixture was added **S20** (500 mg, 2.9 mmol), Pd(PPh₃)₂Cl₂ (50.8 mg, 0.073 mmol), *t*-BuOLi (859 mg, 10.7 mmol) under argon atmosphere at 100 °C and the reaction was further stirred at 100 °C for 2 h (monitored by TLC). Then, the reaction mixture was cooled to room temperature and diluted with EtOAc and passed through a short Celite pad; the solvent was evaporated under reduced pressure, and purified on a silica gel column to obtain the product **S21** as an orange solid (397 mg, 70%).

S21 to S22: Same as **S8 to S9** // **S22 to 72k:** **S9 to 72**

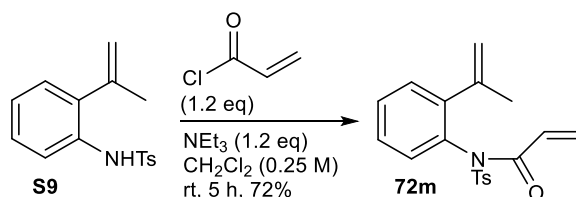
N-allyl-4-methyl-N-(2-(1-phenylvinyl)phenyl)benzenesulfonamide (72k)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.41 (s, 3H), 3.69 (brs, 2H), 4.75 (d, 1H, $J = 16.0$ Hz), 4.82 (d, 1H, $J = 9.2$ Hz), 5.28-5.34 (m, 1H), 5.39 (s, 1H), 5.73 (s, 1H), 6.95 (d, 1H, $J = 8.0$ Hz), 7.22-7.33 (m, 10H), 7.52 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 53.9, 117.4, 118.7, 127.1, 127.5, 127.9, 128.1, 129.3, 129.7, 131.9, 132.8,

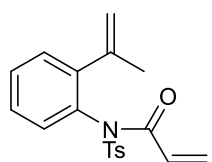
136.8, 137.6, 141.2, 142.8, 143.3, 146.7; IR (ATR) ν : 2984, 1735, 1712, 1240, 1044 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{23}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 412.1347, found 412.1339; colorless solid (82.6 mg, 31%, 2 steps).

Synthesis of 72m



To a stirred solution of crude **S9** (150 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was added NEt_3 (0.1 mL, 0.71 mmol), and acryloyl chloride (0.1 mL, 1.22 mmol) at 0°C , and the reaction mixture was stirred for 5 h at rt. The reaction was quenched with 1 N HCl, extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2 , n -hexane/AcOEt = 4/1) afforded **72m** (163.7 mg, 92%)

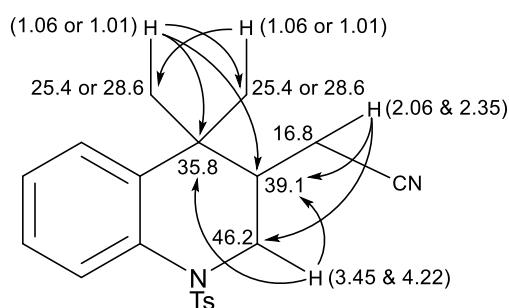
N-(2-(prop-1-en-2-yl)phenyl)-N-tosylacrylamide (72m)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.13 (s, 3H), 2.44 (s, 3H), 5.04 (s, 1H), 5.30 (s, 1H), 5.58 (dd, 1H, $J = 10.4, 1.6$ Hz), 5.83 (dd, 1H, $J = 16.4, 10.4$ Hz), 6.38 (dd, 1H, $J = 16.4, 1.6$ Hz), 7.06 (7.6 Hz), 7.32-7.49 (m, 5H), 7.99 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.6, 23.9, 117.8, 128.0, 128.2, 129.2, 129.5, 130.0, 131.5,

132.8, 136.2, 141.9, 144.8, 164.6; IR (ATR) ν : 2970, 1689, 1358, 1159, 768 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{NNaO}_3\text{S}$, $[\text{M}+\text{Na}]^+$ 364.0983, found 364.0997; yellow oil

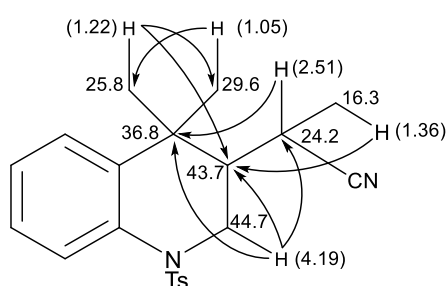
2-(2,4,4-trimethyl-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (73a)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.01 (s, 3H), 1.06 (s, 3H), 1.60-1.72 (m, 1H), 2.06 (dd, 1H, $J = 16.8, 10.0$ Hz), 2.35 (dd, 1H, $J = 16.8, 4.8$ Hz), 2.39 (s, 3H), 3.45 (dd, 1H, $J = 14.0, 10.4$ Hz), 4.22 (dd, 1H, $J = 14.0, 3.6$ Hz), 7.13-7.26 (m, 5H), 7.53 (d, 2H, $J = 8.8$ Hz), 7.83 (d, 1H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 16.8, 21.5, 25.4, 28.6, 35.8, 39.1, 46.2, 118.3, 124.1, 125.3, 126.8, 127.1, 127.2, 129.8, 134.8, 136.2, 136.5, 144.1; IR (ATR) ν : 3000, 1709, 1357,

1219 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 377.1300, found 377.1297; yellow solid (31.1 mg, 71%).

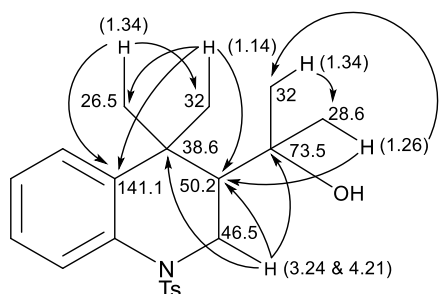
2-(4,4-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)propanenitrile (73b)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.05 (s, 3H), 1.22 (s, 3H), 1.34 (d, 3H, $J = 7.2$ Hz), 1.60-1.66 (m, 1H), 2.38 (s, 3H), 2.51 (q, 1H, $J = 7.2$ Hz), 3.26 (dd, 1H, $J = 14.0, 10.0$ Hz), 4.19 (dd, 1H, $J = 14.0, 3.6$ Hz), 7.14-7.30 (m, 5H), 7.46 (dd, 2H, $J = 8.0, 2.8$ Hz), 7.84 (dd, 1H, $J = 8.0, 1.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ :

16.3, 18.9, 23.2, 24.2, 25.8, 26.0, 28.1, 29.6, 36.8, 37.0, 43.7, 43.8, 44.6, 44.7, 120.7, 122.8, 124.2, 124.7, 125.6, 125.7, 126.7, 126.7, 127.2, 127.2, 127.5, 129.6, 129.7, 135.0, 136.1, 136.8, 137.9, 138.1, 144.0, 144.1; IR (ATR) ν : 2984, 1716, 1344, 1213 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 391.1456, found 391.1469; yellow oil (31.7 mg, 90%).

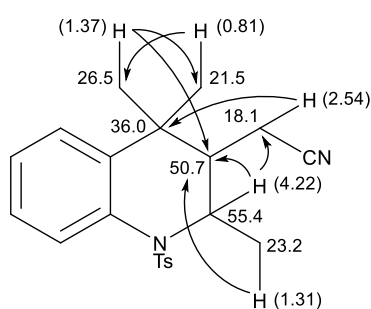
2-(4,4-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-ol (74d)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.14 (s, 3H), 1.26 (s, 3H), 1.34 (s, 6H), 1.54 (dd, 1H, $J = 10.8, 2.8$ Hz), 2.37 (s, 3H), 3.24 (dd, 1H, $J = 14.0, 10.8$ Hz), 4.21 (dd, 1H, $J = 14.0, 2.8$ Hz), 7.12-7.20 (m, 4H), 7.30 (dd, 1H, $J = 8.0, 2.8$ Hz), 7.45 (d, 2H, $J = 8.0$ Hz), 7.78 (d, 1H, $J = 8.0, 2.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 26.5, 28.6, 32.0, 32.1, 38.6, 46.5, 50.2, 73.5, 124.0, 125.3, 126.1, 127.3, 127.6, 129.4, 135.7, 137.2, 141.1, 143.6; IR (ATR) ν :

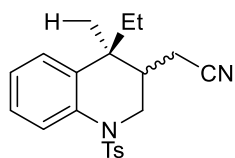
3541, 2970, 1342, 1157 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 405.1613, found 405.1602; yellow oil (9.2 mg, 20%).

2-(2,4,4-trimethyl-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (73f)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.81 (s, 3H), 1.31 (d, 3H, $J = 6.0$ Hz), 1.37 (s, 3H), 1.68 (dt, 1H, $J = 6.4, 6.4$ Hz), 2.39 (s, 3H), 2.54 (dd, 2H, $J = 11.6$ Hz, 6.4 Hz), 4.22 (dq, 1H, $J = 6.4, 6.0$ Hz), 7.13-7.25 (m, 5H), 7.61 (d, 1H, $J = 7.6$ Hz), 7.68 (d, 2H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.1, 21.5, 21.5, 23.2, 26.5, 36.0, 50.7, 55.4, 118.9, 124.1, 124.9, 125.6, 127.1, 127.3, 129.7, 134.7, 137.4, 140.5, 143.8; IR (ATR) ν : 2969, 1710, 1358, 1219, 1162 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 391.1456, found 391.1446; brown oil (9.3 mg, 25%).

2-((4S)-4-ethyl-4-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (73j)

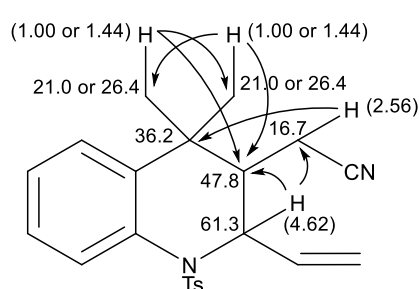


$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.05 (t, 2.3H, $J = 8.0$ Hz), 0.60 (t, 3H, $J = 7.6$ Hz), 0.98 (s, 3H), 1.03 (s, 2.3H), 1.20-1.39 (m, 2+1.5H), 1.53-1.67 (m, 2+1.5H), 2.36 (s, 2.3H), 2.38 (s, 3H), 3.43 (dd, 0.8H, $J = 14.0, 9.6$ Hz), 3.65 (dd, 1H, $J = 14.0, 9.6$ Hz), 4.09 (dd, 1H, $J = 13.6, 4.4$ Hz), 4.34 (dd, 0.8H, $J = 14.0, 3.2$ Hz),

7.10-7.24 (m, 5+3.8H), 7.54 (d, 2H, $J = 8.0$ Hz), 7.59 (d, 1.5H, $J = 8.4$ Hz), 7.88 (d, 1H, $J = 8.0$ Hz), 7.94 (d, 0.8H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 7.6, 9.1, 16.4, 16.6, 21.5, 25.5, 25.8, 28.8, 31.0, 33.8, 38.3, 39.1, 39.7, 45.9, 46.9, 118.4, 123.7, 124.5, 124.7, 125.4, 126.4, 126.8, 127.0, 127.1, 127.4, 129.7, 129.9, 135.3, 136.2, 144.0; IR (ATR) ν : 2682, 1721, 1366, 1238 cm^{-1} ; HRMS (ESI) Calcd for

C₂₁H₂₄N₂NaO₂S, [M+Na]⁺ 391.1456, found 391.1469; yellow oil (11.4 mg, 58%).

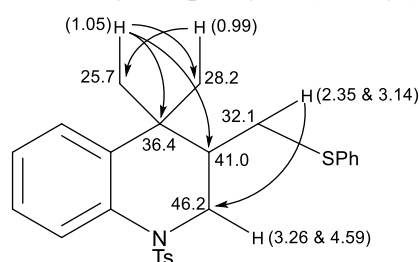
2-(4,4-dimethyl-1-tosyl-2-vinyl-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (73l)



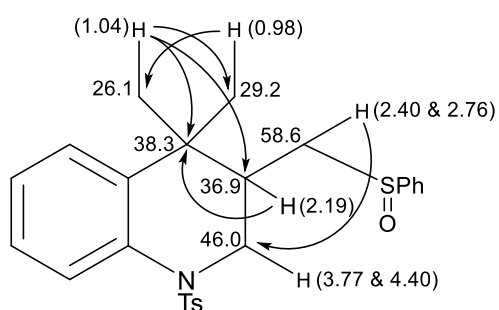
Synthesis of 79d and 80d

EtOH was added to the mixture of **72a** (40.8 mg, 0.13 mmol), Co A (1.5 mg, 0.003 mmol), PhSO₂SPh (38 mg, 0.15 mmol) under an argon atmosphere at rt, then PhSiH₃ (18 μ l) was added at rt and the solution was stirred at room temperature for 16 h. Then, the solvent was removed under reduced pressure gave crude **79d** (30.6 mg) and **80d** (13.0 mg).

4,4-dimethyl-3-((phenylthio)methyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (79d)

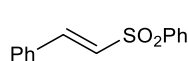


4,4-dimethyl-3-((phenylsulfinyl)methyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (80d)



(E)-2-(phenylsulfonyl)vinylbenzene⁴

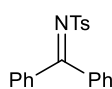
(CAS-Reg# 16212-06-9)



I_2 (3.3 g, 13.11 mmol) was added to a suspension mixture of styrene (1.0 mL, 8.74 mmol), $PhSO_2Na$ (4.3 g, 26.22 mmol), and $NaOAc$ (1.1 g, 13.11 mmol) in MeCN (35 mL) and the reaction mixture was vigorously stirred at refluxing temperature for 12 h. Upon completion of the reaction, the reaction mixture was quenched by the addition of saturated aqueous sodium thiosulfate ($Na_2S_2O_3$) and basified with saturated aqueous sodium hydrogen carbonate ($NaHCO_3$). Further stirring was followed by extraction with ethyl acetate. The combined organic extracts were washed with water and brine, dried (anhydrous Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel) to furnish the analytically pure product, (E)-2-(Phenylsulfonyl)vinylbenzene as a white solid (1.94 g, 91%); 1H -NMR ($CDCl_3$, 400 MHz) δ : 6.89 (d, 1H, $J = 15.4$ Hz), 7.40-7.65 (m, 8H), 7.71 (d, 1H, $J = 15.4$ Hz), 7.98 (d, 2H, $J = 8.4$ Hz)

N-(diphenylmethylene)-4-methylbenzenesulfonamide⁵

(CAS-Reg# 10399-00-5)



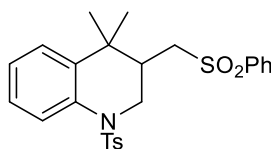
$TsNH_2$ (1.03 g, 6.0 mmol) and benzophenone (1.09 g, 6.0 mmol) were dissolved in dichloroethane (20 mL) and $TiCl_4$ (3.0 mL, 1.0 M in CH_2Cl_2 , 3.0 mmol) was added with stirring, followed by dropwise addition of NEt_3 (1.7 mL, 12.0 mmol), and the reaction mixture was heated at reflux for 3-5 h. The reaction was quenched with H_2O , extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded N-(diphenylmethylene)-4-methylbenzenesulfonamide (1.31 g, 65%); 1H -NMR ($CDCl_3$, 400 MHz) δ : 2.43 (s, 3H), 7.25-7.83 (m, 14H).

Se-phenyl 4-methylbenzenesulfonoselenoate

(CAS-Reg# 68819-94-3)

$Ts-SePh$ To a stirred solution of $PhSeSePh$ (1.98 g, 6.34 mmol) and $TsNa \cdot 4H_2O$ (6.35 g, 25.37 mmol) in CH_2Cl_2 (50 mL) was added $PhI(OCOFCF_3)_2$ (3.0 g, 6.98 mmol) at 0 °C, and the reaction mixture was stirred for 13 h at rt. The reaction was quenched with H_2O , extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2 , n-hexane/ $AcOEt = 15/1$) afforded Se-phenyl 4-methylbenzenesulfonoselenoate (3.34 g, 85%); 1H -NMR ($CDCl_3$, 400 MHz) δ : 2.41 (s, 3H), 7.18 (d, 2H, $J = 8.0$ Hz), 7.31-7.52 (m, 7H)

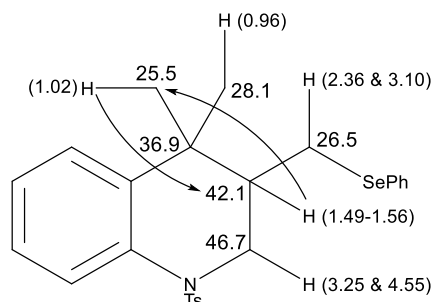
4,4-dimethyl-3-((phenylsulfonyl)methyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (81)



EtOH was added to the mixture of **72a** (61 mg, 0.19 mmol), Co A (2.3 mg, 0.004 mmol), $PhSO_2SPh$ (55.8 mg, 0.22 mmol) under an argon atmosphere at rt, then $PhSiH_3$ (27.4 μ l) was added at rt and the solution was stirred at room temperature for 3 h. Then, the solvent was removed under reduced pressure gave crude mixture of **79d** and **80d**. Then, to the solution of crude mixture in CH_2Cl_2 (1.9 mL), *m*CPBA (208 mg, 0.93 mmol) was added at 0 °C, and the mixture was stirred at rt for 2 h. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography gave **81** (52.4 mg, 60%, 2 steps); 1H -NMR ($CDCl_3$, 600 MHz) δ : 0.90 (s, 3H), 1.00 (s, 3H), 2.25 (ddd, 1H, $J = 9.6, 9.6, 3.6$ Hz), 2.38 (s, 3H), 2.81 (dd, 1H, $J = 14.4, 9.6$ Hz), 3.00 (d, 1H, $J = 14.4$ Hz), 3.42 (dd, 1H, $J = 13.8,$

9.6 Hz), 4.52 (dd, 1H, $J = 13.8, 3.6$ Hz), 7.08 (dd, 1H, $J = 7.8, 7.8$ Hz), 7.16 (d, 1H, $J = 7.8$ Hz), 7.18 (d, 1H, $J = 7.2$ Hz), 7.23 (d, 2H, $J = 7.2$ Hz), 7.58-7.69 (m, 5H), 7.82 (d, 1H, $J = 8.4$ Hz), 7.97 (d, 2H, $J = 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 26.0, 27.8, 35.9, 36.9, 46.4, 55.0, 123.5, 124.9, 126.7, 127.1, 127.5, 128.0, 129.4, 129.6, 133.9, 134.9, 136.2, 136.6, 139.3, 143.8; IR (ATR) ν : 1349, 1308, 1166, 1089 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{27}\text{NNaO}_4\text{S}_2$, $[\text{M}+\text{Na}]^+$ 492.1279, found 492.1283; yellow solid

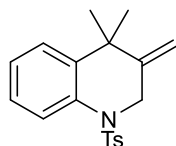
(79e)



EtOH was added to the mixture of **72a** (98.4 mg, 0.3 mmol), Co **A** (3.6 mg, 0.006 mmol), TsSePh (76.6 mg, 0.25 mmol) under an argon atmosphere at rt, then PhSiH_3 (30 μl) was added at rt and the solution was stirred at rt for 16 h. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography gave **79e** (88.2 mg, 61%).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.93 (s, 3H), 0.99 (s, 3H), 1.49-1.56 (m, 1H), 2.28 (s, 3H), 2.36 (dd, 1H, $J = 12.0, 12.0$ Hz), 3.10 (d, 1H, $J = 12.0$ Hz), 3.25 (dd, 1H, $J = 13.6, 11.6$ Hz), 4.55 (dd, 1H, $J = 13.6, 3.2$ Hz), 6.96 (d, 2H, $J = 7.6$ Hz), 7.10-7.45 (m, 10H), 7.86 (d, 1H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.4, 25.5, 26.5, 28.1, 36.9, 42.1, 46.7, 124.2, 125.1, 126.4, 126.8, 127.2, 127.2, 129.2, 129.3, 130.7, 131.7, 135.4, 136.4, 138.3, 143.3; IR (ATR) ν : 2771, 1349, 1165 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{27}\text{NNaO}_2\text{SSe}$, $[\text{M}+\text{Na}]^+$ 508.0825, found 508.0830; colorless solid; mp: 112-115 $^\circ\text{C}$

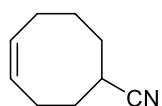
4,4-dimethyl-3-methylene-1-tosyl-1,2,3,4-tetrahydroquinoline (82)



EtOH was added to the mixture of **72a** (53.6 mg, 0.16 mmol), Co **A** (5.0 mg, 0.008 mmol), TsSePh (76.6 mg, 0.25 mmol) under an argon atmosphere at rt, then PhSiH_3 (30 μl) was added at rt and the solution was stirred at room temperature for 16 h. Then, the solvent was removed under reduced pressure gave crude **79e**. Then, to the solution of crude **79e** in THF (7.5 mL), H_2O_2 (0.75 mL) was added at rt, and the mixture was stirred at 60 $^\circ\text{C}$ for 24 h. Then, aq. sodium thiosulfate the solvent was added to the mixture, extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2 , n-hexane/AcOEt = 4/1) afforded **79e** (27.9 mg, 52%)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.00 (s, 6H), 2.31 (s, 3H), 4.34 (s, 2H), 4.77 (s, 1H), 4.94 (s, 1H), 7.05 (d, 2H, $J = 8.4$ Hz), 7.18-7.28 (m, 5H), 7.81 (dd, 1H, $J = 6.8, 2.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.4, 30.9, 38.6, 51.5, 111.0, 126.2, 126.3, 126.3, 127.3, 128.1, 128.7, 135.7, 135.8, 140.0, 143.2, 146.3; IR (ATR) ν : 2969, 1711, 1349, 1219, 1161, 669 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 350.1191, found 350.1199; colorless solid.

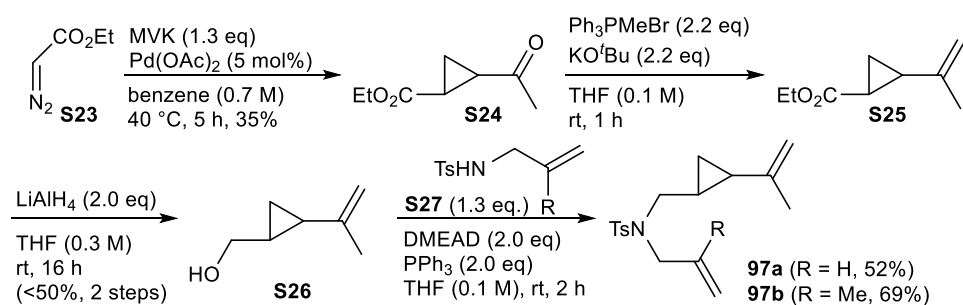
(Z)-cyclooct-4-ene-1-carbonitrile (96)



(CAS-Reg# 112654-91-8)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.51 (m, 1H), 1.85 (m, 4H), 1.97 (m, 1H), 2.14 (m, 2H), 2.24 (m, 1H), 2.39 (m, 1H), 2.77 (m, 1H), 5.69 (m, 2H); (36.6 mg, 33%)

Synthesis of 97a,b



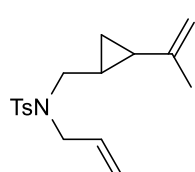
S23 to S24: To a stirred solution of MVK (10.1 mL, 123.1 mmol), Pd(OAc)₂ (500 mg, 2.23 mmol) in benzene (50 mL) was added **S23** (5 mL, 47.3 mmol) in benzene (40 mL) at 40 °C using dropping funnel over 1 h. Then, Pd(OAc)₂ (500 mg, 2.23 mmol) was added and the solution of **S23** (5 mL, 47.3 mmol) in benzene (40 mL) was added at 40 °C using dropping funnel over 1 h. The reaction mixture was stirred for 5 h at 40 °C, and the reaction was quenched with sat. Na₂CO₃, extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO₂, n-hexane/AcOEt = 10/1) afforded **S24** as a yellow oil (5.21 g, 35%).

S24 to S25: To a stirred solution of Ph₃PMeBr (5.5 g, 15.4 mmol) in THF (46 mL) was added *t*-BuOK (1.73 g, 15.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Then, **S24** (1.0 g, 6.4 mmol) in THF (18 mL) was added at 0 °C, and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with H₂O, extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated in vacuo at 0 °C. Purification by flash column chromatography (Et₂O : pentane = 1 : 4) afforded crude **S25** (925 mg) as a colorless liquid.

S25 to S26: LiAlH₄ (456 mg, 12 mmol) was added to a solution of crude **S25** (925 mg) in Et₂O (20 mL) at 0 °C under argon atmosphere. After addition, the mixture was warmed to rt, and the mixture was stirred for 16 h. Then, worked up by precipitation with 0.5 mL of water and 0.5 mL of 15% NaOH and 1.5 mL of water at 0 °C, and filtration through celite and washed thoroughly with Et₂O. The solvent was reduced under vacuum at 0 °C. Purification by flash column chromatography (Et₂O) afforded crude **S26** (362 mg) as a yellow oil.

S26 to 97: To a stirred solution of **S26** (1.0 eq.), **S27** (1.3 eq.), PPh₃ (2.0 eq.) in THF (0.1 M for **S26**) was added DMEAD (2.0 eq.) at 0 °C, and the reaction mixture was stirred for 2 h at rt. Then, the reaction mixture was concentrated in vacuo. Purification by flash column chromatography (hexane/AcOEt = 20/1) gave **97**.

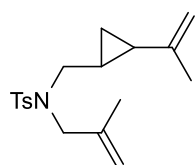
N-allyl-4-methyl-N-((2-(prop-1-en-2-yl)cyclopropyl)methyl)benzenesulfonamide (**97a**)



¹H-NMR (CDCl₃, 400 MHz) δ: 0.47-0.52 (m, 1H), 0.68-0.72 (m, 1H), 0.97-1.05 (m, 1H), 1.56 (s, 3H), 2.42 (s, 3H), 2.99 (dd, 1H, *J* = 14.0, 7.2 Hz), 3.18 (dd, 1H, *J* = 14.0, 6.4 Hz), 3.84 (dd, 1H, *J* = 15.6, 6.4 Hz), 3.93 (dd, 1H, *J* = 15.6, 6.4 Hz), 4.62 (s, 1H), 4.65 (s, 1H), 5.13 (d, 1H, *J* = 11.6 Hz), 5.20 (d, 1H, *J* = 16.8 Hz), 5.60-5.70 (m, 1H), 7.28 (d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 11.0,

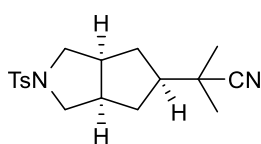
17.2, 20.7, 21.3, 24.6, 49.8, 50.6, 108.7, 118.3, 126.9, 129.5, 133.2, 137.3, 142.9, 144.5; IR (ATR) ν : 2921, 1737, 1338, 1153, 1090, 658 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{23}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 328.1347, found 328.1342; yellow oil (241.3 mg, 52%).

4-methyl-N-(2-methylallyl)-N-((2-(prop-1-en-2-yl)cyclopropyl)methyl)benzenesulfonamide (**97b**)



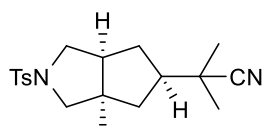
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.43 (br, 1H), 0.63 (br, 1H), 0.98 (br, 1H), 1.18 (br, 1H), 1.50 (s, 3H), 1.71 (s, 3H), 2.40 (s, 3H), 2.90-2.96 (m, 1H), 3.15-3.19 (m, 2H), 3.68-3.86 (m, 3H), 4.57 (d, 1H, $J = 6.4$ Hz), 4.63 (d, 1H, $J = 6.4$ Hz), 4.89 (s, 2H), 7.28 (d, 2H, $J = 8.0$ Hz), 7.72 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 11.1, 16.8, 19.8, 19.9, 21.4, 24.8, 51.1, 53.7, 108.7, 114.0, 127.0, 129.5, 137.3, 140.7, 143.0, 144.7; IR (ATR) ν : 2981, 1735, 1337, 1239, 1156 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{25}\text{NNaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 342.1504, found 342.1515; yellow oil (301.6 mg, 69%).

2-methyl-2-2-tosyloctahydrocyclopenta[c]pyrrol-5-yl)propanenitrile (**98a**)



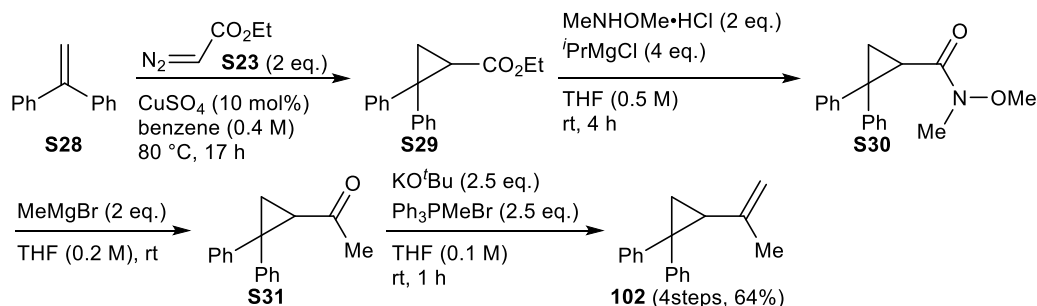
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.21-1.27 (m, 2H), 1.30 (s, 6H), 1.79-1.88 (m, 1H), 1.98-2.08 (m, 2H), 2.44 (s, 3H), 2.54-2.63 (m, 2H), 3.02 (dd, 2H, $J = 9.6$, 6.8 Hz), 3.09 (dd, 1H, $J = 9.6$, 1.6 Hz), 7.32 (d, 2H, $J = 8.0$ Hz), 7.69 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 25.6, 34.5, 35.0, 41.9, 50.5, 53.5, 123.9, 128.0, 129.6, 132.4, 143.6; IR (ATR) ν : 2963, 1736, 1240, 1163, 1045, 664 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 355.1456, found 355.1451; colorless solid (18.4 mg, 38%, mp: 155-158 $^\circ\text{C}$)

2-methyl-2-3a-methyl-2-tosyloctahydrocyclopenta[c]pyrrol-5-yl)propanenitrile (**98b**)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.05 (s, 3H), 1.21-1.31 (m, 2H), 1.29 (s, 6H), 1.54 (dd, 1H, $J = 12.6$, 12.6 Hz), 1.67 (dd, 1H, $J = 12.6$, 7.2 Hz), 1.90-1.99 (m, 1H), 2.01-2.10 (m, 2H), 2.44 (s, 3H), 2.71 (d, 1H, $J = 9.0$ Hz), 3.10 (d, 2H, $J = 4.8$ Hz), 3.20 (d, 1H, $J = 9.0$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 7.70 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.6, 25.5, 25.6, 26.1, 35.2, 41.2, 48.8, 49.1, 49.2, 53.4, 60.1, 124.0, 128.0, 129.6, 132.6, 143.6; IR (ATR) ν : 2969, 1736, 1344, 1158, 664 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{NaO}_2\text{S}$, $[\text{M}+\text{Na}]^+$ 369.1613, found 369.1607; colorless solid (16.9 mg, 31%, 124-127 $^\circ\text{C}$)

Synthesis of **102**



S28 to S29: To a stirred solution of **S28** (1.71 g, 9.49 mmol), CuSO_4 (152 mg, 0.95 mmol) in benzene (13 mL) was added **S23** (5 mL, 47.3 mmol) in benzene (10 mL) at 80 $^\circ\text{C}$ using dropping funnel over 1 h. The

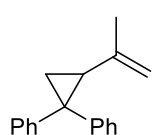
reaction mixture was stirred for 17 h at 80 °C, and the reaction was quenched with H₂O, extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO₂, n-hexane/AcOEt = 10/1) afforded crude **S29** as a colorless oil (2.1 g).

S29 to **S30**: To a stirred solution of crude **S29** (2.1 g), MeNHOMe•HCl (1.57 g, 16.13 mmol) in THF (16 mL) was added *i*PrMgCl (16 mL, 2.0 M in THF, 32 mmol) at -20 °C. The reaction mixture was stirred for 4 h at rt, and the reaction was quenched with sat. NH₄Cl, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo gave crude **S30** which was used without further purification.

S30 to **S31**: To a stirred solution of crude **S30** in THF (40 mL) was added MeMgBr (5.4 mL, 3.0 M in Et₂O, 16.12 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt, and the reaction was quenched with sat. NH₄Cl, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by short column chromatography afforded crude **S31** (1.73 g).

S31 to **102**: To a stirred solution of Ph₃PMeBr (5.8 g, 16.12 mmol) in THF (25 mL) was added *t*-BuOK (1.8 g, 16.12 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Then, crude **S31** (1.73 g) in THF (10 mL) was added at 0 °C, and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with H₂O, extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane) afforded **102** (1.42 g, 63%, 4 steps) as a colorless oil.

(2-(prop-1-en-2-yl)cyclopropane-1,1-diyl)dibenzene (**102**)



(CAS-Reg# 39520-11-1)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.49 (dd, 1H, *J* = 8.8, 5.2 Hz), 1.64 (s, 3H), 1.88 (dd, 1H, *J* = 6.4, 5.2 Hz), 2.36-2.40 (m, 1H), 4.68 (s, 1H), 4.79 (s, 1H), 7.15-7.60 (m, 10H)

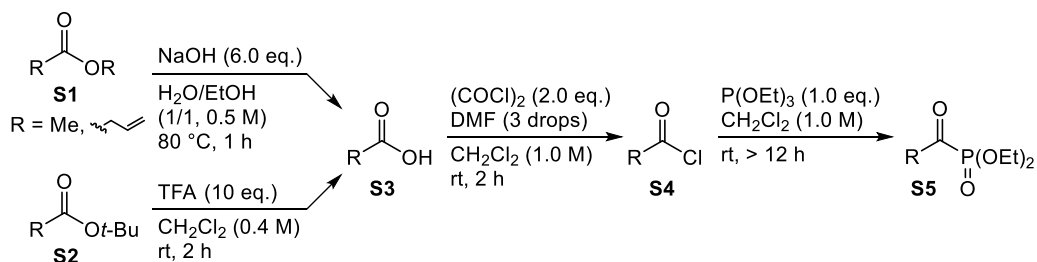
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第三章の実験

General procedure for hydroacylation: EtOH (0.2 M for alkenylacylphosphonate) was added to the mixture of alkenylacylphosphonate (1.0 eq.), Co A (5 mol%) under an argon atmosphere at rt, then PhSiH₃ (1.5 eq.) was added at rt and the solution was stirred at rt. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography.

General procedure for the synthesis of acylphosphonate.



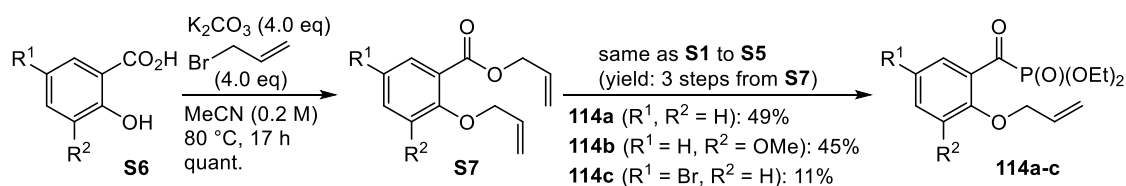
S1 to S3: To a solution of **S1** (1.0 eq.) in EtOH (1.0 M for **S1**) was added H₂O (1.0 M for **S1**) and NaOH (6.0 eq.) at rt, and the reaction mixture was stirred at 80 °C for 1 h. The reaction was quenched with 1 N HCl (pH = 1), extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. **Purification by flash column chromatography** afforded **S3**. (***Caution!!:** Purification of **S3** is necessary even if crude **S3** is seems to be pure.)

S2 to S3: To a solution of **S2** (1.0 eq.) in CH₂Cl₂ (0.4 M for **S2**) was added TFA (10 eq.) at 0 °C, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was evaporated under reduced pressure and diluted with CH₂Cl₂ and 1 N HCl. The organic layer was separated and the mixture was further extracted with CH₂Cl₂. The combined organic extract was then dried over anhydrous sodium sulfate, concentrated under reduced pressure. **Purification by flash column chromatography** afforded **S3**. (***Caution!!:** Purification of **S3** is necessary even if crude **S3** is seems to be pure.)

S3 to S4: To a solution of **S3** (1.0 eq.) in CH₂Cl₂ (1.0 M for **S3**), (COCl)₂ (2.0 eq.) followed by DMF (3 drops) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 15 min. and then, the reaction mixture was allowed to warm to rt. After 2 h, the reaction mixture was evaporated under reduced pressure gave crude **S4**, and **the resulting volatiles were removed under reduced pressure (at 50 °C, 1 h)** to give **S4** which was used in the next step without further purification. (***Caution!!:** Careful removal of volatiles under heating condition is necessary even if crude **S4** seems to be pure.)

S4 to S5: P(OEt)₃ (**1.0 eq.**) was added to the solution of **S4** (1.0 eq.) in CH₂Cl₂ (1.0 M) at 0 °C, and stirred for 1 h at the same temperature. Then, the reaction mixture was allowed to warm to rt, and **stirred for overnight**. Any volatiles were removed under reduced pressure and the crude **S5** was purified by column chromatography. (***Caution!!:** Excess addition of triethylphosphite gave complex mixture. // Even if TLC indicates the generation of **S5** only in a few hours, **stirring for overnight is necessary.**)

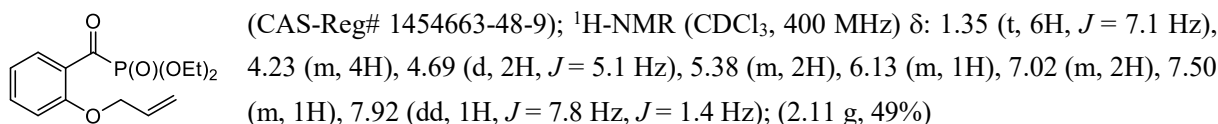
Synthesis of 114a-c



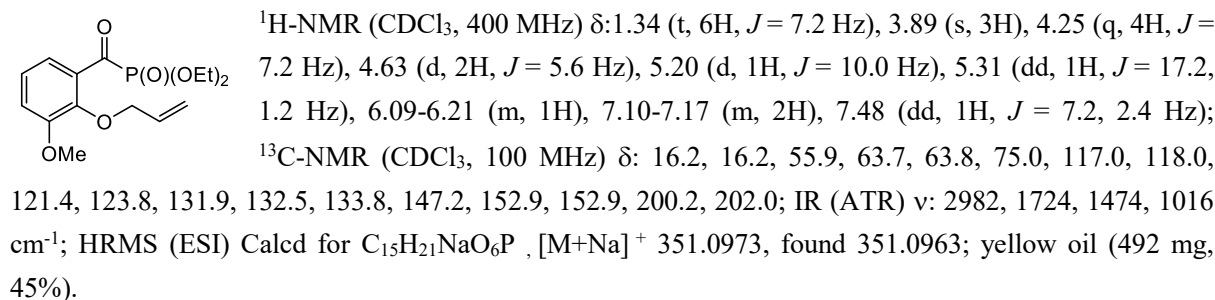
S6 to S7: To a stirred solution of **S6** (1.0 eq.) in MeCN (0.2 M for **S6**) was added K_2CO_3 (4.0 eq.), and allyl bromide (4.0 eq.), and the reaction mixture was stirred at 80 °C for 17 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S7** (quant.).

S7 to 114a-c: Same as general procedure (**S1 to S5**)

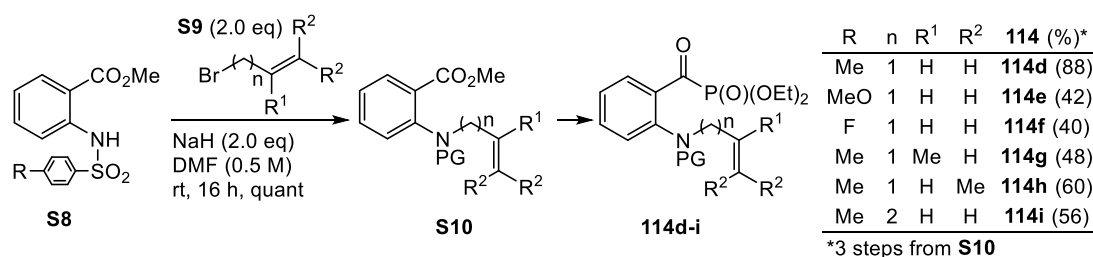
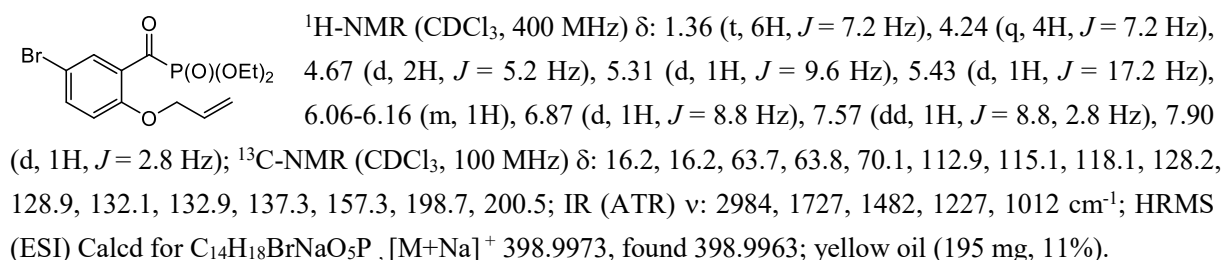
diethyl (2-(allyloxy)benzoyl)phosphonate (**114a**)



diethyl (2-(allyloxy)-3-methoxybenzoyl)phosphonate (**114b**)



diethyl (2-(allyloxy)-5-bromobenzoyl)phosphonate (**114c**)

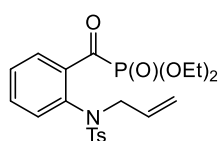


Synthesis of 114d-i

S8 to **S10**: To a solution of **S8** (1.0 eq.) in DMF (0.5 M for **S8**) was added 60% sodium hydride (2.0 eq.) at 0 °C and the mixture was stirred at room temperature for 30 minutes. **S10** (2.0 eq.) was then added and the mixture was stirred for 16 h. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **S10** (quant.).

S10 to **114**: Same as general procedure (**S1** to **S5**)

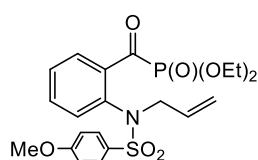
diethyl (2-((N-allyl-4-methylphenyl)sulfonamido)benzoyl)phosphonate (114d)



(CAS-Reg# 1454663-49-0)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.36 (m, 6H), 2.42 (s, 3H), 4.27 (m, 6H), 5.02 (m, 2H), 5.94 (m, 1H), 6.86 (m, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.44 (m, 4H), 8.27 (m, 1H); (354.2 mg, 88%)

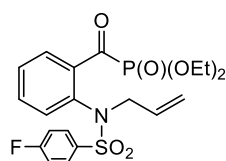
diethyl (2-((N-allyl-4-methoxyphenyl)sulfonamido)benzoyl)phosphonate (114e)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (t, 6H, *J* = 6.8 Hz), 3.86 (s, 3H), 4.21-4.32 (m, 6H), 5.02 (d, 1H, *J* = 16.0 Hz), 5.03 (d, 1H, *J* = 10.8 Hz), 5.90-6.00 (m, 1H), 6.88-6.91 (m, 3H), 7.41-7.47 (m, 2H), 7.51 (d, 2H, *J* = 8.8 Hz), 8.24-8.27 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.0, 16.1, 54.3, 55.3, 63.9, 113.7, 118.8, 127.8, 129.5, 130.0, 130.2, 131.0, 132.5, 132.8, 136.8, 136.9, 137.0, 137.6, 162.7,

199.2, 201.0; IR (ATR) ν: 2969, 1733, 1594, 1158, 1019 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₆NNaO₇PS, [M+Na]⁺ 490.1065, found 490.1053; yellow oil (610.6 mg, 42%).

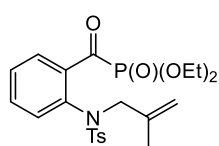
diethyl (2-((N-allyl-4-fluorophenyl)sulfonamido)benzoyl)phosphonate (114f)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (t, 6H, *J* = 6.8 Hz), 4.26 (brs, 6H), 5.03 (d, 1H, *J* = 18.4 Hz), 5.05 (d, 1H, *J* = 9.2 Hz), 5.88-5.98 (m, 1H), 6.94-6.96 (m, 1H), 7.12 (dd, 2H, *J* = 8.4, 8.4 Hz), 7.45-7.50 (m, 2H), 7.60-7.63 (m, 2H), 8.30-8.32 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.0, 16.1, 54.5, 64.0, 115.7, 115.9, 119.1, 128.2, 130.0, 130.1, 130.8, 131.5, 132.5, 132.8, 134.8, 134.8, 136.4, 136.4, 137.0, 163.5,

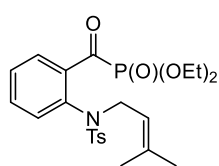
166.1, 198.8, 200.6; IR (ATR) ν: 2984, 1719, 1492, 1154, 1011, 839 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₃FNNaO₆PS, [M+Na]⁺ 478.0865, found 478.0861; yellow oil (588 mg, 40%).

diethyl (2-((4-methyl-N-(2-methylallyl)phenyl)sulfonamido)benzoyl)phosphonate (114g)

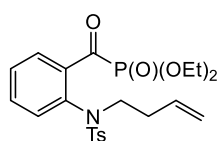


¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (t, 6H, *J* = 7.2 Hz), 1.79 (s, 3H), 2.41 (s, 3H), 4.13 (s, 2H), 4.27 (q, 4H, *J* = 7.2 Hz), 4.69 (s, 1H), 4.76 (s, 1H), 6.93-7.00 (m, 1H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.42-7.49 (m, 4H), 8.35 (dd, 1H, *J* = 6.0, 3.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.2, 20.4, 21.4, 57.1, 64.1, 115.9, 127.6, 129.2, 129.9, 131.7,

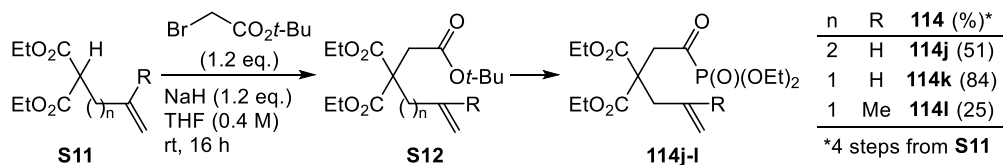
132.6, 135.3, 135.7, 136.3, 136.5, 136.5, 139.9, 143.3, 198.3, 200.1; IR (ATR) ν: 2984, 1346, 1159, 1018 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₂₈NNaO₆PS, [M+Na]⁺ 488.1273, found 488.1280; yellow oil (731 mg, 48%).

diethyl 2-((4-methyl-N-(3-methylbut-2-en-1-yl)phenyl)sulfonamido)benzoyl)phosphonate (114h)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.37 (brs, 6H), 1.41 (s, 3H), 1.58 (s, 3H), 2.42 (s, 3H), 4.27 (brs, 6H), 5.23 (t, 1H, $J = 7.2$ Hz), 6.88 (d, 1H, $J = 8.4$ Hz), 7.22 (d, 2H, $J = 7.6$ Hz), 7.39-7.50 (m, 4H), 8.27 (d, 1H, $J = 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 16.7, 16.2, 17.5, 21.4, 25.5, 49.5, 64.1, 118.6, 127.5, 127.9, 129.2, 130.7, 131.2, 132.5, 136.3, 137.0, 137.0, 137.1, 137.2, 137.6, 143.1, 199.1, 200.9; IR (ATR) ν : 2983, 1725, 1346, 1158, 1017 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{30}\text{NNaO}_6\text{PS}$, $[\text{M}+\text{Na}]^+$ 502.1429, found 502.1438; yellow oil (930 mg, 60%).

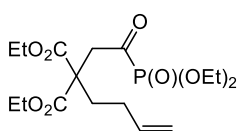
diethyl 2-((N-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoyl)phosphonate (114i)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.36 (m, 6H), 2.41 (s, 3H), 2.39 (brs, 2H), 3.63 (brs, 2H), 4.28 (brs, 4H), 4.97 (d, 1H, $J = 11.2$ Hz), 4.98 (d, 1H, $J = 17.2$ Hz), 5.66-5.76 (m, 1H), 6.91 (dd, 1H, $J = 7.6, 1.6$ Hz), 7.22 (d, 2H, $J = 8.8$ Hz), 7.43-7.50 (m, 4H), 8.32-8.34 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 16.2, 21.3, 32.7, 50.8, 64.0, 116.6, 127.4, 127.8, 129.2, 129.7, 131.3, 132.7, 134.5, 135.4, 136.9, 137.0, 137.0, 137.5, 143.2, 198.8, 200.6; IR (ATR) ν : 2984, 1669, 1346, 1159, 1018, 657 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{NNaO}_6\text{PS}$, $[\text{M}+\text{Na}]^+$ 488.1273, found 488.1254; yellow oil (853 mg, 56%).

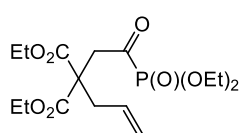
Synthesis of 114j-l

S11 to S12: To a solution of **S11** (1.0 eq.) in THF (0.4 M for **S11**) was added 60% sodium hydride (1.2 eq.) at 0 °C and the mixture was stirred at room temperature for 30 minutes. *tert*-Butyl Bromoacetate (1.2 eq.) was then added and the mixture was stirred for 16 h. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **S12**.

S12 to 114j-l: Same as general procedure (**S2 to S5**)

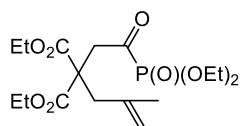
diethyl 2-(but-3-en-1-yl)-2-(2-(diethoxyphosphoryl)-2-oxoethyl)malonate (114j)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.25 (t, 6H, $J = 6.8$ Hz), 1.38 (t, 6H, $J = 7.2$ Hz), 1.92-2.15 (m, 4H), 3.52 (s, 2H), 4.14-4.27 (m, 8H), 4.96 (d, 1H, $J = 10.0$ Hz), 5.00 (d, 1H, $J = 17.2$ Hz), 5.68-5.81 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 13.4, 15.8, 28.5, 32.1, 44.8, 45.4, 54.3, 61.2, 63.5, 114.9, 136.5, 169.4, 206.5, 208.2; IR (ATR) ν : 2983, 1731, 1184, 1012 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{29}\text{NaO}_8\text{P}$, $[\text{M}+\text{Na}]^+$ 415.1498, found 415.1508; colorless oil (794.5 mg, 51%).

diethyl 2-allyl-2-(2-(diethoxyphosphoryl)-2-oxoethyl)malonate (114k)

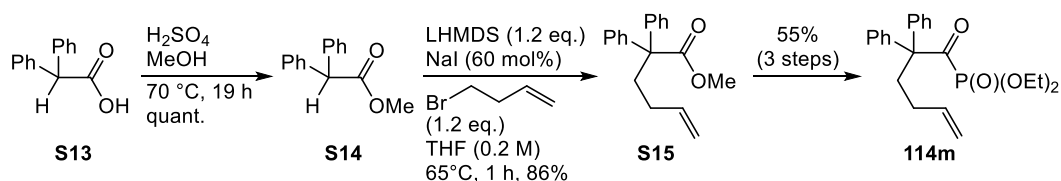
(CAS-Reg# 593254-57-0)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.25 (t, 6H, *J* = 7.2 Hz), 1.37 (t, 6H, *J* = 7.2 Hz), 2.76 (d, 2H, *J* = 7.6 Hz), 3.50 (d, 2H, *J* = 2.8 Hz), 4.21 (m, 8H), 5.10 (m, 2H), 5.66 (m, 1H); (1.60 g, 84%)

diethyl 2-(2-((diethylperoxy)(oxo)-14-phosphanyl)-2-oxoethyl)-2-(2-methylallyl)malonate (114l)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.25 (t, 6H, *J* = 7.2 Hz), 1.37 (t, 6H, *J* = 1.62 (s, 2.4H), 1.65 (s, 0.6H, s 0.6H), 2.84 (s, 1.6H), 2.88 (s, 0.4H), 3.05 (s, 0.6H), 3.55 (s, 1.6H), 4.14-4.24 (m, 8H), 4.65 (s, 0.8H), 4.74 (s, 0.2H), 4.87 (s, 0.8H), 4.90 (s, 0.2H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.7, 16.1, 16.2, 22.7, 40.5, 44.8, 45.4, 54.1,

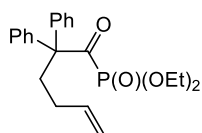
54.2, 61.7, 63.8, 63.9, 116.4, 140.3, 169.8, 170.2, 207.1, 208.8; IR (ATR) ν: 2982, 1731, 1183, 1019 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₂₉NaO₈P, [M+Na]⁺ 415.1498, found 415.1493; yellow oil (357 mg, 25%).

Synthesis of 114m

S13 to S14: To a solution of **S13** (2.0 g) in MeOH (100 mL) was added H₂SO₄ (1.0 mL) at rt and the mixture was stirred at 70 °C for 19 h, then MeOH was removed under reduced pressure. sat. NaHCO₃ aq. was added and the mixture was diluted with CH₂Cl₂. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude **S14** was used in the next step without further purification.

S14 to S15: To a solution of crude **S14** (500 mg, 2.21 mmol) in THF (11 mL) was added LHMDS (2.7 mL, 1.0 M in THF, 2.7 mmol) at -78 °C and the mixture was stirred at 0 °C for 1 h. 4-Bromo-1-butene (0.27 mL, 2.65 mmol) and NaI (199 mg, 1.33 mmol) was then added at -78 °C and the mixture was stirred for 1 h at 65 °C. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **S15** (528 mg, 86%).

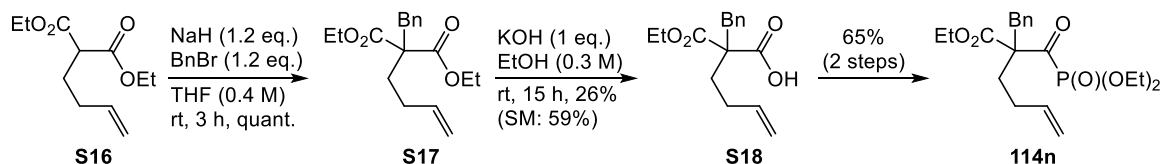
S15 to 114m: Same as general procedure (**S1** to **S5**).

1-((diethylperoxy)(oxo)-14-phosphanyl)-2,2-diphenylhex-5-en-1-one (114m)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.14 (t, 6H, *J* = 7.2 Hz), 1.76-1.83 (m, 2H), 2.65 (dt, 2H, *J* = 8.0, 4.0 Hz), 3.71-3.92 (m, 4H), 5.73-5.83 (m, 1H), 7.27-7.37 (m, 10H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.0, 16.0, 29.2, 29.6, 34.9, 37.1, 63.5, 63.6, 66.6, 67.2, 114.4, 114.8, 126.7, 127.4, 127.7, 128.2, 128.9, 129.8, 137.7, 138.3, 142.7, 207.6,

209.2; IR (ATR) ν : 2981, 1736, 1237, 1016, 700 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{27}\text{NaO}_4\text{P}$, $[\text{M}+\text{Na}]^+$ 409.1545, found 409.1532; yellow oil (399.8 mg, 55%).

Synthesis of 114n



S16 to S17: To a solution of **S16** (549 mg, 2.56 mmol) in THF (6.4 mL) was added 60% sodium hydride (123 mg, 3.07 mmol) at 0 °C and the mixture was stirred at room temperature for 30 minutes. Benzyl bromide (0.36 mL, 3.07 mmol) was then added and the mixture was stirred for 3 h. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **S17** (779 mg, quant.).

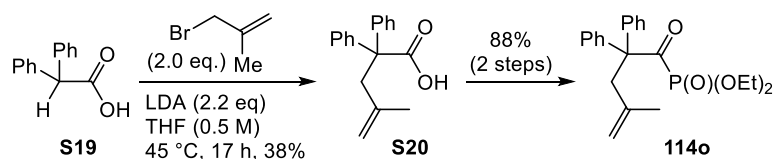
S17 to S18: To a stirred solution of **S17** (779 mg, 2.56 mmol) in EtOH (8.5 mL) at rt, KOH (143 mg, 2.56 mmol) was added. After 15 h, the mixture was acidified with 1 N HCl and filtered. The filter cake (KCl) was washed with EtOH. The combined filtrate was concentrated and residual liquid was subjected to column chromatography to afford **S18** (186 mg, 26%) and unreacted **S17** (481 mg, 59%).

S18 to 114n: Same as general procedure (**S3** to **S5**).

ethyl 2-benzyl-2-(((diethylperoxy)(oxo)-14-phosphanyl)carbonyl)hex-5-enoate (114n)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.19 (t, 3H, $J = 7.6$ Hz), 1.36 (t, 6H, $J = 7.2$ Hz), 1.90-2.05 (m, 4H), 3.22 (d, 1H, $J = 14.0$ Hz), 3.29 (d, 1H, $J = 14.0$ Hz), 4.10-4.18 (m, 2H), 4.22-4.28 (m, 4H), 4.96 (d, 1H, $J = 10.0$ Hz), 5.01 (d, 1H, $J = 17.2$ Hz), 5.69-5.83 (m, 1H), 7.08 (d, 2H, $J = 8.0$ Hz), 7.20-7.25 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 13.6, 16.1, 16.1, 27.7, 29.2, 36.2, 61.4, 63.8, 63.8, 63.9, 64.1, 64.6, 115.1, 126.8, 128.0, 129.9, 135.2, 136.8, 169.9, 207.1, 208.8; IR (ATR) ν : 2981, 1731, 1197, 1011, 700 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{29}\text{NaO}_6\text{P}$, $[\text{M}+\text{Na}]^+$ 419.1599, found 419.1604; yellow oil (165 mg, 55%).

Synthesis of 114o

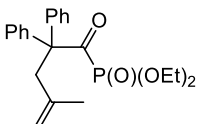


S19 to S20: To a solution of diisopropylamine (4.4 mL, 31.1 mmol) in THF (16 mL) at -78 °C was slowly added *n*-BuLi (1.6 M in hexane, 19.4 mL, 31.1 mmol), and the mixture was stirred at 0 °C for 1 h. To the

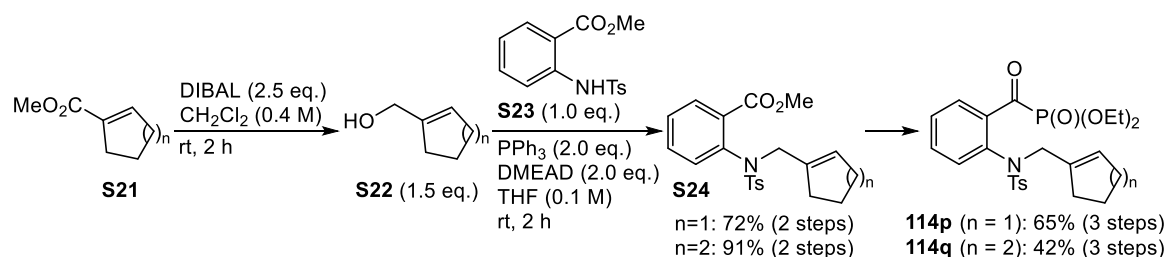
solution was added **S19** (3.0 g, 14.1 mmol) in THF (14 mL) at 0 °C, and the mixture was stirred at 45 °C for 30 min. 3-Bromo-2-methyl-1-propene (2.9 mL, 31.1 mmol) was added to the solution and the mixture was stirred at 45 °C for 17 h. 1 N HCl was added to the mixture and the aqueous layer was washed with AcOEt. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator. Short column chromatography gave solid residue, which was recrystallized from CHCl₃ and hexane to give **S20** as a white solid (1.41 g, 38%).

S20 to 114o: Same as general procedure (**S3 to S5**)

1-((diethylperoxy)(oxo)-14-phosphanyl)-4-methyl-2,2-diphenylpent-4-en-1-one (**114o**)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 1.11 (t, 6H, *J* = 7.2 Hz), 1.33 (s, 3H), 3.40 (s, 2H), 3.65-3.75 (m, 2H), 3.79-3.89 (m, 2H), 4.45 (s, 1H), 4.67 (s, 1H), 7.28-7.38 (m, 10H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.0, 16.0, 24.5, 43.8, 63.3, 63.4, 66.9, 67.4, 115.8, 127.3, 127.9, 130.2, 138.3, 141.2, 207.4, 208.9; IR (ATR) ν: 2983, 1682, 1443, 1255, 1013, 751 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₂₇NaO₄P. [M+Na]⁺ 409.1545, found 409.1548; yellow oil (1.49 g, 88%).

Synthesis of **114p,q**

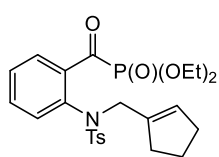


S21 to S22: To a stirred solution of **S21** (1.0 eq.) in CH₂Cl₂ (0.4 M for **S21**) at 0 °C was added DIBAL (2.5 eq., 1.0 M in toluene) dropwise. The mixture was stirred at 0 °C to rt for 2 h then treated with ice cold Rochelles salt (saturated Na/K tartrate) and allowed to stir at 0 °C open to air. The reaction became a gray-white gelatinous suspension that solubilized over the course of 30 min to 1 h with stirring at room temperature open to air. The mixture was poured into diethyl ether and H₂O. The layers were separated, and the aqueous layer was extracted twice more with diethyl ether. The organic layers were combined, dried over Na₂SO₄, and concentrated to afford a crude **S22** which was used without further purification.

S22 to S24: To a stirred solution of **S22** (1.5 eq.), **S23** (1.0 eq.), PPh₃ (2.0 eq.) in THF (0.1 M for **S23**) was added DMEAD (2.0 eq.) at 0 °C, and the reaction mixture was stirred for 2 h at rt. Then, the reaction mixture was concentrated in vacuo. Purification by flash column chromatography gave **S24**.

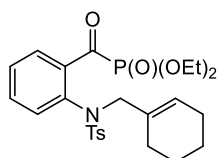
S24 to 114p,q: Same as general procedure (**S1 to S5**)

diethyl (2-((N-(cyclopent-1-en-1-ylmethyl)-4-methylphenyl)sulfonamido)benzoyl)phosphonate (114p)



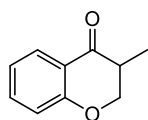
¹H-NMR (CDCl₃, 400 MHz) δ: 1.36 (t, 6H, *J* = 7.2 Hz), 1.75 (dt, 2H, *J* = 15.2, 7.2 Hz), 2.11-2.24 (m, 4H), 2.41 (s, 3H), 4.23-4.31 (m, 6H), 5.42 (s, 1H), 6.95-6.98 (m, 1H), 7.21 (d, 2H, *J* = 8.0 Hz), 7.42-7.48 (m, 4H), 8.36 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.3, 21.5, 23.4, 32.2, 33.6, 51.5, 64.2, 127.6, 127.7, 129.2, 130.4, 131.7, 132.7, 135.9, 136.5, 136.9, 138.8, 143.2, 198.3, 200.2; IR (ATR) ν: 2982, 1670, 1159, 1018, 750 cm⁻¹; HRMS (ESI) Calcd for C₂₄H₃₀NNaO₆PS, [M+Na]⁺ 514.1429, found 514.1430; yellow oil (301.5 mg, 65%).

diethyl (2-((N-(cyclohex-1-en-1-ylmethyl)-4-methylphenyl)sulfonamido)benzoyl)phosphonate (114q)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.33-2.18 (m, 14H), 2.41 (s, 3H), 4.07 (s, 2H), 4.19-4.35 (m, 4H), 5.34 (brs, 1H), 6.94 (m, 1H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.43-7.48 (m, 4H), 3.36 (dd, 1H, *J* = 6.0, 3.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.2, 16.3, 21.4, 21.8, 22.2, 25.0, 26.5, 57.7, 64.0, 64.1, 127.5, 128.0, 129.1, 130.5, 131.7, 132.3, 132.5, 135.8, 135.9, 136.4, 136.7, 136.8, 143.1, 198.2, 199.9; IR (ATR) ν: 2930, 1672, 1161, 1027 cm⁻¹; HRMS (ESI) Calcd for C₂₅H₃₂NNaO₆S, [M+Na]⁺ 528.1586, found 528.1582; yellow oil (310 mg, 42%).

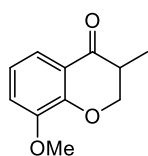
3-methylchroman-4-one (115a)



(CAS-Reg# 16982-86-8)

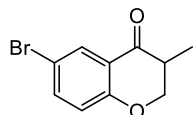
¹H-NMR (CDCl₃, 400 MHz) δ: 1.19 (d, 3H, *J* = 6.8 Hz), 2.78-2.91 (m, 1H), 4.13 (dd, 1H, *J* = 11.2, 11.2 Hz), 4.46 (dd, 1H, *J* = 11.2, 5.2 Hz), 6.93 (d, 1H, *J* = 8.4 Hz), 6.99 (dd, 1H, *J* = 7.6, 7.2 Hz), 7.43 (dd, 1H, *J* = 8.4, 7.2 Hz), 7.89 (d, 1H, *J* = 7.6 Hz); (28.5 mg, 65%)

8-methoxy-3-methylchroman-4-one (115b)



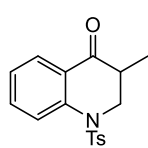
¹H-NMR (CDCl₃, 400 MHz) δ: 1.23 (d, 3H, *J* = 7.2 Hz), 2.84-2.93 (m, 1H), 3.92 (s, 3H), 4.23 (dd, 1H, *J* = 10.8, 10.8 Hz), 4.61 (dd, 1H, *J* = 10.8, 4.8 Hz), 6.96 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.04 (d, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 10.7, 40.5, 56.1, 72.7, 116.2, 118.4, 120.8, 121.0, 148.6, 151.5, 194.7; IR (ATR) ν: 2983, 1736, 1373, 1237, 1045 cm⁻¹; HRMS (ESI) Calcd for C₁₁H₁₂NaO₃, [M+Na]⁺ 215.0684, found 215.0678; colorless solid (15.5 mg, 69%).

6-bromo-3-methylchroman-4-one (115c)



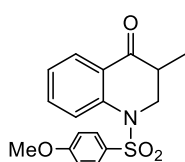
¹H-NMR (CDCl₃, 400 MHz) δ: 1.21 (d, 3H, *J* = 7.2 Hz), 2.82-2.91 (m, 1H), 4.15 (dd, 1H, *J* = 11.2, 11.2 Hz), 4.50 (dd, 1H, *J* = 11.2, 5.2 Hz), 6.87 (d, 1H, *J* = 8.4 Hz), 7.53 (dd, 1H, *J* = 8.4, 2.8 Hz), 8.00 (d, 1H, *J* = 2.8 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 10.6, 40.4, 72.2, 114.0, 119.8, 121.7, 129.7, 138.3, 160.6, 193.5; IR (ATR) ν: 2991, 1738, 1239, 822 cm⁻¹; HRMS (ESI) Calcd for C₁₀H₉BrNaO₂, [M+Na]⁺ 262.9684, found 262.9681; colorless solid (26.4 mg, 59%).

3-methyl-1-tosyl-2,3-dihydroquinolin-4(1H)-one (115d)



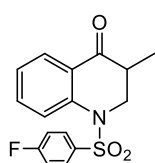
(CAS-Reg# 30504-93-9); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.13 (d, 3H, $J = 7.2$ Hz), 2.39 (s, 3H), 2.42-2.49 (ddq, 1H), 3.64 (dd, 1H, $J = 13.8, 13.8$ Hz), 4.46 (dd, 1H, $J = 13.8, 4.8$ Hz), 7.22-7.27 (m, 3H), 7.53 (dd, 1H, $J = 8.4, 8.4$ Hz), 7.60 (d, 2H, $J = 8.4$ Hz), 7.84 (d, 1H, $J = 8.4$ Hz), 7.95 (d, 1H, $J = 8.4$ Hz); (28.5 mg, 57%)

1-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3-dihydroquinolin-4(1H)-one (115e)



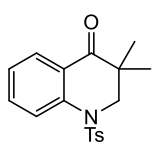
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.13 (d, 3H, $J = 7.2$ Hz), 2.41-2.51 (m, 1H), 3.63 (dd, 1H, $J = 13.6, 13.6$ Hz), 3.83 (s, 3H), 4.45 (dd, 1H, $J = 13.6, 4.8$ Hz), 6.89 (d, 2H, $J = 9.2$ Hz), 7.22 (dd, 1H, $J = 7.6, 7.6$ Hz), 7.53 (ddd, 1H, $J = 8.4, 7.6, 1.6$ Hz), 7.64 (d, 2H, $J = 9.2$ Hz), 7.84 (d, 1H, $J = 8.4$ Hz), 7.95 (dd, 1H, $J = 7.6, 1.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.3, 40.2, 52.2, 55.6, 114.5, 123.1, 124.6, 125.0, 128.1, 128.9, 131.1, 134.4, 142.4, 163.4, 195.5; IR (ATR) ν : 2983, 1736, 1372, 1233, 1043 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{17}\text{NNaO}_4\text{S}$, $[\text{M}+\text{Na}]^+$ 354.0776, found 354.0785; yellow oil (32.6 mg, 56%).

1-((4-fluorophenyl)sulfonyl)-3-methyl-2,3-dihydroquinolin-4(1H)-one (115f)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.14 (d, 3H, $J = 6.8$ Hz), 2.42-2.52 (m, 1H), 3.65 (dd, 1H, $J = 13.6, 13.6$ Hz), 4.46 (dd, 1H, $J = 13.6, 4.8$ Hz), 7.15 (dd, 2H, $J = 8.8, 8.8$ Hz), 7.23 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.55 (ddd, 1H, $J = 8.8, 8.0, 1.6$ Hz), 7.75 (dd, 2H, $J = 8.8, 4.8$ Hz), 7.81 (d, 1H, $J = 8.8$ Hz), 7.97 (dd, 1H, $J = 8.0, 1.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 12.4, 40.4, 52.4, 116.7, 116.9, 122.9, 124.7, 125.4, 128.3, 129.5, 129.6, 134.5, 135.7, 142.0, 164.5, 166.2, 195.2; IR (ATR) ν : 2932, 1690, 1355, 1170, 734 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{14}\text{FNNaO}_3\text{S}$, $[\text{M}+\text{Na}]^+$ 342.0576, found 342.0586; colorless solid (20.2 mg, 46%).

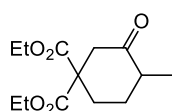
3,3-dimethyl-1-tosyl-2,3-dihydroquinolin-4(1H)-one (115g)



(CAS-Reg# 112565-67-0)

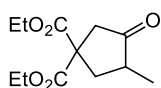
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.27 (s, 6H), 2.42 (s, 3H), 3.97 (s, 2H), 7.10 (dd, 1H, $J = 7.6, 7.6$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 7.42 (dd, 1H, $J = 8.0, 7.6$ Hz), 7.61 (d, 1H, $J = 8.0$ Hz), 7.80 (d, 2H, $J = 8.0$ Hz), 8.00 (d, 1H, $J = 7.6$ Hz); (36.5 mg, 57%)

diethyl 4-methyl-3-oxocyclohexane-1,1-dicarboxylate (115j)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.06 (d, 3H, $J = 6.4$ Hz), 1.22-1.27 (m, 6H), 1.40-1.51 (m, 1H), 2.02-2.11 (m, 1H), 2.18 (ddd, 1H, $J = 13.6, 13.6, 3.6$ Hz), 2.32 (qd, 1H, $J = 6.4, 6.4$ Hz), 2.41 (dd, 1H, $J = 13.6, 2.8$ Hz), 2.51 (d, 1H, $J = 14.8$ Hz), 2.96 (d, 1H, $J = 14.8$ Hz), 4.13-4.26 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 13.9, 13.9, 14.5, 29.9, 30.2, 44.0, 45.1, 57.6, 61.8, 61.8, 170.3, 170.4, 208.2; IR (ATR) ν : 2980, 1735, 1229, 1045 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{20}\text{NaO}_5$, $[\text{M}+\text{Na}]^+$ 279.1208, found 279.1214; yellow oil (26.4 mg, 37%).

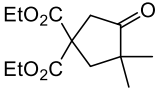
diethyl 3-methyl-4-oxocyclopentane-1,1-dicarboxylate (115k)



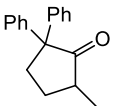
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.11 (d, 3H, $J = 7.6$ Hz), 1.27 (t, 6H, $J = 7.2$ Hz), 1.97 (dd, 1H, $J = 12.8, 12.8$ Hz), 2.41 (m, 1H), 2.72 (d, 1H, $J = 18.8$ Hz), 2.84 (dd, 1H, $J = 12.8, 8.8$ Hz), 2.95 (d, 1H, $J = 18.8$ Hz), 4.22 (q, 4H, $J = 7.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz)

δ : 13.9, 38.1, 42.5, 44.4, 54.8, 61.9, 62.0, 170.7, 171.0, 215.8; IR (ATR) ν : 2984, 1731, 1238, 1044 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{18}\text{NaO}_5$, $[\text{M}+\text{Na}]^+$ 265.1052, found 265.1060; yellow oil (56 mg, 81%).

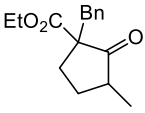
diethyl 3,3-dimethyl-4-oxocyclopentane-1,1-dicarboxylate (115l)

 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.07 (s, 6H), 1.27 (t, 6H, $J = 7.2$ Hz), 2.52 (s, 2H), 2.98 (s, 2H), 4.23 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 13.9, 25.2, 43.9, 44.3, 45.2, 53.9, 62.1, 171.4, 218.5; IR (ATR) ν : 2970, 1731, 1366, 1184 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{20}\text{NaO}_5$, $[\text{M}+\text{Na}]^+$ 279.1208, found 279.1203; yellow oil (25.1 mg, 54%).

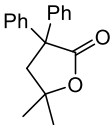
5-methyl-2,2-diphenylcyclopentan-1-one (115m)

 (CAS-Reg# 1912-08-9); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.16 (d, 3H, $J = 7.6$ Hz), 1.56-1.62 (m, 1H), 2.18-2.26 (m, 1H), 2.37-2.45 (m, 1H), 2.52-2.59 (m, 1H), 2.78-2.84 (m, 1H), 7.18-7.32 (m, 10H); (24.9 mg, 53%)

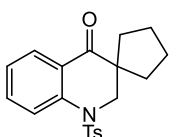
ethyl 1-benzyl-3-methyl-2-oxocyclopentane-1-carboxylate (115n)

 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.62-0.73 (m, 1H), 0.88 (d, 3H, $J = 7.2$ Hz), 1.25 (t, 3H, $J = 7.2$ Hz), 1.89-2.01 (m, 1H), 2.06-2.12 (m, 1H), 2.24-2.41 (m, 2H), 3.11 (d, 1H, $J = 14.0$ Hz), 3.17 (d, 1H, $J = 14.0$ Hz), 4.16 (q, 2H, $J = 7.2$ Hz), 7.11 (d, 2H, $J = 7.6$ Hz), 7.21-7.26 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 26.4, 26.6, 37.6, 39.2, 46.6, 50.5, 64.1, 64.6, 116.9, 118.0, 119.6, 124.6, 152.8, 188.6; IR (ATR) ν : 2964, 1747, 1722, 1454, 1156, 702 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_3$, $[\text{M}+\text{Na}]^+$ 283.1310, found 283.1303; yellow oil (20.4 mg, 50%)

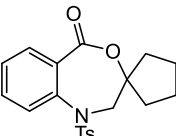
5,5-dimethyl-3,3-diphenyldihydrofuran-2(3H)-one (116o)

 (CAS-Reg# 109394-96-9) $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.36 (s, 6H), 3.03 (s, 2H), 7.40-7.24 (m, 10H); (23.6 mg, 56%)

1'-tosyl-1',2'-dihydro-4'H-spiro[cyclopentane-1,3'-quinolin]-4'-one (115p)

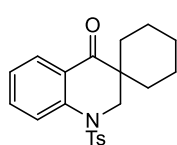
 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.68-1.87 (m, 6H), 2.00-2.11 (m, 2H), 2.41 (s, 3H), 3.99 (s, 2H), 7.08 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.32 (d, 2H, $J = 8.4$ Hz), 7.39 (dd, 1H, $J = 7.8, 7.8$ Hz), 7.59 (d, 1H, $J = 8.4$ Hz), 7.78 (d, 2H, $J = 8.4$ Hz), 8.00 (d, 1H, $J = 7.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 25.7, 33.2, 53.9, 54.9, 118.4, 122.3, 123.3, 126.8, 129.0, 130.0, 134.2, 136.9, 142.3, 144.4, 197.6; IR (ATR) ν : 2953, 1683, 1351, 1161 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{21}\text{NNaO}_3\text{S}$, $[\text{M}+\text{Na}]^+$ 378.1140, found 378.1153; colorless solid (19.5 mg, 30%, mp: 117-119 $^\circ\text{C}$)

1-tosyl-1,2-dihydro-5H-spiro[benzo[e][1,4]oxazepine-3,1'-cyclopentan]-5-one (116p)

 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.20-1.72 (m, 8H), 2.41 (s, 3H), 4.12 (s, 2H), 7.22 (d, 2H, $J = 8.8$ Hz), 7.40 (d, 2H, $J = 8.8$ Hz), 7.44-7.48 (m, 1H), 7.57-7.71 (m, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.6, 24.3, 39.9, 59.3, 88.7, 127.3, 129.2, 129.8, 130.9, 132.1, 132.5, 133.3, 134.9, 135.3, 144.3, 167.4; IR (ATR) ν : 2924, 1721, 1350, 1166, 1088 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{21}\text{NNaO}_4\text{S}$, $[\text{M}+\text{Na}]^+$ 394.1089, found 394.1092; yellow solid (6.4

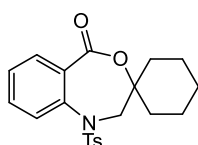
mg, 9%).

1'-tosyl-1',2'-dihydro-4'H-spiro[cyclohexane-1,3'-quinolin]-4'-one (115q)



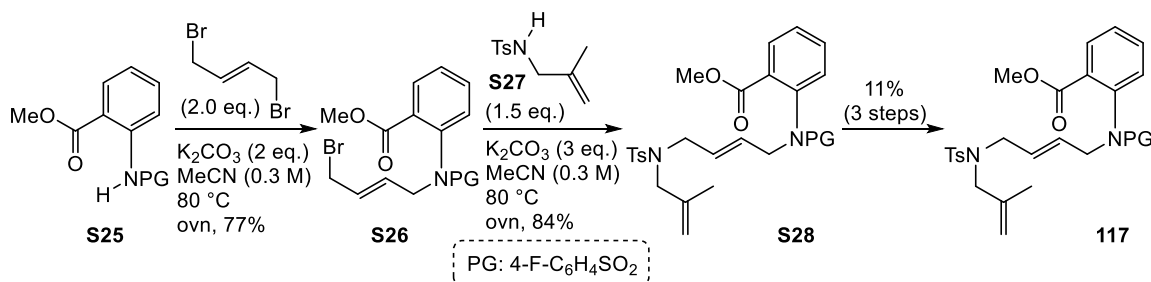
¹H-NMR (CDCl₃, 400 MHz) δ : 1.33-1.87 (m, 10H), 2.42 (s, 3H), 4.10 (s, 2H), 7.09 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.32 (d, 2H, $J = 8.4$ Hz), 7.40 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.62 (d, 1H, $J = 8.8$ Hz), 7.81 (d, 2H, $J = 8.8$ Hz), 7.99 (dd, 1H, $J = 7.6, 1.2$ Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 21.2, 21.6, 25.6, 29.1, 45.6, 53.1, 118.2, 122.2, 123.2, 126.9, 129.1, 130.0, 134.2, 136.8, 141.9, 144.4, 198.0; IR (ATR) ν : 2926, 1683, 1351, 1162, 658 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₃NNaO₃S, [M+Na]⁺ 392.1296, found 392.1295; yellow solid (14 mg, 25%).

1-tosyl-1,2-dihydro-5H-spiro[benzo[e][1,4]oxazepine-3,1'-cyclohexan]-5-one (116q)



¹H-NMR (CDCl₃, 400 MHz) δ : 1.25-1.63 (m, 10H), 2.41 (s, 3H), 3.99 (s, 2H), 7.22 (d, 2H, $J = 8.0$ Hz), 7.43-7.47 (m, 3H), 7.61 (m, 2H), 7.66 (d, 1H, $J = 7.2$ Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 21.6, 21.8, 24.8, 31.3, 37.3, 38.2, 59.4, 59.6, 80.6, 127.5, 129.4, 129.9, 131.0, 131.4, 132.6, 133.7, 135.6, 136.2, 144.3, 167.0; IR (ATR) ν : 2920, 1745, 1357, 1092 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₃NNaO₄S, [M+Na]⁺ 408.1246, found 408.1232; colorless solid (7.4 mg, 13%, mp: 118-122 °C).

Synthesis of 117

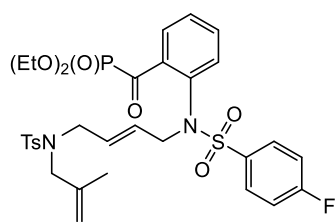


S25 to S26: To a stirred solution of **S25** (1.0 g, 3.23 mmol) in MeCN (11 mL) was added K₂CO₃ (891 mg, 6.46 mmol), and *trans*-1,4-dibromo-2-butene (1.38 g, 6.46 mmol), and the reaction mixture was stirred at 80 °C. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S26** (1.1 g, 77%).

S26 to S28: To a stirred solution of **S26** (442.3 mg, 1.0 mmol) in MeCN (3.3 mL) was added K₂CO₃ (414 mg, 3.0 mmol), and **S27** (338 mg, 1.5 mmol), and the reaction mixture was stirred at 80 °C. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S28** (491 mg, 84%).

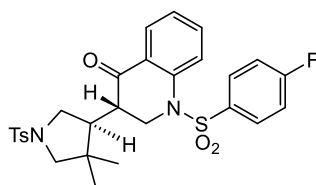
S28 to 117: Same as general procedure (**S1 to S5**)

diethyl(E)-2-((4-fluoro-N-(4-((4-methyl-N-(2-methylallyl)phenyl)sulfonamido)but-2-en-1-yl)phenyl)sulfonamido)benzoyl)phosphonate (117)



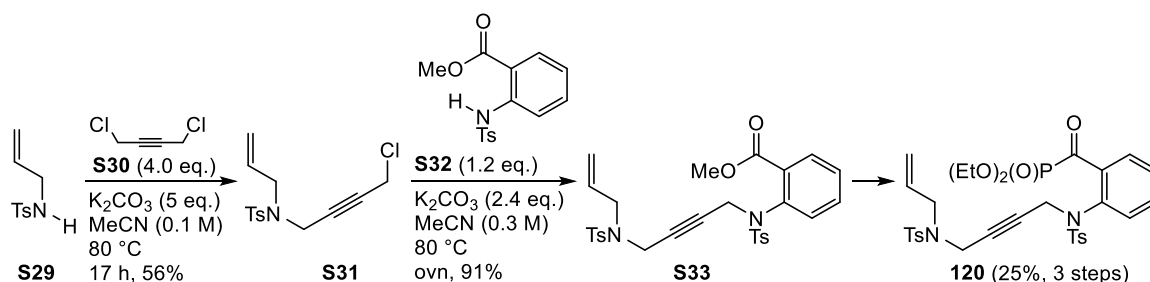
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.31-1.43 (m, 6H), 1.52 (s, 3H), 2.42 (s, 3H), 3.31-3.69 (br, 4H), 4.15 (q, 4H, $J = 6.8$ Hz), 4.26 (brs, 2H), 4.63 (s, 1H), 4.79 (s, 1H), 5.30 (dt, 1H, $J = 15.2, 6.8$ Hz), 5.68 (d, 1H, $J = 15.2, 6.8$ Hz), 6.84 (d, 1H, $J = 6.8$ Hz), 7.09 (d, 1H, $J = 8.4$ Hz), 7.14 (d, 1H, $J = 8.8$ Hz), 7.21-7.39 (m, 2H), 7.44-7.49 (m, 2H), 7.54 (d, 1H, $J = 8.8$ Hz), 7.58 (d, 1H, $J = 8.8$ Hz), 7.61 (d, 2H, $J = 8.0$ Hz), 8.26 (dd, 1H, $J = 6.8, 2.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 16.2, 16.3, 19.7, 21.4, 47.9, 52.7, 53.3, 114.4, 115.9, 116.2, 127.1, 128.3, 129.2, 129.5, 129.5, 130.2, 130.3, 130.7, 131.6, 133.0, 134.5, 136.5, 136.5, 136.7, 136.9, 137.3, 139.8, 143.2, 163.8, 166.3, 199.2, 201.0; IR (ATR) ν : 2809, 1348, 1158, 1022 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{32}\text{H}_{38}\text{FN}_2\text{NaO}_8\text{PS}$, $[\text{M}+\text{Na}]^+$ 715.1689, found 715.1685; yellow oil (100.2 mg, 11%).

3-(4,4-dimethyl-1-tosylpyrrolidin-3-yl)-1-((4-fluorophenyl)sulfonyl)-2,3-dihydroquinolin-4(1H)-one (118)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.74 (s, 3H), 1.07 (s, 3H), 2.44 (s, 3H), 2.59-2.68 (m, 1H), 2.87 (d, 1H, $J = 9.6$ Hz), 3.10 (dd, 1H, $J = 10.8, 7.6$ Hz), 3.20 (d, 1H, $J = 9.6$ Hz), 3.57-3.62 (m, 2H), 3.92 (dd, 1H, $J = 13.6, 9.6$ Hz), 4.20 (dd, 1H, $J = 13.6, 4.4$ Hz), 7.14-7.22 (m, 3H), 7.32 (d, 2H, $J = 8.4$ Hz), 7.48-7.56 (m, 2H), 7.70 (d, 2H, $J = 8.4$ Hz), 7.76-7.84 (m, 2H), 7.92 (d, 1H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 21.6, 26.0, 40.4, 44.0, 45.5, 49.2, 49.4, 61.2, 116.8, 117.0, 120.8, 123.9, 124.8, 127.4, 128.7, 129.6, 129.7, 129.8, 133.4, 134.9, 141.7, 143.6, 193.9; IR (ATR) ν : 1734, 1345, 1158, 634 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{28}\text{H}_{29}\text{FN}_2\text{NaO}_5\text{S}_2$, $[\text{M}+\text{Na}]^+$ 579.1400, found 579.1399; colorless solid (23.5 mg, 28%, 135-137 $^\circ\text{C}$).

Synthesis of 120



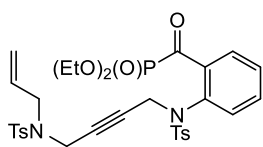
S29 to S31: To a stirred solution of **S29** (1.5 g, 7.1 mmol) in MeCN (71 mL) was added K_2CO_3 (4.9 g, 6.46 mmol), and **S30** (2.8 mL, 28.4 mmol), and the reaction mixture was stirred at 80 $^\circ\text{C}$ for 17 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S31** (1.18 g, 56%).

S31 to S33: To a stirred solution of **S31** (452 mg, 1.45 mmol) in MeCN (4.8 mL) was added K_2CO_3 (480 mg, 3.48 mmol), and **S32** (531 mg, 1.74 mmol), and the reaction mixture was stirred at 80 $^\circ\text{C}$ for 17 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in

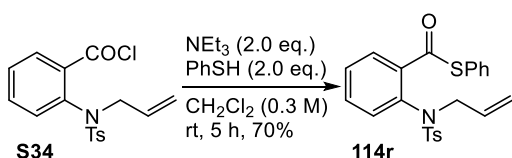
vacuo. Purification by flash column chromatography afforded **S33** (765 mg, 91%).

S33 to 120: Same as general procedure (**S1 to S5**)

diethyl-(2-((N-(4-((N-allyl-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylphenyl)sulfonamido)benzoyl)phosphonate (120)


¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (t, 6H, *J* = 7.2 Hz), 2.38 (s, 3H), 2.41 (s, 3H), 3.64 (d, 2H, *J* = 6.0 Hz), 3.95 (s, 2H), 4.16 (q, 4H, *J* = 7.2 Hz), 4.26 (brs, 2H), 5.08 (d, 1H, *J* = 17.2 Hz), 5.16 (d, 1H, *J* = 10.0 Hz), 5.62 (ddt, 1H, *J* = 17.2, 10.0, 6.0 Hz), 6.99 (d, 1H, *J* = 8.4 Hz), 7.21-7.32 (m, 4H), 7.38-7.44 (m, 3H), 7.51 (dd, 1H, *J* = 8.4, 6.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 8.15 (d, 1H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.2, 16.3, 21.4, 21.5, 35.9, 41.5, 49.0, 61.8, 64.1, 78.4, 80.2, 119.6, 127.5, 127.9, 128.9, 129.1, 129.3, 129.4, 130.7, 131.0, 131.8, 132.9, 135.7, 135.8, 137.0, 137.6, 138.2, 143.7, 143.8, 200.2, 202.0; IR (ATR) ν: 2719, 1350, 1163, 666 cm⁻¹; HRMS (ESI) Calcd for C₃₂H₃₇N₂NaO₈PS₂, [M+Na]⁺ 695.1627, found 695.1622; yellow oil (226 mg, 25%).

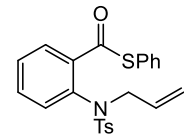
Synthesis of 114r



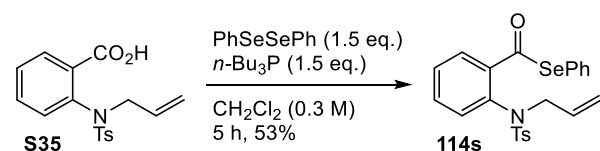
S34: See **S8 to 114d**

S34 to 114r: To a stirred solution of **S34** (1.39 g, 3.99 mmol) in CH₂Cl₂ (13.3 mL) was added NEt₃ (1.1 mL, 7.98 mmol), and PhSH (0.81 mL, 7.98 mmol) at 0 °C, and the reaction mixture was stirred at rt for 5 h. The reaction was quenched with sat. NH₄Cl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **114r** (1.18 g, 70%).

S-phenyl 2-((N-allyl-4-methylphenyl)sulfonamido)benzothioate (114r)


¹H-NMR (CDCl₃, 400 MHz) δ: 2.42 (s, 3H), 4.23 (d, 2H, *J* = 6.8 Hz), 4.97 (d, 1H, *J* = 17.2 Hz), 5.04 (d, 1H, *J* = 9.2 Hz), 5.93 (ddt, 1H, *J* = 17.2, 9.2, 6.8 Hz), 6.97-6.99 (m, 1H), 7.21-7.30 (m, 3H), 7.41-7.52 (m, 6H), 7.56 (d, 2H, *J* = 6.8 Hz), 7.89-7.92 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.6, 55.0, 119.4, 127.9, 128.5, 129.2, 129.5, 131.0, 131.9, 132.9, 134.7, 136.0, 136.1, 138.9, 139.1, 143.5, 190.1; IR (ATR) ν: 1735, 1364, 1216, 611 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₃NNaO₄S, [M+Na]⁺ 408.1246, found 408.1242; yellow solid

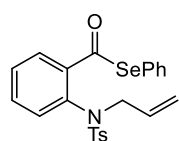
Synthesis of 114s



S35: See **S8 to 114d**

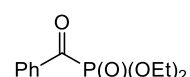
S35 to 114s: To a stirred solution of **S35** (275 mg, 0.83 mmol) in CH₂Cl₂ (2.8 mL) was added PhSeSePh (390 mg, 1.25 mmol), and *n*-Bu₃P (0.31 mL, 1.25 mmol) at 0 °C, and the reaction mixture was stirred at rt for 5 h. The reaction was quenched with H₂O, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography gave crude **114s**, and recrystallization from hexane/AcOEt afforded pure **114s** as a white solid (206 mg, 53%).

Se-phenyl 2-((N-allyl-4-methylphenyl)sulfonamido)benzoselenoate (114s)



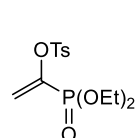
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.42 (s, 3H), 4.21 (d, 2H, $J = 6.8$ Hz), 4.97 (d, 1H, $J = 17.2$ Hz), 5.04 (d, 1H, $J = 10.2$ Hz), 6.99 (ddt, 1H, $J = 17.2, 10.2, 6.8$ Hz), 6.99 (dd, 1H, $J = 5.6, 3.6$ Hz), 7.39-7.49 (m, 6H), 7.50-7.63 (m, 5H), 7.87 (dd, 1H, $J = 6.0, 3.2$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 54.9, 119.5, 127.0, 127.5, 127.8, 128.5, 128.8, 129.2, 129.4, 130.8, 132.1, 132.6, 135.1, 135.5, 135.8, 140.2, 143.6, 192.7; IR (ATR) ν : 2969, 1737, 1362, 1216, 662 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{21}\text{NNaO}_3\text{SSe}$, $[\text{M}+\text{Na}]^+$ 494.0305, found 494.0288; colorless solid

diethyl benzoylphosphonate (124)



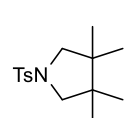
(CAS-Reg# 3277-27-8) $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.36 (t, 6H, $J = 7.2$ Hz), 4.22-4.30 (m, 4H), 7.49 (t, 2H, $J = 7.6$ Hz), 7.62 (t, 1H, $J = 7.6$ Hz), 8.25 (d, 2H, $J = 7.6$ Hz)

1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (127)



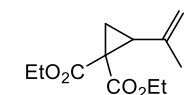
(CAS-Reg# 1309980-37-7) $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.28 (td, 6H, $J = 7.2, 0.8$ Hz), 2.45 (s, 3 H), 3.95-4.12 (m, 4 H), 5.94-5.96 (m, 1 H), 5.97-6.01 (m, 1 H), 7.36 (d, 2H, $J = 8.0$ Hz), 7.83 (d, 2H, $J = 8.0$ Hz)

3,3,4,4-tetramethyl-1-tosylpyrrolidine (128)



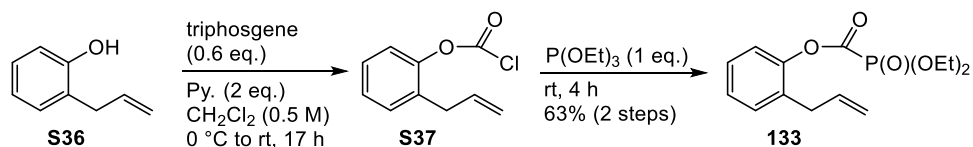
(CAS-Reg# 1456776-51-4) $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.74 (s, 12H), 2.42 (s, 3H), 3.13 (s, 4H), 7.30 (d, 2H, $J = 8.0$ Hz), 7.71 (d, 2H, $J = 8.0$ Hz); (25.3 mg, 37%)

diethyl 2-(prop-1-en-2-yl)cyclopropane-1,1-dicarboxylate (130)



(CAS-Reg# 86726-22-9) $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.23 (t, 3H, $J = 7.2$ Hz), 1.27 (t, 3H, $J = 7.2$ Hz), 1.43 (dd, 1H, $J = 8.4, 5.2$ Hz), 1.81 (s, 3H), 1.83 (dd, 1H, $J = 8.4, 5.2$ Hz), 2.45 (dd, 1H, $J = 8.4, 8.4$ Hz), 4.09-4.27 (m, 4H), 4.71 (s, 1H), 4.86 (s, 1H)

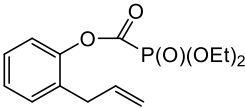
Synthesis of 133



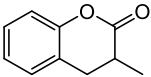
S36 to S37: To a solution of **S36** (1.0 mL, 7.6 mmol) and triphosgene (1.35 g, 4.56 mmol) in CH_2Cl_2 (7 mL), pyridine (1.2 mL, 15.2 mmol) was added using dropping funnel over 1 h at 0 °C. The temperature was allowed to rise to room temperature gradually after the addition of pyridine and the solutions was stirred for 17 h at room temperature (color of the solution: clear yellow to clear dark orange). The reaction was quenched with 1N HCl, extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo gave crude **S37** as a deep red oil which was used without further purification.

S37 to 133: P(OEt)₃ (0.18 mL, 1.07 mmol) was directly added to the crude **S37** (210 mg, 1.07 mmol) at 0 °C, and the mixture was stirred at rt for 4 h. Any volatiles were removed under reduced pressure and the crude **S5** was purified by column chromatography (201 mg, 63%, 2 steps).

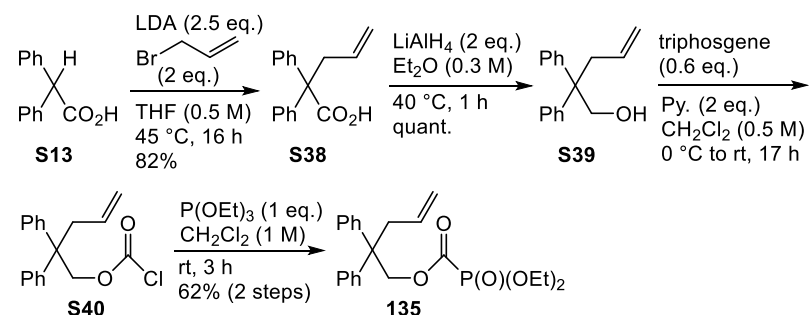
2-allylphenyl (diethoxyphosphoryl)formate (133)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 1.45 (t, 6H, *J* = 7.2 Hz), 3.31 (d, 2H, *J* = 6.4 Hz), 4.40 (q, 4H, *J* = 7.2 Hz), 5.05 (d, 1H, *J* = 17.2 Hz), 5.10 (d, 1H, *J* = 10.8 Hz), 5.84-5.94 (m, 1H), 7.08 (d, 1H, *J* = 8.0 Hz), 7.21-7.29 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 16.3, 16.3, 34.3, 64.8, 64.9, 116.7, 121.9, 126.9, 127.5, 130.6, 131.6, 135.3, 147.9, 164.1; IR (ATR) ν: 2982, 1721, 1011, 772 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₉NaO₅P, [M+Na]⁺ 321.0868, found 321.0857; yellow oil

3-methylchroman-2-one (134)

 (CAS-Reg# 66122-70-1) ¹H-NMR (CDCl₃, 400 MHz) δ: 1.54 (d, 3H, *J* = 6.8 Hz), 2.89-2.99 (m, 2H), 4.64-4.73 (m, 1H), 7.26 (t, 1H, *J* = 6.8 Hz), 7.39 (t, 1H, *J* = 7.6 Hz), 7.53 (dt, 1H, *J* = 7.6, 1.6 Hz), 8.10 (d, 1H, *J* = 7.6 Hz); (17.8 mg, 52%)

Synthesis of 135



S13 to S38: To a solution of diisopropylamine (1.7 mL, 11.8 mmol) in THF (3 mL), *n*-BuLi (1.6 M in hexane, 7.4 mL, 11.8 mmol) was slowly added at 0 °C, and the mixture was stirred at 0 °C for 1 h. To the solution was added **S13** (1.0 g, 4.71 mmol) in

THF (6 mL) at 0 °C, and the mixture was stirred at 45 °C for 1.5 h. Allyl bromide (0.81 mL, 9.4 mmol) was added to the solution and the mixture was stirred at 45 °C for 16 h. 1 N HCl was added to the mixture and the aqueous layer was washed with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave solid residue, which was recrystallized from CHCl₃ and hexane to give **S38** as a white solid (796 mg, 67%).

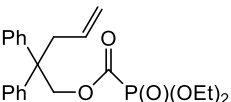
S38 to S39: LiAlH₄ (138 mg, 3.62 mmol) was added to a solution of **S38** (456.7 mg, 1.81 mmol) in Et₂O (6 mL) at 0 °C under argon atmosphere. After addition, the mixture was stirred for 1 h at 40 °C. Then, worked up by precipitation with 0.2 mL of water and 0.2 mL of 15% NaOH and 0.6 mL of water at 0 °C, and filtration through celite and washed thoroughly with Et₂O. The solvent was reduced under vacuum at 0 °C. Purification by flash column chromatography (Et₂O) afforded **S39** (530 mg, quant.) as a colorless oil.

S39 to S40: To a solution of **S39** (530 mg, 1.81 mmol) and triphosgene (322 mg, 1.09 mmol) in CH₂Cl₂ (1.8 mL), pyridine (0.29 mL, 3.62 mmol) in CH₂Cl₂ (1.8 mL) was added using dropping funnel over 1 h at 0 °C. The temperature was allowed to rise to room temperature gradually after the addition of pyridine and

the solutions was stirred for 17 h at room temperature (color of the solution: clear yellow to dark orange). The reaction was quenched with 1N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo gave crude **S40** (485.8 mg) as an orange oil which was used without further purification.

S40 to **135**: P(OEt)₃ (0.28 mL, 1.62 mmol) was added to the crude **S40** (485.8 mg, 1.62 mmol) at 0 °C, and the mixture was stirred at rt for 3 h. Any volatiles were removed under reduced pressure and the crude **135** was purified by column chromatography (454 mg, 62%, 2 steps).

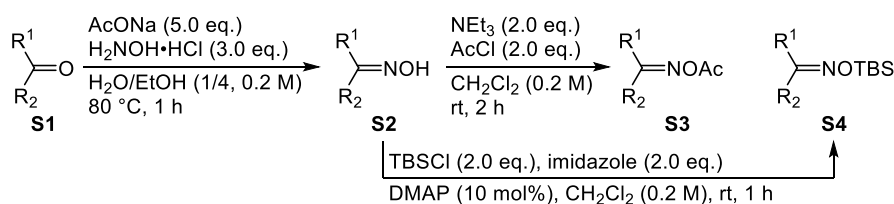
2,2-diphenylpent-4-en-1-yl (diethoxyphosphoryl)formate (**135**)


¹H-NMR (CDCl₃, 400 MHz) δ: 1.24 (t, 6H, *J* = 6.8 Hz), 3.01(d, 2H, *J* = 7.2 Hz), 3.92-4.15 (m, 4H), 4.85 (s, 2H), 5.02 (d, 1H, *J* = 10.0 Hz), 5.07 (d, 1H, *J* = 16.8 Hz), 5.38 (ddt, 1H, *J* = 16.8, 10.0, 7.2 Hz), 7.16-7.23 (m, 6H), 7.27-7.31 (m, 4H);
¹³C-NMR (CDCl₃, 100 MHz) δ: 16.0, 16.1, 41.2, 49.0, 64.3, 64.3, 69.5, 69.6, 117.9, 119.0, 126.2, 126.4, 127.5, 128.0, 128.1, 133.2, 134.4, 144.3, 145.2, 165.1, 167.8; IR (ATR) ν: 2985, 1717, 1212, 1013, 756 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₂₇NaO₅P, [M+Na]⁺ 425.1494 found 425.1478; yellow oil

第四章の実験

General procedure for cyclization: EtOH (0.2 M for alkenyloxime) was added to the mixture of alkenyloxime (1.0 eq.), Co A (5 mol%) under an argon atmosphere at rt, then PhSiH₃ (1.5 eq.) was added at rt and the solution was stirred at rt. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography.

General procedure for the synthesis of alkenyloximes

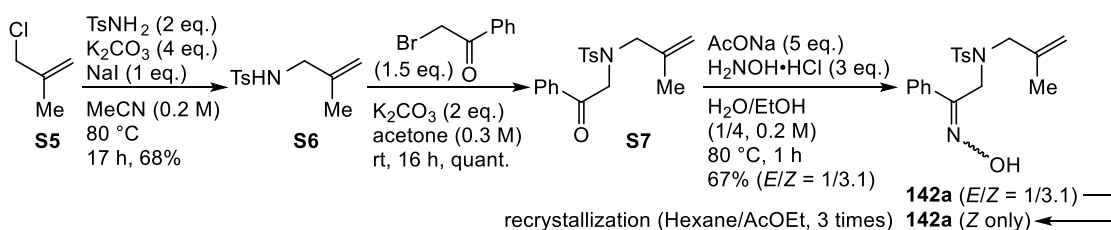


S1 to S2: To a solution of **S1** (1.0 eq.) in H₂O/EtOH (1/4, 0.2 M for **S1**), H₂NOH·HCl (5.0 eq.) and AcONa (5.0 eq.) was added at rt, and the mixture was stirred for 1 h at 80 °C. Then, the mixture was diluted with water and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave crude **S2** which was purified by column chromatography.

S2 to S3: To a solution of **S2** (1.0 eq.) in CH₂Cl₂ (0.2 M for **S2**), NEt₃ (2.0 eq.) and AcCl (2.0 eq.) was added at 0 °C, and the mixture was stirred for 2 h at rt. Then, the mixture was diluted with 1N HCl and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave crude **S3** which was purified by column chromatography.

S2 to S4: To a solution of **S2** (1.0 eq.) in CH₂Cl₂ (0.2 M for **S2**), imidazole (2.0 eq.) and TBSCl (2.0 eq.) was added at 0 °C, and the mixture was stirred for 1 h at rt. Then, the mixture was diluted with H₂O and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave crude **S4** which was purified by column chromatography.

Synthesis of 142a

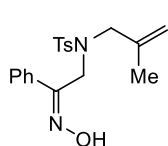


S5 to S6: To a stirred solution of **S5** (3.0 mL, 30.81 mmol) in MeCN (154 mL) was added K₂CO₃ (17.0 g, 123.2 mmol), NaI (4.6 g, 30.81 mmol) and TsNH₂ (10.5 g, 61.6 mmol), and the reaction mixture was stirred at 80 °C. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S6** (4.5 g, 65%).

S6 to S7: To a stirred solution of **S6** (2.55 g, 10.0 mmol) in acetone (33 mL) was added K₂CO₃ (2.76 g, 20 mmol), phenyl bromide (2.99 g, 15.0 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S7** (3.42 g, quant.).

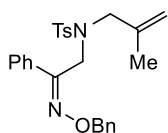
S7 to 142a: Same as general procedure (**S1 to S2**).

1-(4-isopropyl-2,3,5-trimethoxyphenyl)-5-methylhex-5-en-1-ol (**142a**)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.33 (s, 3H), 2.43 (s, 3H), 3.51 (s, 2H), 4.50 (s, 2H), 4.72 (s, 1H), 4.76 (s, 1H), 7.28 (d, 2H, *J* = 8.4 Hz), 7.33-7.40 (m, 3H), 7.60-7.69 (m, 4H), 9.30 (brs, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.8, 21.5, 42.4, 56.0, 114.4, 127.3, 127.5, 128.3, 129.4, 129.7, 133.7, 135.0, 140.0, 143.6, 154.9; IR (ATR) ν: 3245, 3069, 2906, 1327, 1155, 752, 661 cm⁻¹; HRMS (ESI) Calcd for C₁₉H₂₂N₂NaO₃S, [M+Na]⁺ 381.1249, found 381.1252; colorless solid (323 mg, 67%, mp: 140-143 °C)

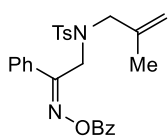
(*Z*)-N-(2-((benzyloxy)imino)-2-phenylethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (**142b**)



To a stirred solution of **142a** (103.3 mg, 0.289 mmol) in THF (1.4 mL) was added NaH (35 mg, 0.88 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Then, benzyl bromide (0.1 mL, 0.84 mmol) was added at 0 °C, and the mixture was stirred for 2 h at rt. The reaction mixture was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **142b** (*E/Z* mixture) which was recrystallized from hexane and AcOEt to give **142b** (*Z* only, 45.9 mg, 35%).

¹H-NMR (CDCl₃, 400 MHz) δ: 1.31 (s, 3H), 2.42 (s, 3H), 3.47 (s, 2H), 4.46 (s, 2H), 4.62 (s, 1H), 4.67 (s, 1H), 5.14 (s, 2H), 7.20-7.41 (m, 10H), 7.57-7.72 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.7, 21.5, 42.7, 55.7, 76.6, 114.4, 127.4, 127.5, 128.0, 128.2, 128.4, 128.5, 129.2, 129.6, 133.4, 135.3, 137.2, 139.9, 143.4, 153.9; IR (ATR) ν: 2970, 1738, 1365, 1216, 612 cm⁻¹; HRMS (ESI) Calcd for C₂₆H₂₈N₂NaO₃Si, [M+Na]⁺ 471.1718, found 471.1716; colorless solid

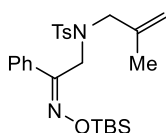
(*Z*)-N-(2-((benzyloxy)imino)-2-phenylethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (**142c**)



To a solution of **142a** (319 mg, 0.89 mmol) in CH₂Cl₂ (1.8 mL), NEt₃ (0.25 mL, 1.78 mmol) and BzCl (0.21 mL, 1.78 mmol) was added at 0 °C, and the mixture was stirred for 2 h at rt. Then, the mixture was diluted with water and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave crude **142c** which was purified by column chromatography (378 mg, 92%).

¹H-NMR (CDCl₃, 400 MHz) δ: 1.39 (s, 3H), 2.44 (s, 3H), 3.54 (s, 2H), 4.70 (s, 2H), 4.80 (s, 1H), 4.84 (s, 1H), 7.24 (d, 2H, *J* = 7.6 Hz), 7.38 (dd, 2H, *J* = 7.6, 7.6 Hz), 7.44-7.66 (m, 8H), 8.07 (d, 2H, *J* = 7.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.5, 21.2, 43.0, 55.4, 115.3, 127.2, 128.1, 128.1, 128.3, 128.4, 129.4, 129.5, 130.3, 132.2, 133.4, 134.8, 139.0, 143.6, 162.6, 163.0; IR (ATR) ν: 2942, 1763, 1344, 1212 cm⁻¹; HRMS (ESI) Calcd for C₂₆H₂₆N₂NaO₄S, [M+Na]⁺ 485.1510, found 485.1506; colorless solid

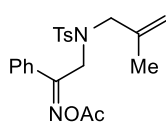
(Z)-N-(2-(((tert-butyldimethylsilyloxy)imino)-2-phenylethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (142d)



142a to 142d: Same as general procedure (S2 to S4).

¹H-NMR (CDCl₃, 400 MHz) δ: 0.17 (s, 6H), 0.91 (s, 9H), 1.34 (s, 3H), 2.43 (s, 3H), 3.50 (s, 2H), 4.53 (s, 2H), 4.69 (s, 1H), 4.72 (s, 1H), 7.28 (d, 2H, *J* = 8.4 Hz), 7.32-7.35 (m, 3H), 7.66-7.70 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ: -5.1, 18.0, 19.8, 21.5, 26.0, 42.1, 55.3, 113.9, 127.2, 127.5, 128.1, 129.1, 129.6, 134.3, 135.2, 140.0, 143.4, 157.0; IR (ATR) ν: 2954, 1737, 1372, 1238, 1045, 744, 666 cm⁻¹; HRMS (ESI) Calcd for C₂₅H₃₆N₂NaO₃SSi, [M+Na]⁺ 495.2114, found 495.2096; colorless oil (143.8 mg, quant.).

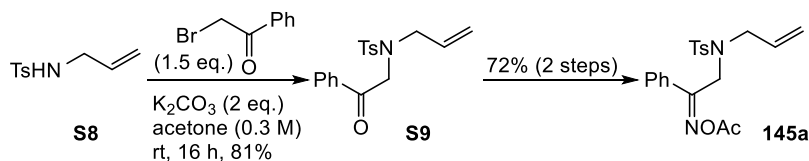
N-(2-(acetoxymino)-2-phenylethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (142e)



142a to 142d: Same as general procedure (S2 to S3).

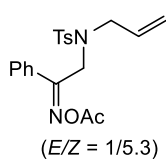
¹H-NMR (CDCl₃, 400 MHz) δ: 1.36 (s, 1.8 H), 1.41 (s, 1.2H), 2.03 (s, 1.2H), 2.24 (s, 1.8 H), 2.42 (s, 1.2H), 2.44 (s, 1.8H), 3.51 (s, 1.2H), 3.63 (s, 0.8H), 4.31 (s, 0.8H), 4.54 (s, 1.2H), 4.75 (s, 0.6H), 4.81 (s, 0.6H), 4.83 (s, 0.4H), 4.86 (s, 0.4H), 7.23 (dd, 2H, *J* = 8.4, 8.4 Hz), 7.36-7.46 (m, 4H), 7.62-7.73 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.4, 19.6, 19.7, 19.7, 21.5, 43.6, 50.8, 55.1, 55.9, 115.2, 115.8, 127.4, 127.5, 128.1, 128.2, 128.3, 128.4, 129.6, 129.7, 130.0, 130.1, 130.5, 132.3, 135.1, 135.3, 139.5, 139.8, 143.6, 143.8, 161.4, 161.5, 168.2, 168.9; IR (ATR) ν: 2928, 1739, 1349, 1160, 812, 782 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₄N₂NaO₄Si, [M+Na]⁺ 423.1255, found 423.1347; yellow oil (45.1 mg, 80%).

Synthesis of 145a



S8 to S9: Same as S6 to S7 // **S9 to 145a:** Same as general procedure (S2 to S3).

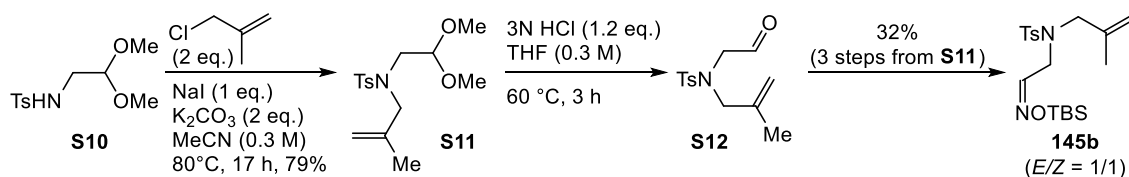
N-(2-(acetoxymino)-2-phenylethyl)-N-allyl-4-methylbenzenesulfonamide (145a)



¹H-NMR (CDCl₃, 400 MHz) δ: 2.05 (s, 0.48H), 2.24 (s, 2.52H), 2.42 (s, 0.48H), 2.45 (s, 2.52H), 3.57 (d, 1.68H, *J* = 6.4 Hz), 3.70 (d, 0.32H, *J* = 6.4 Hz), 4.39 (s, 0.32H), 4.60 (s, 1.68H), 5.04-5.18 (m, 2H), 5.39-5.51 (m, 1H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.39-7.52 (m, 3H), 7.60 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 7.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.4, 19.7, 21.4, 21.5, 42.5, 50.1, 50.7, 51.3, 119.9, 120.1, 127.4, 128.1, 128.2, 128.5, 129.6, 129.8, 130.1, 130.2, 130.6, 131.5, 131.8, 132.1, 135.6, 135.8, 143.6, 143.8, 161.5, 168.2, 168.6; IR

(ATR) ν : 2925, 1771, 1348, 1199, 1163, 928 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{NaO}_4\text{Si}$, $[\text{M}+\text{Na}]^+$ 409.1198, found 409.1195; yellow oil (253 mg, 72%).

Synthesis of 145b



S10 to S11: To a stirred solution of **S10** (1.25 g, 4.83 mmol) in MeCN (16 mL) was added K_2CO_3 (1.33 g, 9.65 mmol), NaI (724 mg, 4.83 mmol) and 3-chloro-2-methyl-1-propene (0.94 mL, 9.65 mmol), and the reaction mixture was stirred at 80 °C for 17 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S11** (1.2 g, 79%).

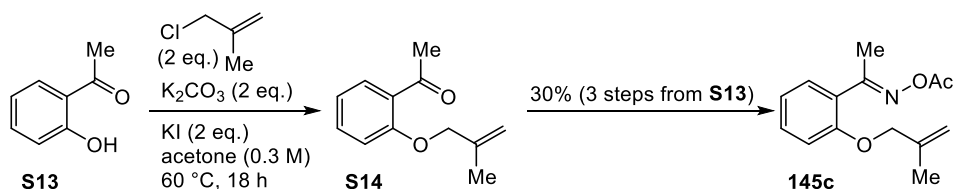
S11 to S12: To a stirred solution of **S11** (1.2 g, 3.83 mmol) in THF (12 mL) was added 3N HCl (1.5 mL, 4.5 mmol) at rt, and the reaction mixture was stirred at 60 °C for 3 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded crude **S12** (864 mg) and **S11** (223 mg, 19%).

S12 to 145b: Same as general procedure (**S1** to **S4**).

N-(2-(((tert-butyldimethylsilyl)oxy)imino)ethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (145b)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.69 (s, 1.5H), 1.75 (s, 1.5H), 2.43 (s, 3H), 3.68 (s, 1H), 3.69 (s, 1H), 3.85 (d, 1H, $J = 6.0$ Hz), 4.03 (d, 1H, $J = 3.6$ Hz), 4.86 (s, 1H), 4.93 (s, 1H), 6.74 (t, 0.5H, $J = 4.0$ Hz), 7.28-7.33 (m, 2.5H), 7.69 (d, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : -5.5, -5.5, 17.9, 19.7, 21.4, 25.8, 25.8, 42.5, 45.5, 53.7, 55.2, 115.0, 115.5, 127.1, 129.7, 129.8, 135.8, 136.4, 139.3, 139.3, 143.4, 143.6, 149.9, 152.1; IR (ATR) ν : 2929, 1739, 1350, 1249, 1160, 912, 754 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{NaO}_3\text{SSi}$, $[\text{M}+\text{Na}]^+$ 419.1801, found 419.1791; colorless oil (250 mg, 32%).

Synthesis of 145c

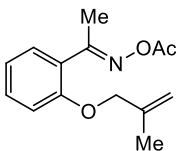


S13 to S14: To a stirred solution of **S13** (1.0 mL, 8.3 mmol) in acetone (28 mL) was added K_2CO_3 (2.3 g, 16.6 mmol), KI (2.8 g, 16.6 mmol) and 3-chloro-2-methyl-1-propene (1.6 mL, 16.6 mmol), and the

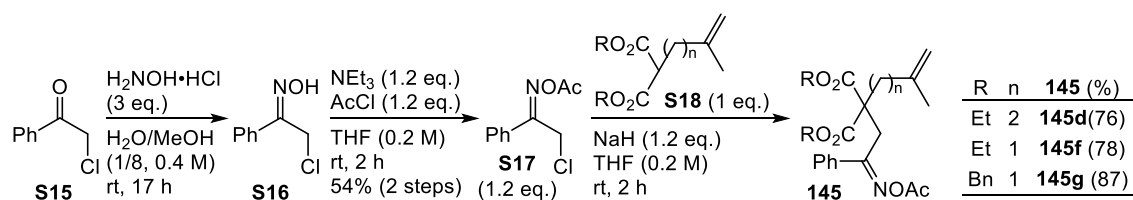
reaction mixture was stirred at 60 °C for 18 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S14** (1.11 g, 75%) and **S13** (283 mg, 25%) as an *inseparable mixture*. (*You should use excess amount of 3-chloro-2-methyl-1-propene)

S14 to 145c: Same as general procedure (**S1 to S3**).

(E)-1-(2-((2-methylallyl)oxy)phenyl)ethan-1-one O-acetyl oxime (145c)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 1.81 (s, 3H), 2.25 (s, 3H), 2.37 (s, 3H), 4.46 (s, 2H), 4.99 (s, 1H), 5.06 (s, 1H), 6.89 (d, 1H, *J* = 8.4 Hz), 6.96 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.33-7.40 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 17.5, 19.4, 19.8, 71.9, 112.0, 112.8, 120.7, 125.3, 129.9, 131.1, 140.2, 156.6, 164.7, 168.9; IR (ATR) ν: 2980, 1752, 1120 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₇NNaO₃, [M+Na]⁺ 270.1106, found 270.1115; yellow oil (93.7 mg, 30%)

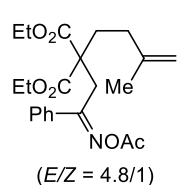
Synthesis of 145d, f, g



S15 to S16: To a slurry of phenacyl chloride (3.0 g, 19.4 mmol) and hydroxylamine hydrochloride (4.02 g, 58.2 mmol) in 5 mL of water was added with stirring portionwise methanol (40 mL) to yield a clear solution. The clear solution was stirred for 17 h at room temperature and was added cold water, whereupon an orange solid precipitated out. The oxime product was filtered out, washed several times with water, and dried under reduced pressure gave crude **S16** which was used in the next step without further purification.

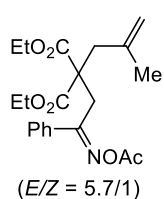
S16 to S17: To a solution of crude **S16** in THF (116 mL), NEt₃ (3.3 mL, 23.3 mmol) and AcCl (1.7 mL, 23.3 mmol) was added at 0 °C, and the mixture was stirred for 2 h at rt. Then, the mixture was diluted with H₂O and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated on a rotary evaporator gave crude **S17** which was purified by column chromatography (2.2 g, 54%, 2 steps).

S17 to 145: To a solution of **S18** (1.0 eq.) in THF (0.2 M for **S18**) was added 60% sodium hydride (1.2 eq.) at 0 °C and the mixture was stirred at room temperature for 30 minutes. **S17** (1.2 eq.) was then added and the mixture was stirred for 2 h. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **145**.

diethyl 2-(2-(acetoxylimino)-2-phenylethyl)-2-(3-methylbut-3-en-1-yl)malonate (145d)

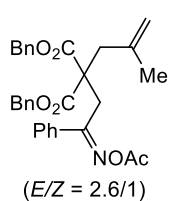
¹H-NMR (CDCl₃, 400 MHz) δ: 1.17 (t, 6H, *J* = 6.8 Hz), 1.63 (s, 0.52H), 1.67 (s, 2.48H), 1.82-2.31 (m, 7H), 3.39 (s, 1.66H), 3.57 (s, 0.34H), 3.80-4.20 (m, 4H), 4.58 (s, 0.17H), 4.61 (s, 0.17H), 4.64 (s, 1.83H), 4.68 (s, 1.83H), 7.29-7.82 (m, 5H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.8, 19.5, 22.2, 30.4, 32.0, 37.3, 56.0, 61.4, 110.5, 127.7, 127.9, 129.7, 132.2, 144.5, 162.4, 168.4, 170.1; IR (ATR) ν: 2982, 1728, 1183, 903, 697 cm⁻¹;

HRMS (ESI) Calcd for C₂₂H₂₉NNaO₆, [M+Na]⁺ 426.1893, found 426.1902; yellow oil (404.0 mg, 76%).

diethyl 2-(2-(acetoxylimino)-2-phenylethyl)-2-(2-methylallyl)malonate (145f)

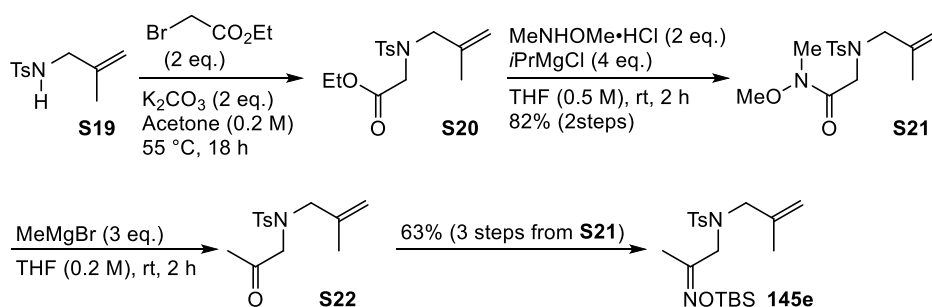
¹H-NMR (CDCl₃, 400 MHz) δ: 1.13 (t, 0.9H, *J* = 6.8 Hz), 1.22 (t, 5.1H, *J* = 6.8 Hz), 1.62 (s, 0.45H), 1.65 (s, 2.55H), 2.02 (s, 2.55H), 2.21 (s, 0.45H), 2.65 (s, 0.3H), 2.97 (s, 1.7H), 3.35 (s, 1.7H), 3.61 (s, 0.3H), 3.86-4.18 (m, 4H), 4.72 (s, 0.15H), 4.80 (s, 0.85H), 4.85 (s, 0.15H), 4.88 (s, 0.85H), 7.28-7.59 (m, 5H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.7, 19.6, 23.0, 37.6, 39.6, 55.4, 61.5, 116.0, 127.3, 128.0, 129.5, 132.9, 140.6, 162.5, 168.6, 170.3;

IR (ATR) ν: 2981, 1770, 1732, 1202, 760 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₇NNaO₆, [M+Na]⁺ 412.1736, found 412.1725; yellow oil (284.2 mg, 78%).

dibenzyl 2-(2-(acetoxylimino)-2-phenylethyl)-2-(2-methylallyl)malonate (145g)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.56 (s, 3H), 1.98 (s, 2.17H), 2.17 (s, 0.83H), 2.69 (s, 0.56H), 3.03 (s, 1.44H), 3.37 (s, 1.44H), 3.68 (s, 0.56H), 4.58-5.06 (m, 6H), 7.11-7.55 (m, 15H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.1, 19.5, 20.9, 22.9, 23.8, 31.3, 37.7, 39.8, 40.9, 55.5, 56.0, 60.2, 67.3, 67.3, 113.8, 116.2, 127.3, 128.0, 128.1, 128.1, 128.3, 129.5, 130.2, 132.7, 134.1, 134.6, 135.1, 140.3, 140.4, 162.0, 163.5, 168.7, 169.8, 169.9; IR (ATR) ν:

2943, 1730, 1194, 903, 736 cm⁻¹; HRMS (ESI) Calcd for C₃₁H₃₁NNaO₆, [M+Na]⁺ 536.2049, found 536.2049; yellow oil (504.5 mg, 87%).

Synthesis of 145e

S19 to S20: To a stirred solution of **S19** (1.0 g, 4.44 mmol) in acetone (22 mL) was added K₂CO₃ (1.23 g, 8.88 mmol), ethyl bromoacetate (0.98 mL, 8.88 mmol) and the reaction mixture was stirred at 55 °C for 18 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Short column chromatography gave crude **S20**.

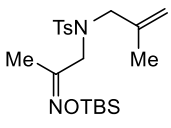
S20 to S21: To a solution of crude **S20** and MeNHOMe·HCl (866 mg, 8.88 mmol) in THF (9 mL) was added *i*PrMgCl (2.0 M in THF, 8.9 mL, 17.8 mmol) at -20 °C and the mixture was stirred at room

temperature for 2 h. Sat. NH₄Cl aq. was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding **S21** as a yellow oil (1.19 g, 82%, 2 steps).

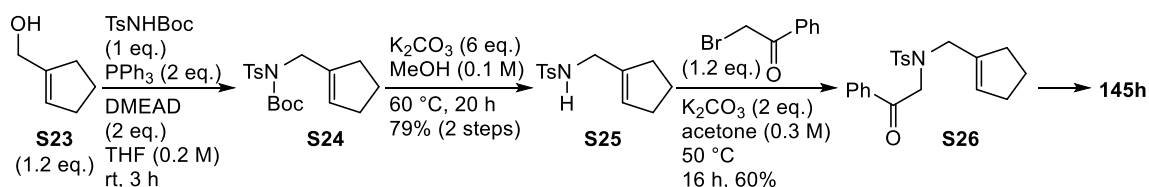
S21 to S22: To a solution of **S21** (136.4 mg, 0.42 mmol) in THF (2 mL) was added MeMgBr (3.0 M in Et₂O, 0.42 mL, 1.3 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. Sat. NH₄Cl aq. was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude **S22** was used in the next step without further purification.

S22 to 145e: Same as general procedure (**S1 to S4**). (108.2 mg, 63%, 3 steps)

N-(2-(((tert-butyldimethylsilyl)oxy)imino)propyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (145e)

 ¹H-NMR (CDCl₃, 400 MHz) δ: 0.13 (s, 5.3H), (s, 0.7H), 0.90 (s, 1.1H), 0.91 (s, 7.9H), 1.65 (s, 2.6H), 1.68 (s, 0.4H), 1.84 (s, 2.6H), 1.92 (s, 0.4H), 2.43 (s, 2.6H), 2.44 (s, 0.4H), 3.62 (s, 0.2H), 3.64 (s, 1.8H), 3.78 (s, 1.8H), 4.04 (s, 0.2H), 4.76 (s, 0.1H), 4.80 (s, 0.9H), 4.87 (s, 1H), 7.29 (d, 2H, *J* = 8.0 Hz), 7.69(d, 2H, *J* = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: -5.3, 12.3, 18.0, 20.0, 21.5, 26.0, 51.9, 54.3, 114.8, 127.3, 129.6, 136.2, 139.7, 143.3, 157.7; IR (ATR) ν: 2928, 1342, 1160, 916, 777, 655 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₃₄N₂NaO₃Si, [M+Na]⁺ 433.1957, found 433.1953; colorless oil

Synthesis of 145h



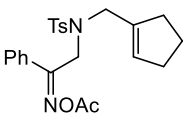
S23 to S24: To a stirred solution of **S23** (469 mg, 4.8 mmol), TsNHBoc (1.08 g, 4.0 mmol), PPh₃ (2.1 g, 8.0 mmol) in THF (20 mL) was added DMEAD (1.9 g, 8.0 mmol) at 0 °C, and the reaction mixture was stirred for 3 h at rt. Then, the reaction mixture was concentrated in vacuo. Short column chromatography gave crude **S24** which was used in the next step without further purification.

S24 to S25: To a stirred solution of crude **S24** in MeOH (40 mL) was added K₂CO₃ (3.3 g, 24 mmol) and the reaction mixture was stirred for 20 h at 60 °C. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **S25** (790 mg, 79%, 2 steps).

S25 to S26: To a stirred solution of **S25** (385 mg, 1.53 mmol) in acetone (5 mL) was added K_2CO_3 (422 mg, 3.06 mmol), phenyl bromide (366 mg, 1.84 mmol) and the reaction mixture was stirred at 50 ° for 16 h. The reaction was quenched with H_2O , extracted with AcOEt, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S26** as an orange oil (338.8 g, 60%).

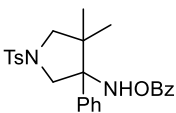
S26 to 145h: Same as general procedure (**S1 to S3**). (350 mg, 89%, 2 steps)

N-(2-(acetoxylimino)-2-phenylethyl)-N-(cyclopent-1-en-1-ylmethyl)-4-methylbenzenesulfonamide (145 h)



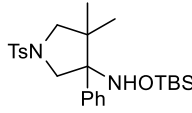
1H -NMR ($CDCl_3$, 400 MHz) δ : 1.58-2.47 (m, 12H), 3.62 (s, 1.58H), 3.73 (s, 0.42H), 4.32 (s, 0.42H), 4.55 (s, 1.58H), 5.39 (s, 0.79H), 5.47 (s, 0.21H), 7.28-7.72 (m, 9H); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ : 19.7, 21.4, 22.9, 32.2, 32.9, 49.6, 127.3, 127.9, 128.2, 129.6, 130.5, 130.5, 132.1, 135.2, 138.0, 143.7, 161.4, 168.7; IR (ATR) ν : 2923, 1708, 1358, 1220, 1160, 662 cm^{-1} ; HRMS (ESI) Calcd for $C_{23}H_{26}N_2NaO_4Si$, $[M+Na]^+$ 449.1511, found 449.1500; yellow oil

O-benzoyl-N-(4,4-dimethyl-3-phenyl-1-tosylpyrrolidin-3-yl)hydroxylamine (143c)



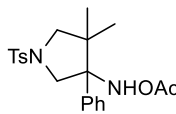
1H -NMR ($CDCl_3$, 400 MHz) δ : 0.70 (s, 3H), 1.10 (s, 3H), 2.28 (s, 3H), 3.37 (d, 1H, $J = 9.2$ Hz), 3.46 (d, 1H, $J = 9.2$ Hz), 3.94 (d, 1H, $J = 11.2$ Hz), 4.21 (d, 1H, $J = 11.2$ Hz), 7.17 (d, 2H, $J = 8.4$ Hz), 7.28-7.38 (m, 7H), 7.53 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.64 (d, 2H, $J = 8.4$ Hz), 7.76 (d, 2H, $J = 7.6$ Hz), 7.92 (s, 1H); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ : 19.6, 21.4, 24.9, 44.8, 53.1, 60.0, 72.8, 126.5, 127.4, 127.8, 128.3, 128.4, 129.0, 129.6, 133.3, 143.5, 165.5; IR (ATR) ν : 2924, 1718, 1343, 1157, 705 cm^{-1} ; HRMS (ESI) Calcd for $C_{26}H_{28}N_2NaO_3Si$, $[M+Na]^+$ 487.1662, found 487.1160; colorless solid (20.9 mg, 35%).

O-(tert-butyltrimethylsilyl)-N-(4,4-dimethyl-3-phenyl-1-tosylpyrrolidin-3-yl)hydroxylamine (143d)

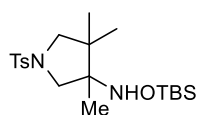


1H -NMR ($CDCl_3$, 400 MHz) δ : -0.21 (s, 3H), -0.09 (s, 3H), 0.46 (s, 3H), 0.71 (s, 9H), 1.05 (s, 3H), 2.43 (s, 3H), 3.26 (d, 1H, $J = 9.6$ Hz), 3.30 (d, 1H, $J = 9.6$ Hz), 3.87 (d, 1H, $J = 10.0$ Hz), 4.19 (d, 1H, $J = 10.0$ Hz), 4.97 (brs, 1H), 7.19-7.30 (m, 5H), 7.33 (d, 2H, $J = 8.0$ Hz), 7.79 (d, 2H, $J = 8.0$ Hz); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ : -5.53, -5.45, 17.8, 19.6, 21.5, 25.6, 25.9, 44.0, 51.2, 59.9, 73.5, 127.1, 127.3, 127.5, 127.6, 129.7, 134.5, 138.4, 143.4; IR (ATR) ν : 2926, 1713, 1345, 1158, 1092, 826 cm^{-1} ; HRMS (ESI) Calcd for $C_{25}H_{38}N_2NaO_3Si$, $[M+Na]^+$ 497.2270, found 497.2257; colorless solid (23.7 mg, 60%).

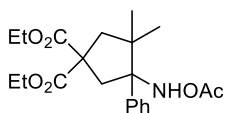
O-acetyl-N-(4,4-dimethyl-3-phenyl-1-tosylpyrrolidin-3-yl)hydroxylamine (143e)



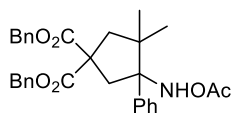
1H -NMR ($CDCl_3$, 400 MHz) δ : 0.58 (s, 3H), 1.04 (s, 3H), 1.80 (s, 3H), 2.44 (s, 3H), 3.28 (d, 1H, $J = 9.6$ Hz), 3.40 (d, 1H, $J = 9.6$ Hz), 3.83 (d, 1H, $J = 11.2$ Hz), 4.08 (d, 1H, $J = 11.2$ Hz), 7.25-7.31 (m, 4H), 7.33 (d, 2H, $J = 8.0$ Hz), 7.79-7.81 (m, 3H); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ : 18.8, 19.7, 21.5, 24.7, 44.6, 53.1, 59.8, 72.4, 126.5, 127.4, 127.7, 128.2, 129.5, 134.2, 136.9, 143.5, 169.7; IR (ATR) ν : 2969, 1739, 1343, 1220, 1157, 813 cm^{-1} ; HRMS (ESI) Calcd for $C_{21}H_{26}N_2NaO_4Si$, $[M+Na]^+$ 425.1511, found 425.1504; colorless solid (32.8 mg, 61%).

O-(tert-butyltrimethylsilyl)-N-(3,4,4-trimethyl-1-tosylpyrrolidin-3-yl)hydroxylamine (146e)

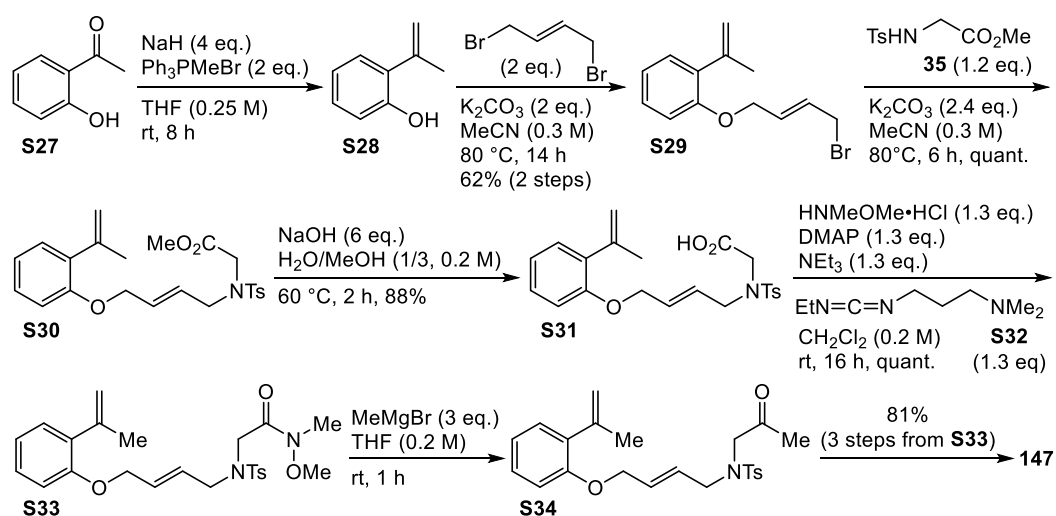
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : -0.02 (s, 3H), 0.02 (s, 3H), 0.78 (s, 3H), 0.84 (s, 3H), 0.87 (s, 3H), 0.96 (s, 3H), 2.42 (s, 3H), 3.04 (d, 1H, $J = 10.8$ Hz), 3.16 (brs, 2H), 3.64 (d, 1H, $J = 10.8$ Hz), 4.42 (brs, 1H), 7.30 (d, 2H, $J = 7.6$ Hz), 7.72 (d, 2H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : -5.6, -5.5, 16.0, 17.9, 19.1, 21.5, 24.3, 26.1, 43.0, 54.2, 59.9, 68.1, 127.3, 129.6, 134.4, 143.2; IR (ATR) ν : 2952, 1542, 1344, 1158, 1094, 665 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{36}\text{N}_2\text{NaO}_3\text{SSi}$, $[\text{M}+\text{Na}]^+$ 435.2114, found 435.2107; yellow oil (25.7 mg, 66%).

diethyl 3-(acetoxylamino)-4,4-dimethyl-3-phenylcyclopentane-1,1-dicarboxylate (146f)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.66 (s, 3H), 1.15 (s, 3H), 1.28 (t, 6H, $J = 7.2$ Hz), 1.79 (s, 3H), 2.17 (d, 1H, $J = 14.4$ Hz), 2.91 (d, 1H, $J = 14.4$ Hz), 3.06 (d, 1H, $J = 14.4$ Hz), 3.35 (d, 1H, $J = 14.4$ Hz), 4.16-4.32 (m, 4H), 7.24-7.40 (m, 5H), 8.09 (brs, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 14.0, 18.9, 21.4, 27.4, 39.3, 45.7, 47.4, 56.7, 61.5, 61.7, 74.6, 126.5, 127.1, 127.9, 138.8, 169.8, 172.1, 173.0; IR (ATR) ν : 2980, 1730, 1369, 1238, 1044, 700 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{29}\text{NNaO}_6$, $[\text{M}+\text{Na}]^+$ 414.1893, found 414.1906; orange oil (57.5 mg, 96%).

dibenzyl 3-(acetoxylamino)-4,4-dimethyl-3-phenylcyclopentane-1,1-dicarboxylate (146g)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.63 (s, 3H), 1.13 (s, 3H), 1.64 (s, 3H), 2.18 (d, 1H, $J = 14.4$ Hz), 2.97 (d, 1H, $J = 14.4$ Hz), 3.11 (d, 1H, $J = 14.4$ Hz), 3.37 (d, 1H, $J = 14.4$ Hz), 5.06-5.20 (m, 4H), 7.24-7.36 (m, 15H), 8.14 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 18.8, 21.4, 27.5, 39.5, 45.6, 47.5, 56.9, 67.3, 67.4, 74.7, 126.4, 127.1, 127.9, 127.9, 128.0, 128.0, 128.2, 128.4, 128.5, 135.4, 135.8, 138.6, 169.9, 171.8, 172.7; IR (ATR) ν : 2969, 1731, 1239, 698 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{31}\text{H}_{33}\text{NNaO}_6$, $[\text{M}+\text{Na}]^+$ 538.2206, found 538.2193; yellow oil (69.2 mg, 83%).

Synthesis of 147

S27 to S28: To a suspension of NaH (3.4 g, 84 mmol) in THF (84 mL) was added Ph_3PMeBr in one portion (15 g, 42 mmol) at 0 °C, and the resulting mixture was stirred at rt for 1 h. Then, **S27** (2.5 mL, 21 mmol) was added at 60 °C, and the mixture was stirred 8 h at rt. Water was added and the aqueous phase

was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by short column chromatography to give crude **S28** (2.13 g).

S29 to S30: To a stirred solution of **S29** (753 mg, 2.1 mmol) in MeCN (7 mL) was added K₂CO₃ (696 mg, 5.1 mmol), and **S35** (613 mg, 2.5 mmol), and the reaction mixture was stirred at 80 °C for 6 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S30** (1.1 g, quant.).

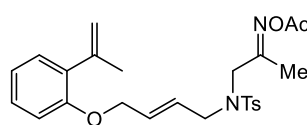
S30 to S31: To a solution of **S30** (1.1 g, 2.1 mmol) in MeOH (9 mL) was added H₂O (3 mL) and NaOH (504 mg, 12.6 mmol) at rt, and the reaction mixture was stirred at 60 °C for 2 h. The reaction was quenched with 1 N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S31** (937.2 mg, 88%).

S31 to S33: To a stirred solution of **S31** (83 mg, 0.2 mmol), HNMeOMe•HCl (25 mg, 0.26 mmol), DMAP (32 mg, 0.26 mmol) and NEt₃ (36 μL, 0.26 mmol) in CH₂Cl₂ (1 mL) was added **S32** (50 mg, 0.26 mmol) at 0 °C and the reaction mixture was stirred at rt for 6 h. The reaction was quenched with 1N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S33** (91.7 mg, quant.).

S33 to S34: To a solution of **S33** (91.7 mg, 0.2 mmol) in THF (1 mL) was added MeMgBr (3.0 M in Et₂O, 0.2 mL, 0.6 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. Sat. NH₄Cl aq. was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude **S34** was used in the next step without further purification.

S34 to 147: Same as general procedure (**S1 to S3**). (40.0 mg, 81%, 3 steps)

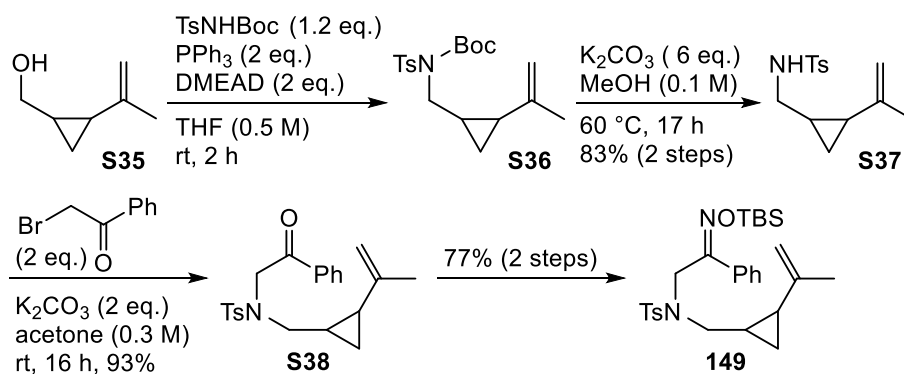
N-(2-(acetoxylimino)propyl)-4-methyl-N-((E)-4-(2-(prop-1-en-2-yl)phenoxy)but-2-en-1-yl)benzenesulfonamide (147)



(*E* or *Z*, single isomer)

¹H-NMR (CDCl₃, 400 MHz) δ: 2.06 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.41 (s, 3H), 3.75 (d, 2H, *J* = 6.8 Hz), 3.91 (s, 2H), 4.44 (d, 2H, *J* = 4.0 Hz), 5.03 (s, 1H), 5.12 (s, 1H), 5.58-5.64 (m, 1H), 5.78-5.84 (m, 1H), 6.76 (d, 1H, *J* = 8.4 Hz), 6.92 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.19 (d, 2H, *J* = 7.2 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.66 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.9, 19.4, 21.5, 23.2, 50.2, 51.4, 67.5, 112.1, 115.1, 120.9, 125.8, 127.2, 128.2, 129.5, 129.8, 129.9, 131.2, 132.9, 135.4, 143.9, 155.2, 162.8, 168.2; IR (ATR) ν: 2920, 1772, 1343, 1201, 1162, 758 cm⁻¹; HRMS (ESI) Calcd for C₂₅H₃₀N₂NaO₅S, [M+Na]⁺ 493.1773, found 493.1773; yellow oil

Synthesis of 149



S35 to S36: To a stirred solution of **S35** (178 mg, 1.59 mmol), TsNHBoc (517 mg, 1.91 mmol), PPh₃ (833 mg, 3.18 mmol) in THF (10 mL) was added DMEAD (744 mg, 3.18 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at rt. Then, the reaction mixture was concentrated in vacuo. Short column chromatography gave crude **S36** which was used in the next step without further purification.

S36 to S37: To a stirred solution of crude **S36** in MeOH (16 mL) was added K₂CO₃ (1.36 g, 9.86 mmol) and the reaction mixture was stirred for 17 h at 60 °C. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **S37** (420 mg, 83%, 2 steps).

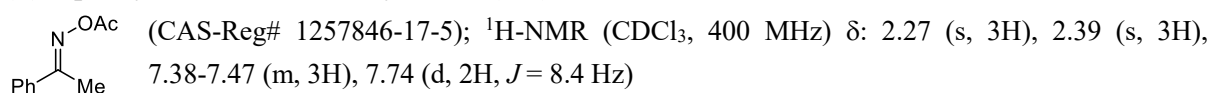
S37 to S38: To a stirred solution of **S37** (420 mg, 1.58 mmol) in acetone (5 mL) was added K₂CO₃ (437 mg, 3.17 mmol), phenyl bromide (630 mg, 3.17 mmol) and the reaction mixture was stirred at 50 ° for 16 h. The reaction was quenched with H₂O, extracted with AcOEt, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography afforded **S38** as a yellow solid (562.5 mg, 93%).

S38 to 149 Same as general procedure (**S1 to S4**). (94.3 mg, 77%, 2 steps)

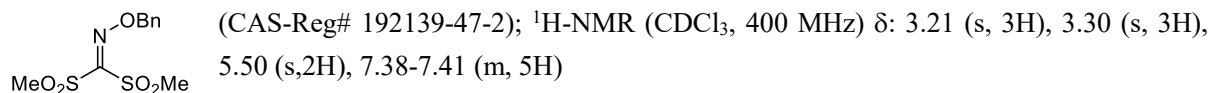
N-(2-(((tert-butyldimethylsilyloxy)imino)-2-phenylethyl)-4-methyl-N-((2-(prop-1-en-2-yl)cyclopropyl)methyl)benzenesulfonamide (149)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.18 (s, 6H), 0.34-1.38 (m, 1H), 0.48-0.52 (m, 1H), 0.92 (s, 9H), 0.93-0.99 (m, 1H), 1.07-1.13 (m, 1H), 1.40 (s, 3H), 2.42 (s, 3H), 2.85 (dd, 1H, *J* = 14.4, 6.8 Hz), 2.93 (dd, 1H, *J* = 14.4, 6.8 Hz), 4.45 (s, 1H), 4.52 (s, 1H), 4.60 (d, 1H, *J* = 13.2 Hz), 4.61 (d, 1H, *J* = 13.2 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.31-7.40 (m, 3H), 7.64 (d, 2H, *J* = 8.0 Hz), 7.72-7.81 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ: -5.2, 11.6, 17.6, 18.1, 20.3, 21.5, 24.7, 26.0, 41.5, 52.6, 108.5, 127.0, 127.4, 128.3, 129.3, 129.6, 134.0, 135.8, 143.3, 144.8, 157.3; IR (ATR) ν: 2928, 1737, 1342, 1158, 936 cm⁻¹; HRMS (ESI) Calcd for C₂₈H₄₀N₂NaO₃SSi, [M+Na]⁺ 535.2427, found 535.2431; colorless solid

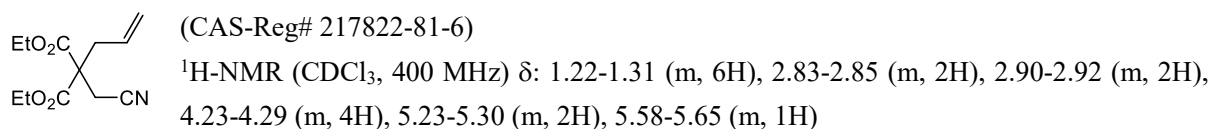
(E)-1-phenylethan-1-one O-acetyl oxime (152)



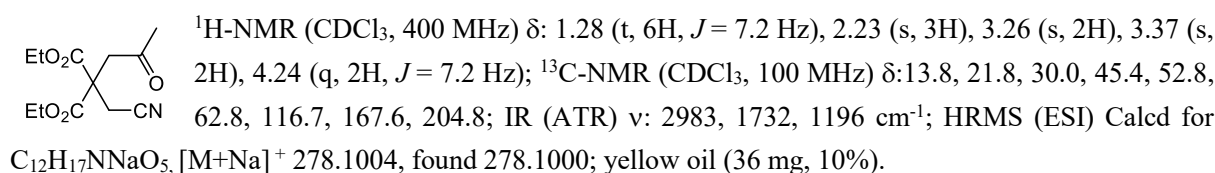
bis(methylsulfonyl)methanone O-benzyl oxime (154)



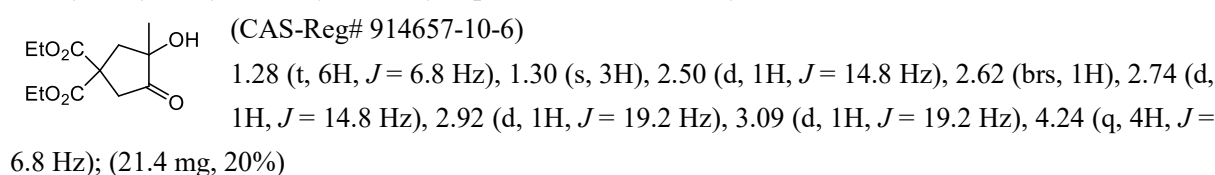
diethyl 2-allyl-2-(cyanomethyl)malonate (156)



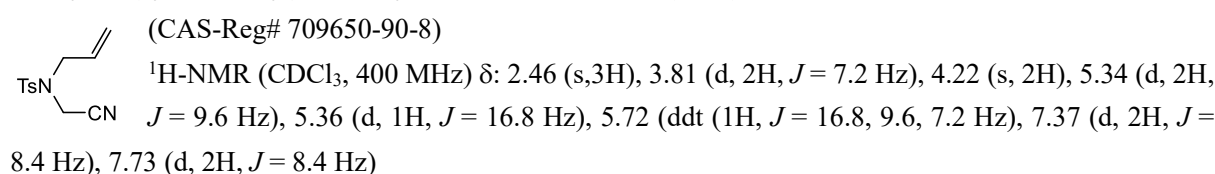
diethyl 2-(cyanomethyl)-2-(2-oxopropyl)malonate (158)



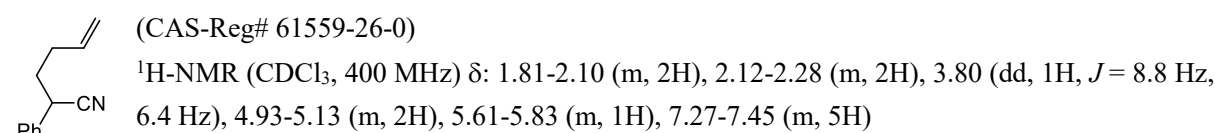
diethyl 3-hydroxy-3-methyl-4-oxocyclopentane-1,1-dicarboxylate (159)



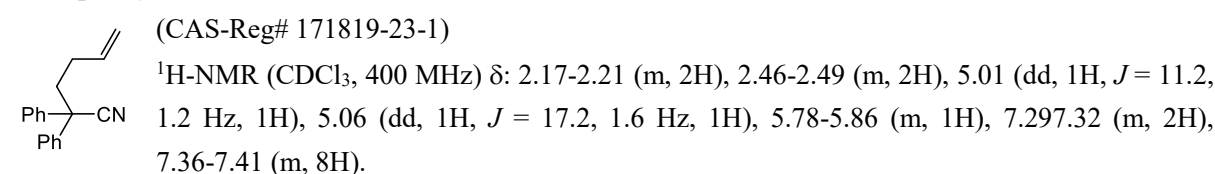
N-allyl-N-(cyanomethyl)-4-methylbenzenesulfonamide (162a)



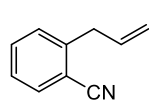
2-phenylhex-5-enenitrile (162a)



2,2-diphenylhex-5-enenitrile (162c)



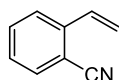
2-allylbenzonitrile (162d)



(CAS-Reg# 61463-61-4)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 3.53 (d, 2H, $J = 6.0$ Hz), 5.06 (dd, 1H, $J = 17.2, 2.0$ Hz), 5.08 (dd, 1H, $J = 10.0, 2.0$ Hz), 5.88 (ddt, 1H, $J = 17.2, 10.0, 6.0$ Hz), 7.24-7.56 (m, 4H)

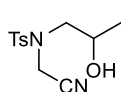
2-vinylbenzonitrile (162e)



(CAS-Reg# 656807-25-9)

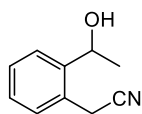
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 3.76 (s, 2H), 5.43 (d, 1H, $J = 10.2$ Hz), 5.67 (d, 1H, $J = 17.6$ Hz), 6.84 (dd, 1H, $J = 17.6, 10.2$ Hz), 7.28-7.40 (m, 3H), 7.50 (d, 1H, $J = 6.8$ Hz)

N-(cyanomethyl)-N-(2-hydroxypropyl)-4-methylbenzenesulfonamide (164a)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.24 (d, 3H, $J = 6.4$ Hz), 1.96 (d, 1H, $J = 4.0$ Hz), 2.45 (s, 3H), 3.08 (dd, 1H, $J = 14.4, 8.0$ Hz), 3.23 (dd, 1H, $J = 14.4, 2.0$ Hz), 4.03-4.16 (m, 1H), 4.39 (d, 1H, $J = 18.4$ Hz), 4.50 (d, 1H, $J = 18.4$ Hz), 7.37 (d, 2H, $J = 8.4$ Hz), 7.73 (d, 2H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 20.9, 21.6, 37.2, 54.1, 67.1, 114.2, 127.5, 130.1, 134.3, 144.8; IR (ATR) ν : 3212, 1549, 1357 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{NaO}_3\text{S}$, $[\text{M}+\text{Na}]^+$ 291.0779, found 291.0775; yellow oil (26.5 mg, 35%).

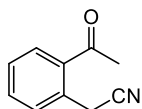
2-(2-(1-hydroxyethyl)phenyl)acetonitrile (164e)



(CAS-Reg# 1897827-29-0)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.52 (d, 3H, $J = 6.4$ Hz), 2.10 (brs, 1H), 3.88 (d, 2H, $J = 2.4$ Hz), 5.04 (q, 1H, $J = 6.4$ Hz), 7.29-7.41 (m, 3H), 7.46 (d, 1H, $J = 7.2$ Hz); (18.6 mg, 36%)

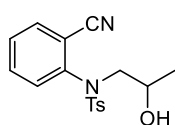
2-(2-acetylphenyl)acetonitrile (165e)



(CAS-Reg# 58422-85-8)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 2.65 (s, 3H), 4.16 (s, 2H), 7.46-7.61 (m, 3H), 7.90 (d, 1H, $J = 7.6$ Hz); (21.2 mg, 42%)

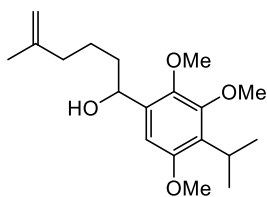
N-(2-cyanophenyl)-N-(2-hydroxypropyl)-4-methylbenzenesulfonamide (164f)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.17 (d, 3H, $J = 6.0$ Hz), 2.45 (s, 3H), 3.53-3.61 (m, 2H), 3.89 (brs, 1H), 7.23 (d, 1H, $J = 7.8$ Hz), 7.31 (d, 2H, $J = 7.8$ Hz), 7.45 (dd, 1H, $J = 7.8, 7.8$ Hz), 7.58-7.61 (m, 3H), 7.67 (d, 1H, $J = 7.8$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 20.3, 21.6, 59.2, 66.1, 115.0, 116.6, 128.1, 128.7, 129.9, 130.2, 133.6, 133.8, 134.6, 142.8, 144.5; IR (ATR) ν : 3170, 1595, 1488, 1352, 1165 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{NaO}_3\text{S}$, $[\text{M}+\text{Na}]^+$ 353.0936, found 353.0948; yellow oil (12.3 mg, 30%).

第五章の実験

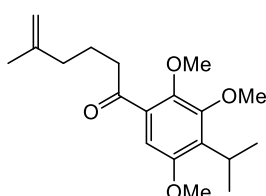
1-(4-isopropyl-2,3,5-trimethoxyphenyl)-5-methylhex-5-en-1-ol (**226**)



To a solution of Mg (324 mg, 13.35 mmol) and I₂ (2 blocks) in Et₂O (3 mL) was added a solution of **225** (5-bromo-2-methylpent-1-ene, 1.45 g, 8.90 mmol) in Et₂O (4 mL) slowly at rt, and the mixture was stirred for 1 h at rt. Then the solution was cool down to 0 °C, and the solution of aldehyde **215** (1.06 g, 4.45 mmol) in Et₂O (7 mL) was added and the solution was stirred for another 4 h at room temperature. The solution was dissolved in AcOEt, sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 10/1) to afford **226** (1.37 g, 96%).

¹H-NMR (CDCl₃, 400 MHz) δ: 1.29 (d, 6H, *J* = 7.2 Hz), 1.45-1.82 (m, 4H), 1.72 (s, 3H), 2.07 (t, 2H, *J* = 6.8 Hz), 2.29 (d, 1H, *J* = 5.2 Hz), 3.48 (septet, 1H, *J* = 7.2 Hz), 3.78 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.68 (s, 1H), 4.71 (s, 1H), 4.86-4.97 (m, 1H), 6.60 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.1, 21.1, 22.2, 24.0, 25.0, 37.5, 37.9, 55.6, 60.5, 60.6, 69.8, 104.1, 109.9, 129.4, 135.2, 144.1, 145.6, 151.3, 154.7; IR (ATR) ν: 3413, 2935, 1741, 1407, 1027 cm⁻¹; HRMS (ESI) Calcd for C₁₉H₃₀NaO₄, [M+Na]⁺ 345.2042, found 345.2038; yellow oil

1-(4-isopropyl-2,3,5-trimethoxyphenyl)-5-methylhex-5-en-1-one (**227**)



MnO₂ (102 mg, 1.18 mmol) was added to a stirred solution of **226** (38 mg, 0.118 mmol) in CH₂Cl₂ (2 mL) at rt, and the solution was stirred for another 70 h at 40 °C. The solution was dissolved in CH₂Cl₂, sat. NH₄Cl aq. was added and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford **227** (22.0mg, 65%) and **227** (12.3 mg, 32%)

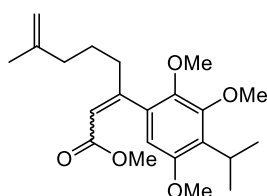
¹H-NMR (CDCl₃, 400 MHz) δ: 1.29 (d, 6H, *J* = 7.6 Hz), 1.74 (s, 3H), 1.80-1.89 (m, 2H), 2.05-2.12 (m, 2H), 2.96-3.01 (m, 2H), 3.52 (septet, 1H, *J* = 7.6 Hz), 3.80 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.71 (s, 1H), 4.73 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 20.8, 22.1, 22.2, 25.5, 37.3, 42.6, 55.6, 60.9, 61.1, 105.9, 110.3, 130.5, 135.5, 145.4, 147.1, 152.0, 154.5, 202.1 IR (ATR) ν: 2935, 1676, 1403, 1058, 1024, 886 cm⁻¹; HRMS (ESI) Calcd for C₁₉H₂₈NaO₄, [M+Na]⁺ 343.1885, found 343.1873; yellow oil

Synthesis of **214**

Diethylphosphonoacetic acid methyl ester (0.22 mL, 1.36 mmol) was added to a stirred solution of NaH (54 mg, 1.36 mmol) in THF (2 mL) at 0 °C, and the solution was stirred for another 30 min at 0 °C. Then **227** (217 mg, 0.68 mmol) in THF (1.4 mL) was added at 0 °C, and the solution was stirred for 18 h at 60 °C. The solution was dissolved in AcOEt, H₂O was added and the aqueous phase was extracted with

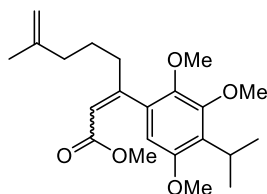
AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford **214-less** (133.6mg, 53%) and **214-more** (121.4 mg, 47%)

methyl 3-(4-isopropyl-2,3,5-trimethoxyphenyl)-7-methylocta-2,7-dienoate (214-less polar)



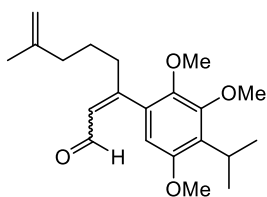
¹H-NMR (CDCl₃, 400 MHz) δ: 1.30 (d, 6H, *J* = 7.2 Hz), 1.53 (tt, 2H, *J* = 7.2, 7.2 Hz), 1.66 (s, 3H), 2.05 (t, 2H, *J* = 7.2 Hz), 3.05 (t, 2H, *J* = 7.2 Hz), 3.50 (septet, 1H, *J* = 7.2 Hz), 3.72 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.62 (s, 1H), 4.67 (s, 1H), 5.90 (s, 1H), 6.35 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.1, 22.2, 25.2, 26.5, 31.9, 37.7, 51.0, 55.7, 60.8, 60.9, 106.8, 109.9, 118.8, 130.7, 133.7, 144.4, 145.7, 151.8, 154.2, 160.9, 166.7; IR (ATR) ν: 2935, 1687, 1401, 1232, 1110, 1025, 884, 809 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₂NaO₅, [M+Na]⁺ 399.2147, found 399.2155: yellow oil

methyl 3-(4-isopropyl-2,3,5-trimethoxyphenyl)-7-methylocta-2,7-dienoate (214-more polar)



¹H-NMR (CDCl₃, 400 MHz) δ: 1.30 (d, 6H, *J* = 7.2 Hz), 1.59 (tt, 2H, *J* = 7.2, 7.2 Hz), 1.68 (s, 3H), 2.05 (t, 2H, *J* = 7.2 Hz), 2.43 (t, 2H, *J* = 7.2 Hz), 3.49 (septet, 1H, *J* = 7.2 Hz), 3.55 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 4.66 (s, 1H), 4.71 (s, 1H), 5.93 (s, 1H), 6.22 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.2, 22.2, 25.1, 25.2, 37.1, 39.0, 50.9, 55.8, 60.5, 60.8, 106.2, 110.3, 117.7, 129.8, 131.6, 143.4, 145.2, 151.5, 154.1, 157.1, 166.2; IR (ATR) ν: 2938, 1690, 1397, 1234, 1106, 888 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₂NaO₅, [M+Na]⁺ 399.2147, found 399.2155: yellow oil

3-(4-isopropyl-2,3,5-trimethoxyphenyl)-7-methylocta-2,7-dienal (235-more polar)



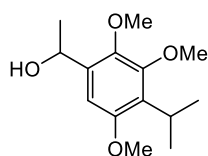
DIBAL (1.0 M in toluene, 1.0 mL, 1.0 mmol) was added to a stirred solution of **214** (122.6 mg, 0.326 mmol) in toluene (2.5 mL) at -78 °C, and the solution was slowly warmed up to rt, and stirred for additional 4 h at rt, the reaction mixture was quenched by addition of methanol and saturated aqueous Rochelle salt. An organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was used without further purification.

MnO₂ (250 mg, 1.29 mmol) was added to a stirred solution of crude mixture (89.6 mg, 0.257 mmol) in CH₂Cl₂ (2 mL) at rt, and the solution was stirred for another 16 h at 40 °C. The solution was dissolved in CH₂Cl₂, sat. NH₄Cl aq. was added and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford **227** (110 mg, quant, 2steps)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.31 (d, 6H, *J* = 7.2 Hz), 1.64 (tt, 2H, *J* = 7.2, 7.2 Hz), 1.69 (s, 3H), 2.08 (t,

2H, $J = 7.2$ Hz), 2.57 (t, 2H, $J = 7.2$ Hz), 3.53 (septet, 1H, $J = 7.2$ Hz), 3.71 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 4.67 (s, 1H), 4.73 (s, 1H), 6.11 (d, 1H, $J = 8.4$ Hz), 6.33 (s, 1H), 9.44 (d, 1H, $J = 8.4$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.0, 22.1, 25.1, 37.0, 38.5, 55.7, 60.6, 60.8, 107.4, 110.5, 128.6, 129.1, 131.3, 144.2, 144.8, 151.9, 154.1, 163.9, 193.7; IR (ATR) ν : 2935, 1674, 1402, 1024, 752 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{30}\text{NaO}_4$, $[\text{M}+\text{Na}]^+$ 369.2042, found 369.2028; yellow oil

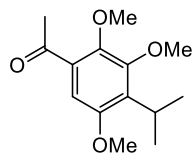
1-(4-isopropyl-2,3,5-trimethoxyphenyl)ethan-1-ol (**215'**)



MeMgBr (7.28 mL, 21.84 mmol) was added to a stirred solution of **215** (2.6 g, 10.92 mmol) in THF (5.5 mL) at 0 °C, and the solution was stirred for another 1 h at rt. Then, sat. NH_4Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na_2SO_4 . The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 10/1) to afford **215'** (2.58 g, 93%)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.26 (d, 6H, $J = 6.8$ Hz), 1.44 (d, 3H, $J = 6.4$ Hz), 2.96 (brs, 1H), 3.45 (septet, 1H, $J = 6.8$ Hz), 3.74 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 5.07 (q, 1H, $J = 6.4$ Hz), 6.64 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.0, 24.1, 25.0, 55.5, 60.5, 65.2, 65.4, 103.5, 129.3, 136.2, 143.9, 151.2, 154.7; IR (ATR) ν : 3410, 2958, 1407, 1026 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{22}\text{NaO}_4$, $[\text{M}+\text{Na}]^+$ 277.1416, found 277.1408; yellow oil

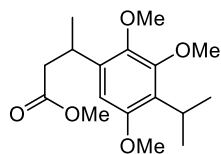
1-(4-isopropyl-2,3,5-trimethoxyphenyl)ethan-1-one (**239**)



To an oven-dried 100 mL round-bottomed flask equipped with a stir bar was added 40 mL of CH_2Cl_2 and dimethyl sulfoxide (0.17 mL, 2.32 mmol), and the reaction mixture was cooled in a -78 °C. Oxalyl chloride (0.1 mL, 1.16 mmol) was added carefully, and the reaction stirred for 30 min at -78 °C, then **215'** (147 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction mixture was stirred 30 min at -78 °C. Triethylamine (0.8 mL, 5.8 mmol) was added, and the reaction was allowed to warm to r.t. over 2 h. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and 1 M HCl (aq). The layers were separated, and the aqueous layer was extracted with EtOAc ($\times 1$). The combined organic layers were washed with sat. NaHCO_3 (aq), water, brine, dried over MgSO_4 , and concentrated in vacuo. This crude mixture was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford **239** (135.9 mg, 93%)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.30 (d, 6H, $J = 6.8$ Hz), 2.65 (s, 3H), 3.53 (septet, 1H, $J = 6.8$ Hz), 3.80 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 6.97 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 20.7, 25.4, 31.1, 55.5, 60.7, 60.9, 105.9, 129.8, 136.0, 147.8, 152.0, 154.4, 198.7; IR (ATR) ν : 2935, 1676, 1403, 1117, 1021 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{20}\text{NaO}_4$, $[\text{M}+\text{Na}]^+$ 275.1259, found 275.1265; yellow oil

methyl 3-(4-isopropyl-2,3,5-trimethoxyphenyl)butanoate (**240'**)



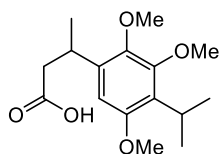
To a mixture of diethylphosphonoacetic acid methyl ester (1.8 mL, 11.2 mmol) in THF (20 mL) was added NaH (536 mg, 60% in mineral oil, 11.18 mmol) under argon at 0 °C, and stirred at same temperature for 1 h. **239** (1.41 g, 5.59 mmol) in THF (8 mL) was added slowly to the reaction mixture at 0 °C. The reaction mixture

was stirred at 60 °C for 16 h. Then, the reaction mixture was quenched with H₂O, and extracted with AcOEt. The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel short column chromatography to give **240** (1.7 g).

To a solution of **240** (1.7 g, 5.52 mmol) in MeOH (15 mL) was added palladium on carbon (350 mg). The mixture was stirred at room temperature for 12 h under hydrogen atmosphere. The catalyst was filtered off through celite pad, then the filtrate was concentrated and purified via flash chromatograph gave **240'** (1.71 g, quant, 2steps)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.26 (d, 3H, *J* = 7.6 Hz), 1.30 (d, 6H, *J* = 7.6 Hz), 2.52 (dd, 1H, *J* = 15.2, 9.2 Hz), 2.64 (dd, 1H, *J* = 15.2, 6.0 Hz), 3.47 (septet, *J* = 7.6 Hz), 3.59-3.68 (m, 1H), 3.65 (s, 3H), 3.76 (s, 3H), 3.80 (s, 6H), 6.41 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.0, 21.2, 29.9, 41.7, 51.3, 55.6, 60.5, 104.4, 128.4, 136.2, 144.7, 151.7, 154.4, 172.8; IR (ATR) ν: 2954, 1736, 1600, 1407, 1223, 1117, 1054, 1025, 832 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₂₇NaO₅, [M+H]⁺ 311.1859, found 311.1187; yellow oil

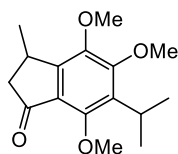
3-(4-isopropyl-2,3,5-trimethoxyphenyl)butanoic acid (**241**)



NaOH (1.32 g, 33.1 mmol) was added to a stirred solution of **240'** (1.71 g, 5.52 mmol) in EtOH (22 mL) and H₂O (6 mL) at rt, and the solution was stirred for another 30 min at 80 °C. 1N HCl was added and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 2/1) to afford **241** (1.63 g, quant.)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.29 (d, 6H, *J* = 7.6 Hz), 1.30 (d, 3H, *J* = 7.6 Hz), 2.55 (dd, 1H, *J* = 15.6, 9.2 Hz), 2.68 (dd, 1H, *J* = 15.6, 6.0 Hz), 3.47 (septet, 1H, *J* = 7.6 Hz), 3.58-3.68 (m, 1H), 3.76 (s, 3H), 3.80 (s, 6H), 6.42 (s, 1H), 10.78 (brs, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.0, 21.2, 25.0, 29.7, 41.7, 55.7, 60.5, 104.5, 128.6, 136.0, 144.7, 151.7, 154.5, 178.8; IR (ATR) ν: 2957, 1706, 1407, 1226, 1025, 832 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₂₄NaO₅, [M+Na]⁺ 319.1521, found 319.1522; colorless solid

6-isopropyl-4,5,7-trimethoxy-3-methyl-2,3-dihydro-1H-inden-1-one (**242**)



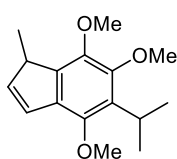
Oxalyl chloride (0.19 mL, 2.18 mmol) was charged to a stirred solution of **241** (322 mg, 1.09 mmol) in CH₂Cl₂ (5.5 mL) at 0 °C. Anhydrous N,N-dimethylformamide (3 drops) was added and the reaction continued to stir for an hour at room temperature. When the reaction was complete, the solvent was removed in vacuo to yield crude oil. To remove additional oxalyl chloride, additional CH₂Cl₂ (10 mL) was added and removed in vacuo. The product was used in the next step without further purification.

To a stirred solution of crude oil from the previous procedure in anhydrous CH₂Cl₂ (3 mL) was added AlCl₃ (188 mg, 1.42 mmol) in small portions to prevent the reaction from overheating. Upon the addition of AlCl₃, the reaction turned dark green. After stirring for 1 h at room temperature, the reaction was poured over ice. Once the ice melted, the product was extracted using 2 x 50 mL of CH₂Cl₂. The organic layers

were combined and dried with MgSO₄. The solvent was removed in vacuo to produce a crude **242**, which was passed through a silica plug using (*n*-hexane/AcOEt = 30/1) as the eluent to give **242** (267.3 mg, 88%, 2 steps)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.25 (d, 6H, *J* = 6.8 Hz), 1.34 (d, 3H, *J* = 6.8 Hz), 2.17 (d, 1H, *J* = 18.8 Hz), 2.81 (dd, 1H, *J* = 18.8 Hz, 8.0 Hz), 3.34-3.54 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.2, 21.7, 21.7, 25.2, 30.3, 46.3, 60.0, 60.4, 62.3, 124.5, 134.8, 146.2, 151.6, 152.9, 158.3, 202.6; IR (ATR) ν: 2957, 1704, 1320, 1032, 753 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₂₂NaO₄, [M+Na]⁺ 301.1416, found 301.1419; colorless oil

5-isopropyl-4,6,7-trimethoxy-1-methyl-1H-indene (**237b**)

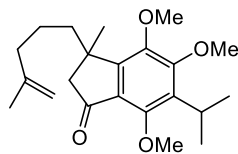


NaBH₄ (36 mg, 0.96 mmol) was added to a stirred solution of **242** (133 mg, 0.48 mmol) in EtOH (2.4 mL) at 0 °C and the solution was stirred for another 1 h at 80 °C. H₂O was added and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 10/1) to afford crude **243** (134 mg).

243 (98 mg, 3.36 mmol) was dissolved in CH₂Cl₂ (5 mL) at 0 °C and NEt₃ (0.3 mL, 2.14 mmol) was added. After slow addition of MsCl (0.11 mL, 1.43 mmol) the solution became yellow colored and was stirred for 20 h at rt. The reaction was stopped by adding aq. K₂CO₃ (5 mL) and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over MgSO₄. After filtration the solvent was removed under reduced pressure to provide a yellow oil. Pure **237b** (89.9 mg, 96%, 2 steps) was obtained by flash column chromatography (*n*-Hexane/AcOEt = 10/1) as the eluent.

¹H-NMR (CDCl₃, 400 MHz) δ: 1.26 (d, 6H, *J* = 7.6 Hz), 1.29 (d, 3H, *J* = 7.2 Hz), 3.40 (septet, 1H, *J* = 7.6 Hz), 3.52 (q, 1H, *J* = 7.2 Hz), 3.75 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 6.23 (d, 1H, *J* = 5.2 Hz), 6.71 (d, 1H, *J* = 5.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 15.1, 22.1, 22.2, 25.7, 44.5, 59.9, 60.7, 62.0, 126.3, 132.3, 133.2, 139.2, 139.9, 146.3, 147.8, 149.9; IR (ATR) ν: 2932, 1740, 1454, 1415, 1336, 1119, 1041 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₂₂NaO₃, [M+Na]⁺ 285.1467, found 285.1458; yellow oil

6-isopropyl-4,5,7-trimethoxy-3-methyl-3-(4-methylpent-4-en-1-yl)-2,3-dihydro-1H-inden-1-one (**213**)

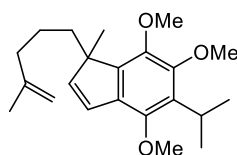


Preparation of LDA: *n*-BuLi (4.15 mL, 6.43 mmol) was added to a solution of *i*Pr₂NH (0.9 mL, 6.43 mmol) in THF (12.9 mL) at -78 °C, and the solution was stirred at 0 °C for 30 min. Resulting LDA was added to a solution of **242** (1.38 g, 4.94 mmol) in THF (9.9 mL) at -78 °C, and the solution was stirred for 1 h. Then, freshly distilled TMSCl (0.81 mL, 6.43 mmol) was added at -78 °C, and the solution was stirred for 1 h. Then, LDA (prepared by previous procedure, 7.41 mmol) was added at -78 °C, and the solution was stirred for 1 h, and then, **225** (1.21 g, 7.41 mmol) in THF (7.4 mL) was added at -78 °C, and the solution was warmed to rt, and stirred overnight. 1N HCl was added to quench the reaction, and the phases were separated. The aqueous layer was extracted with AcOEt and the combined organic layers were dried over MgSO₄. After filtration the solvent was removed under reduced pressure to provide a crude mixture, which

was purified by flash column chromatography (n-Hexane/AcOEt = 50/1) as the eluent to give **213** (1.36 g, 77%)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.02-1.13 (m, 1H), 1.31 (d, 6H, *J* = 6.8 Hz), 1.33-1.41 (m, 1H), 1.49 (s, 3H), 1.65 (s, 3H), 1.72-2.04 (m, 4H), 2.37 (d, 1H, *J* = 18.8 Hz), 2.60 (d, 1H, *J* = 18.8 Hz), 3.50 (q, 1H, *J* = 6.8 Hz), 3.85 (s, 3H), 3.88 (brs, 6H), 4.61 (s, 1H), 4.67 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.9, 22.3, 23.2, 25.3, 27.4, 38.1, 39.9, 41.7, 51.6, 59.9, 60.3, 62.4, 110.2, 124.8, 135.2, 145.5, 146.7, 152.8, 153.1, 158.8, 202.4; IR (ATR) ν: 2935, 1704, 1321, 1034, 753 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₂NaO₄, [M+Na]⁺ 383.2198, found 383.2196; orange oil

5-isopropyl-4,6,7-trimethoxy-1-methyl-1-(4-methylpent-4-en-1-yl)-1H-indene (**212**)

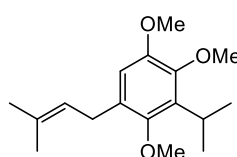


NaBH₄ (261 mg, 6.92 mmol) was added to a stirred solution of **213** (1.25 g, 3.46 mmol) in EtOH (17.3 mL) at 0 °C and the solution was stirred for another 1 h at 80 °C. H₂O was added and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to give crude alcohol (1.23 g).

Crude alcohol (416 mg, 1.15 mmol) was dissolved in CH₂Cl₂ (11.5 mL) at 0 °C and NEt₃ (0.48 mL, 3.45 mmol) was added. After slow addition of MsCl (0.18 mL, 2.3 mmol) the solution became yellow colored and was stirred for 17 h at rt. The reaction was stopped by adding aq. K₂CO₃ (15 mL) and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over MgSO₄. After filtration the solvent was removed under reduced pressure to provide a crude oil, which was purified by flash column chromatography (n-Hexane/AcOEt = 100/1) as the eluent to give **212** (360 mg, 91%, 2 steps)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.95-1.06 (m, 1H), 1.21-1.28 (m, 1H), 1.34 (d, 6H, *J* = 7.2 Hz), 1.39 (s, 3H), 1.62 (s, 3H), 1.77-1.93 (m, 4H), 3.46 (q, 1H, *J* = 7.2 Hz), 3.81 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 4.59 (s, 1H), 4.64 (s, 1H), 6.13 (d, 1H, *J* = 5.6 Hz), 6.66 (d, 1H, *J* = 5.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: 22.3, 23.0, 25.8, 36.4, 38.3, 54.9, 60.0, 60.5, 62.2, 109.9, 124.9, 131.7, 133.2, 142.0, 144.5, 145.9, 146.2, 147.7, 150.2; IR (ATR) ν: 2934, 1453, 1414, 1119, 1041, 757 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₂NaO₃, [M+Na]⁺ 367.2249, found 367.2262; orange oil

3-isopropyl-1,2,4-trimethoxy-5-(3-methylbut-2-en-1-yl)benzene (**257**)

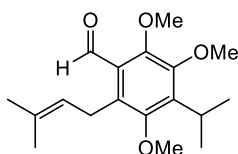


n-BuLi (7.15 mL, 1.55 M in hexane, 7.15 mmol) was added to a stirred solution of **256** (1.88 g, 6.5 mmol) in THF (14 mL) at -78 °C and the solution was stirred for another 30 min at -78 °C. Then, 1-Bromo-3-methyl-2-butene (0.98 mL, 8.45 mmol) was added at -78 °C, and the solution was stirred at rt for 5 h. sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt

= 100/1) to give **257** (1.15 g, 64%), **216** (21%). *It is very difficult to separate **257** and **216** completely.

¹H-NMR (CDCl₃, 400 MHz) δ: 1.34 (d, 6H, *J* = 7.2 Hz), 1.74 (s, 3H), 1.75 (s, 3H), 3.32 (d, 2H, *J* = 7.2 Hz), 3.43 (q, 1H, *J* = 7.2 Hz), 3.67 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 5.29 (t, 1H, *J* = 7.2 Hz), 6.58 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 18.0, 22.1, 25.9, 26.2, 28.5, 55.9, 60.7, 61.9, 111.0, 123.3, 129.5, 132.5, 134.9, 146.9, 149.6, 149.6; IR (ATR) ν: 2935, 1481, 1252, 1114, 1038 cm⁻¹; HRMS (ESI) Calcd for C₁₇H₂₆NaO₃, [M+Na]⁺ 301.1780, found 301.1778; yellow oil

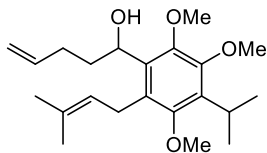
4-isopropyl-2,3,5-trimethoxy-6-(3-methylbut-2-en-1-yl)benzaldehyde (**258**)



To a solution of **257** (178 mg, 0.64 mmol) in CH₂Cl₂ (3.8 mL) was added 1,1-dichlorodimethyl ether (0.11 mL, 1.28 mmol), followed by TiCl₄ (3.07 mL, 3.07 mmol) at -78 °C. After stirring for 1 h at -78 °C, the reaction was quenched with 1N HCl and the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 10/1) to afford **258** (105.8 mg, 54%)

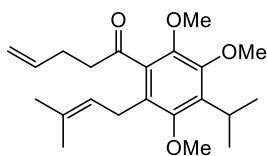
¹H-NMR (CDCl₃, 400 MHz) δ: 1.33 (d, 6H, *J* = 6.4 Hz), 1.93 (s, 3H), 2.27 (s, 3H), 3.41 (q, 1H, *J* = 6.4 Hz), 3.64 (brs, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 3.81 (s, 3H), 6.32 (s, 1H), 10.26 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 19.7, 22.1, 24.0, 24.6, 26.1, 55.9, 60.7, 61.8, 110.3, 127.7, 134.7, 135.9, 147.0, 149.5, 149.5, 158.0, 191.0; IR (ATR) ν: 2935, 1665, 1454, 1227, 1105, 1038 cm⁻¹; HRMS (ESI) Calcd for C₁₈H₂₆NaO₄, [M+Na]⁺ 329.1729, found 329.1740; orange oil

1-(4-isopropyl-2,3,5-trimethoxy-6-(3-methylbut-2-en-1-yl)phenyl)pent-4-en-1-ol (**259**)



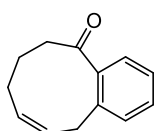
To a solution of Mg (53.8 mg, 2.21 mmol) and I₂ (2 blocks) in THF (3.6 mL) was added a solution of 4-bromo-1-butene (0.15 mL, 1.48 mmol) in THF (1.2 mL) slowly at rt, and the mixture was stirred for 10 min at rt. Then the solution was stirred at 60 °C for 1 h, the solution of **258** (226 mg, 0.74 mmol) in THF (1.2 mL) was added at 0 °C, and the solution was stirred for another 2 h at room temperature. The solution was dissolved in AcOEt, sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 15/1) to afford **259** (217.1 g, 81%)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.32 (d, 6H, *J* = 6.8 Hz), 1.38-1.43 (m, 1H), 1.46-1.53 (m, 1H), 1.75 (s, 3H), 1.80 (s, 3H), 1.88 (brs, 1H), 1.96-2.05 (m, 1H), 2.08-2.17 (m, 1H), 3.39 (q, 1H, *J* = 6.8 Hz), 3.47 (d, 2H, *J* = 9.6 Hz), 3.72 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.67 (t, 1H, *J* = 6.4 Hz), 4.91 (d, 1H, *J* = 11.2 Hz), 4.99 (d, 1H, *J* = 16.8 Hz), 5.75 (m, 1H), 6.55 (brs, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 20.2, 22.0, 22.1, 22.2, 26.2, 26.4, 30.4, 35.4, 55.9, 60.7, 61.7, 71.3, 110.5, 114.7, 129.0, 129.8, 133.1, 134.9, 138.5, 147.0, 149.2, 149.6; IR (ATR) ν: 3465, 2934, 1455, 1220, 1039, 753 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₄NaO₄, [M+Na]⁺ 385.2355, found 385.2395; orange oil

1-(4-isopropyl-2,3,5-trimethoxy-6-(3-methylbut-2-en-1-yl)phenyl)pent-4-en-1-one (260)

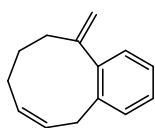
To an oven-dried 100 mL round-bottomed flask equipped with a stir bar was added 3 mL of CH₂Cl₂ and dimethyl sulfoxide (0.25 mL, 3.45 mmol), and the reaction mixture was cooled in a -78 °C. Oxalyl chloride (0.15 mL, 1.73 mmol) was added carefully, and the reaction stirred for 30 min at -78 °C, then **259** (313 mg, 0.86 mmol) in CH₂Cl₂ (1.3 mL) was added, and the reaction mixture was stirred 30 min at -78 °C. Triethylamine (1.2 mL, 8.63 mmol) was added, and the reaction was allowed to warm to r.t. over 3 h. The reaction mixture was concentrated in vacuo and partitioned between AcOEt and 1 N HCl. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with sat. NaHCO₃ aq., water, brine, dried over MgSO₄, and concentrated in vacuo. This crude mixture was filtered through a short silica gel column (eluting with hexane/AcOEt = 50/1) to afford **260** (254.7 mg, 82%)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.33 (d, 6H, *J* = 6.8 Hz), 1.83 (s, 3H), 1.89 (s, 3H), 2.20 (dt, 2H, *J* = 6.8, 6.8 Hz), 2.44 (t, 2H, *J* = 6.8 Hz), 3.40 (q, 1H, *J* = 6.8 Hz), 3.64 (s, 2H), 3.68 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.87 (d, 1H, *J* = 9.2 Hz), 4.94 (d, 1H, *J* = 16.8 Hz), 5.71 (ddt, 1H, *J* = 16.8, 9.2, 6.8 Hz), 6.48 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.5, 22.1, 22.7, 26.1, 27.9, 29.6, 41.6, 56.0, 60.7, 61.6, 110.7, 115.0, 126.7, 135.0, 135.3, 137.5, 137.8, 147.4, 149.6, 149.7, 207.5; IR (ATR) ν: 2936, 1684, 1480, 1226, 1105, 1039, 754 cm⁻¹; HRMS (ESI) Calcd for C₂₂H₃₂NaO₄, [M+Na]⁺ 383.2198, found 383.2190; yellow oil

(Z)-6,7,8,11-tetrahydro-5H-benzo[9]annulen-5-one (272)

(CAS-Reg# 1310584-58-7)

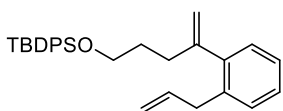
¹H-NMR (CDCl₃, 400 MHz) δ: 1.99 (tt, 2H, *J* = 6.8, 6.4 Hz), 2.34 (dt, 2H, *J* = 7.2, 6.8 Hz), 2.67 (t, 2H, *J* = 6.4 Hz), 3.63 (d, 2H, *J* = 7.2 Hz), 5.48-5.58 (m, 2H), 7.17-7.24 (m, 3H), 7.35 (ddd, 1H, *J* = 7.2, 7.2, 1.6 Hz)

(Z)-5-methylene-6,7,8,11-tetrahydro-5H-benzo[9]annulene (273)

To a suspension of MePPh₃Br (165.6 mg, 0.464 mmol) in THF (1 mL) was added NaH in one portion (19 mg, 0.46 mmol) at 0 °C, and the resulting mixture was stirred at 60 °C for 1 h. Then, **272** (43.2 mg, 0.23 mmol) in THF (1 mL) was added at 60 °C, and the mixture was stirred 7 h at 60 °C. A saturated ammonium chloride solution was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (100:1 Hex:EtOAc) to give **273** (17.9 mg, 42%)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.79 (brs, 2H), 2.21 (brs, 2H), 2.40 (brs, 2H), 3.40 (brs, 2H), 5.13 (s, 1H), 5.22 (s, 1H), 5.35 (dt, 1H, *J* = 10.0, 8.8 Hz), 5.59 (dt, 1H, *J* = 10.0, 8.8 Hz), 7.00 (d, 1H, *J* = 6.8 Hz), 7.12-7.21 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 23.3, 27.1, 32.1, 32.8, 114.1, 126.1, 127.1, 127.9, 128.2, 129.7, 130.1, 137.2, 146.5, 149.8; IR (ATR) ν: 2921, 1738, 1457 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₆Na, [M+Na]⁺ 207.1150, found 207.1150; yellow oil

((4-(2-allylphenyl)pent-4-en-1-yl)oxy)(tert-butyl)diphenylsilane (279)



A solution of Mg (566 mg, 23.28 mmol) and 1,2-dibromoethane (0.1 mL, 1.16 mmol) in THF (3.6 mL) was stirred at 60 °C for 15 min, then cooled to rt, and a solution of Br(CH₂)₃OTBS (2.95 g, 11.64 mmol) in THF (6 mL) was added slowly at rt, and the mixture was stirred for 10 min at rt. Then the solution was stirred at 60 °C for 1 h, the solution of **269** (850.8 mg, 5.82 mmol) in THF (6 mL) was added at 0 °C, and the solution was stirred for another 2 h at room temperature. The solution was dissolved in AcOEt, sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 50/1) to afford crude **275** (940 mg).

To an oven-dried 100 mL round-bottomed flask equipped with a stir bar was added 13 mL of CH₂Cl₂ and dimethyl sulfoxide (0.89 mL, 12.48 mmol), and the reaction mixture was cooled in a -78 °C. Oxalyl chloride (0.54 mL, 6.24 mmol) was added carefully, and the reaction stirred for 30 min at -78 °C, then crude **275** (940 mg) in CH₂Cl₂ (3 mL) was added, and the reaction mixture was stirred 30 min at -78 °C. Triethylamine (4.3 mL, 31.2 mmol) was added, and the reaction was allowed to warm to r.t. over 13 h. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and 1 M HCl (aq). The layers were separated, and the aqueous layer was extracted with EtOAc (×1). The combined organic layers were washed with sat. NaHCO₃ (aq), water, brine, dried over MgSO₄, and concentrated in vacuo. This crude mixture was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford crude **276** (614.6 mg)

To a suspension of MePPh₃Br (1.38 g, 3.86 mmol) in THF (8 mL) was added NaH in one portion (204 mg, 4.25 mmol) at 0 °C, and the resulting mixture was stirred at 60 °C for 1 h. Then, crude **276** (614.6 mg) in THF (2 mL) was added at 60 °C, and the mixture was stirred 1 h at 60 °C. A saturated ammonium chloride solution was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (10:1 Hex:EtOAc) to give crude **277** (497 mg)

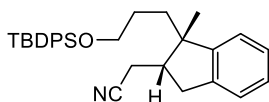
TBAF (4.7 mL, 1.0 M in THF, 4.7 mmol) was added to the solution of crude **278** (497 mg) in THF (15.7 mL) at 0 °C, and the solution was stirred at rt for 1 h. H₂O was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (150:1 Hex:EtOAc) to give crude **278** (220 mg)

To a solution of crude **278** (78.2 mg), 1H-imidazole (31.6 mg, 0.46 mmol), DMAP (2 blocks) in CH₂Cl₂ (1.9 mL) was added TBDPSCl (0.1 mL, 0.387 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. sat. NH₄Cl aq. was added and the aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (75:1 Hex:EtOAc) to give **279** (147.1 mg, 21%, 5 steps)

¹H-NMR (CDCl₃, 400 MHz) δ: 1.03 (s, 9H), 1.66 (tt, 2H, *J* = 8.0, 6.4 Hz), 2.47 (t, 2H, *J* = 8.0 Hz), 3.36 (d,

2H, $J = 6.4$ Hz), 3.66 (t, 2H, $J = 6.4$ Hz), 4.86 (d, 1H, $J = 1.2$ Hz), 4.96-5.04 (m, 2H), 5.16 (d, 1H, $J = 1.2$ Hz), 5.87-5.97 (m, 1H), 7.03-7.47 (m, 10H), 7.64 (dd, 4H, $J = 8.0, 2.0$ Hz); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 19.2, 26.8, 30.7, 34.5, 37.1, 63.4, 114.0, 115.6, 125.7, 126.8, 127.6, 128.5, 129.4, 129.5, 133.9, 135.5, 136.6, 138.0, 142.9, 149.2; IR (ATR) ν : 2938, 1740, 1239, 1047 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{30}\text{H}_{36}\text{NaO}_{\text{Si}}$, $[\text{M}+\text{Na}]^+ 463.2433$, found 463.2435; yellow oil

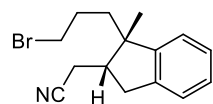
2-(1-(3-((tert-butyl)diphenylsilyloxy)propyl)-1-methyl-2,3-dihydro-1H-inden-2-yl)acetonitrile (**280a**)



To the solution of **279** (74.3 mg, 0.169 mmol), TsCN (36.7 mg, 0.203 mmol), Co **A** (2.0 mg, 0.034 mmol) in EtOH (0.85 mL), PhSiH_3 (25 μl , 0.203 mmol) was added at rt, and the solution was stirred for 16 h at rt. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to give **280a** (43.2 mg, 55%), and **280b** (20.1 mg, 25%).

^1H -NMR (CDCl_3 , 400 MHz) δ : 1.00 (s, 9H), 1.32 (s, 3H), 1.24-1.45 (m, 4H), 2.33 (dd, 1H, $J = 15.6, 8.8$ Hz), 2.44 (dddd, 1H, $J = 9.6, 8.8, 7.2, 5.2$ Hz), 2.50 (dd, 1H, $J = 15.6, 5.2$ Hz), 2.71 (dd, 1H, $J = 15.2, 9.6$ Hz), 3.11 (dd, 1H, $J = 15.2, 7.2$ Hz), 3.56 (dd, 2H, $J = 10.4, 5.6$ Hz), 7.07 (dd, 1H, $J = 8.8, 3.2$ Hz), 7.17-7.21 (m, 3H), 7.34-7.44 (m, 6H), 7.58 (d, 4H, $J = 7.6$ Hz); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 17.2, 19.1, 24.5, 26.8, 27.5, 31.3, 36.4, 47.9, 48.0, 64.0, 119.5, 123.5, 124.6, 126.4, 126.8, 127.6, 129.6, 133.8, 135.5, 140.1, 149.2; IR (ATR) ν : 2930, 2857, 1736, 1427, 1241, 1105, 755, 700 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{31}\text{H}_{37}\text{NnaO}_{\text{Si}}$, $[\text{M}+\text{Na}]^+ 490.2542$, found 490.2529; yellow oil

2-(1-(3-bromopropyl)-1-methyl-2,3-dihydro-1H-inden-2-yl)acetonitrile (**282**)

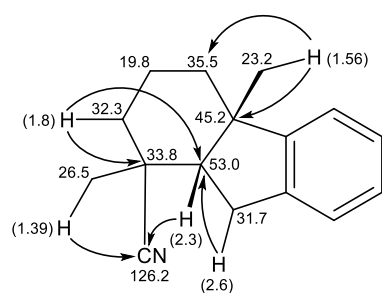


TBAF (1.23 mL, 1.0 M in THF, 1.23 mmol) was added to the solution of **280a** (191.9 mg) in THF (2.1 mL) at 0 $^\circ\text{C}$, and the solution was stirred at rt for 1 h. H_2O was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The compound was purified by flash (10:1 Hex:EtOAc) to give crude **281** (79.8 mg)

To a solution of crude **281** (79.8 mg) in CH_2Cl_2 (1.7 mL) was added CBr_4 (23.1 mg, 0.07 mmol) and PPh_3 (18.4 mg, 0.07 mmol) at 0 $^\circ\text{C}$, and the solution was stirred at rt for 1 h. The solution was directly poured to flash column chromatography to give **282** (95.3 mg, 80%, 2 steps)

^1H -NMR (CDCl_3 , 400 MHz) δ : 1.39 (s, 3H), 1.44-1.83 (m, 4H), 2.48-2.54 (m, 2H), 2.58-2.65 (m, 1H), 2.78 (dd, 1H, $J = 16.0, 9.6$ Hz), 3.14 (dd, 1H, $J = 16.0, 7.2$ Hz), 7.09-7.26 (m, 4H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 17.1, 24.2, 27.8, 33.7, 34.0, 36.3, 47.8, 48.0, 119.2, 123.5, 124.7, 126.5, 127.1, 140.0, 148.5; IR (ATR) ν : 2959, 1740, 1477, 1216, 909, 754, 729 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{18}\text{BrNNa}$, $[\text{M}+\text{Na}]^+ 314.0520$, found 314.0520; yellow oil

1,4a-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-fluorene-1-carbonitrile (**283**)

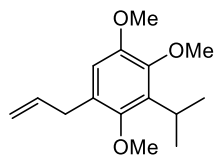


Preparation of LDA: *n*-BuLi (0.92 mL, 1.43 mmol) was added to a solution of *i*Pr₂NH (0.2 mL, 1.43 mmol) in THF (6.02 mL) at -78 °C, and the solution was stirred at 0 °C for 1 h. Resulting LDA was added to the solution of **282** (26.4 mg, 0.09 mmol) in THF (3 mL) at -78 °C, and the solution was slowly warmed to rt, and stirred for 2 h. Then, sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (20:1 Hex:EtOAc) to give crude **274** (16.9 mg)

LDA (prepared by the same scale for the synthesis of **274**) was added to the solution of crude **283** (16.9 mg) in THF (0.82 mL) at -78 °C, and stirred for 1h at the same temperature. Then, MeI (50 μL, 0.803 mmol) was added to the solution at -78 °C, and the solution was slowly warmed to rt, stirred for 6 h. Then, sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The compound was purified by flash (20:1 Hex:EtOAc) to give **283** (15.2 mg) as a single diastereomer.

¹H-NMR (CDCl₃, 600 MHz) δ: 1.10-1.29 (m, 3H), 1.39 (s, 3H), 1.43-1.62 (m, 2H), 1.56 (s, 3H), 1.77-1.84 (m, 1H), 2.33-2.36 (m, 1H), 2.64-2.69 (m, 1H), 2.72-2.77 (m, 1H), 7.02-7.19 (m, 4H); ¹³C-NMR (CDCl₃, 150 MHz) δ: 19.8, 23.2, 26.5, 31.7, 32.3, 33.8, 35.5, 45.2, 53.0, 121.5, 124.7, 126.2, 126.5, 126.8, 138.6, 153.0; IR (ATR) ν: 2980, 1755, 1234 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₁₉NNa, [M+Na]⁺ 248.1452, found 248.1414; yellow oil

1- allyl-3-isopropyl-2,4,5-trimethoxybenzene (**284**)

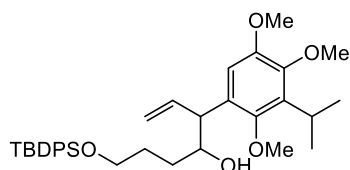


n-BuLi (0.76 mL, 1.55 M in hexane, 1.18 mmol) was added to a stirred solution of **256** (311 mg, 1.08 mmol) in THF (4.3 mL) at -78 °C and the solution was stirred for another 30 min at -78 °C. Then, CuI (245 mg, 1.29 mmol) was added at -78 °C, and the solution was stirred at 0 °C for 30 min, and allyl bromide (0.27 mL, 3.23 mmol)

was added to the solution at 0 °C. Then, the solution was slowly warmed to rt for 1 h. sat. NH₄Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na₂SO₄. The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 75/1) to give **284** (280.2 mg, 89%), **216** (11%). *It is very difficult to separate **284** and **216** completely.

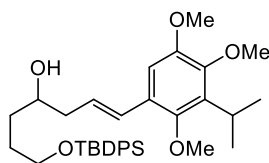
¹H-NMR (CDCl₃, 400 MHz) δ: 1.34 (d, 6H, *J* = 6.8 Hz), 3.40 (d, 2H, *J* = 6.4 Hz), 3.43 (q, 1H, *J* = 6.8 Hz), 3.66 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 5.08 (d, 1H, *J* = 16.8 Hz), 5.10 (d, 1H, *J* = 12.0 Hz), 5.97 (ddt, 1H, *J* = 16.8, 12.0, 6.4 Hz), 6.58 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ: 21.9, 25.9, 34.0, 55.6, 60.5, 61.8, 111.0, 115.7, 127.5, 134.8, 137.3, 147.0, 149.3, 149.4; IR (ATR) ν: 2938, 1480, 1226, 1040 cm⁻¹; HRMS (ESI) Calcd for C₁₅H₂₂NaO₃, [M+Na]⁺ 273.1467, found 273.1469; yellow oil

7-((tert-butyldiphenylsilyloxy)-3-(3-isopropyl-2,4,5-trimethoxyphenyl)hept-1-en-4-ol (286)



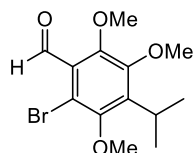
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.04 (s, 9H), 1.34 (d, 6H, $J = 6.8$ Hz), 1.65-1.84 (m, 4H), 3.40 (q, 1H, $J = 6.8$ Hz), 3.66 (s, 3H), 3.68-3.77 (m, 4H), 3.81 (s, 3H), 3.85 (s, 3H), 5.11 (d, 1H, $J = 18.4$ Hz), 5.13 (d, 1H, $J = 9.6$ Hz), 6.01 (ddd, 1H, $J = 18.4, 9.6, 2.4$ Hz), 6.71 (s, 1H), 7.35-7.42 (m, 6H), 7.65-7.68 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 150 MHz) δ : 19.2, 22.0, 26.2, 26.8, 28.7, 31.4, 49.6, 55.9, 60.6, 62.5, 64.0, 74.1, 109.3, 116.6, 127.6, 128.5, 129.5, 133.9, 135.2, 135.6, 139.2, 147.6, 149.8, 150.3; IR (ATR) ν : 3434, 2982, 1439, 699 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{35}\text{H}_{48}\text{NaO}_5\text{Si}$, $[\text{M}+\text{Na}]^+$ 599.3169, found 599.3178; yellow oil (12 mg, 9%).

(E)-7-((tert-butyldiphenylsilyloxy)-1-(3-isopropyl-2,4,5-trimethoxyphenyl)hept-1-en-4-ol (287)



$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.05 (s, 9H), 1.33 (d, 6H, $J = 6.8$ Hz), 1.49-1.75 (m, 4H), 2.28 (brs, 1H), 2.34-2.49 (m, 2H), 3.44 (q, 1H, $J = 6.8$ Hz), 3.65 (s, 3H), 3.71-3.80 (m, 3H), 3.84 (s, 6H), 6.15 (ddd, 1H, $J = 16.0, 7.6, 7.6$ Hz), 6.68 (d, 1H, $J = 16.0$ Hz), 6.85 (s, 1H), 7.35-7.42 (m, 6H), 7.66 (d, 4H, $J = 7.6$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 19.3, 22.1, 25.9, 26.9, 28.9, 33.9, 41.6, 56.0, 60.9, 62.3, 64.3, 71.3, 107.3, 125.9, 126.5, 127.8, 127.9, 129.7, 133.8, 135.2, 135.7, 148.4, 149.6, 149.8; IR (ATR) ν : 3442, 2933, 1427, 1109, 1038, 687 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{35}\text{H}_{48}\text{NaO}_5\text{Si}$, $[\text{M}+\text{Na}]^+$ 599.3169, found 599.3161; yellow oil (36 mg, 27%).

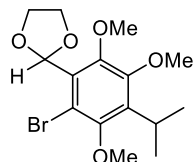
2-bromo-4-isopropyl-3,5,6-trimethoxybenzaldehyde (290)



To a solution of **215** (247.8 mg, 1.04 mmol) in TFA (1.0 mL) was added NBS (222.4 mg, 1.25 mmol) at 0 °C, and the solution was stirred at rt for 1 h. sat. NaHCO_3 aq. was added at 0 °C and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na_2SO_4 . The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 50/1) to give **290** (324 mg, quant.)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.35 (d, 6H, $J = 6.8$ Hz), 3.50 (q, 1H, $J = 6.8$ Hz), 3.81 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 10.32 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 21.5, 27.2, 60.7, 61.6, 61.8, 113.4, 127.3, 142.6, 151.9, 152.1, 152.9, 190.4; IR (ATR) ν : 2936, 1698, 1378, 1018, 752 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{17}\text{BrNaO}_4$, $[\text{M}+\text{Na}]^+$ 341.0187, found 341.0199; yellow oil

2-(2-bromo-4-isopropyl-3,5,6-trimethoxyphenyl)-1,3-dioxolane (291)

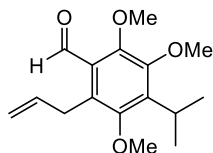


A solution of ethylene glycol (0.62 mL, 11.0 mmol), **290** (348 mg, 1.1 mmol), *p*-TsOH \cdot H $_2$ O (20.9 mg, 0.11 mmol) in toluene (2.2 mL) was heated at 100 °C for 24 h. H $_2$ O was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na_2SO_4 . The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to give **291** (345.4 mg, 87%)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.32 (d, 6H, $J = 6.8$ Hz), 3.46 (q, 1H, $J = 6.8$ Hz), 3.76 (s, 3H), 3.81 (s,

3H), 3.87 (s, 3H), 4.03 (t, 2H, $J = 7.2$ Hz), 4.26 (t, 2H, $J = 7.2$ Hz), 6.35 (s, 1H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 21.6, 26.8, 60.2, 60.7, 61.3, 65.6, 102.0, 113.0, 127.5, 137.8, 150.4, 151.4, 152.6; IR (ATR) ν : 2935, 1453, 1372, 1019, 943 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{21}\text{BrNaO}_5$, $[\text{M}+\text{Na}]^+$ 383.0470 found 383.0463; colorless solid

2-allyl-4-isopropyl-3,5,6-trimethoxybenzaldehyde (**267**)

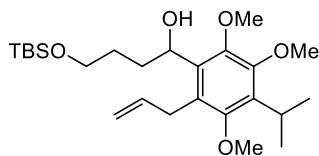


n -BuLi (4.33 mL, 1.55 M in hexane, 6.71 mmol) was added to a stirred solution of **291** (1.87 g, 5.16 mmol) in THF (25.8 mL) at -78 °C and the solution was stirred for another 30 min at -78 °C. Then, CuI (1.28 g, 6.71 mmol) was added at -78 °C, and the solution was stirred at 0 °C for 30 min, and allyl bromide (1.31 mL, 15.48 mmol)

was added to the solution at 0 °C. Then, the solution was solely warmed to rt for 1 h. 1N HCl was added and the solution was stirred for 1h at rt, and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na_2SO_4 . The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 100/1) to give **267** (1.11 g, 77%), **215** (15%). *It is very difficult to separate **267** and **215** completely.

^1H -NMR (CDCl_3 , 400 MHz) δ : 1.35 (d, 6H, $J = 6.8$ Hz), 3.46 (q, 1H, $J = 6.8$ Hz), 3.69 (s, 3H), 3.76 (d, 2H, $J = 6.0$ Hz), 3.89 (s, 3H), 3.91 (s, 3H), 4.93 (d, 1H, $J = 15.6$ Hz), 4.97 (d, 1H, $J = 10.0$ Hz), 6.00 (ddt, 1H, $J = 15.6, 10.0, 6.0$ Hz), 10.44 (s, 1H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 21.7, 26.7, 30.0, 60.5, 61.7, 62.5, 114.8, 126.7, 130.0, 137.8, 142.6, 151.6, 152.8, 154.2, 191.8; IR (ATR) ν : 2134, 1651, 1133 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{22}\text{NaO}_4$, $[\text{M}+\text{Na}]^+$ 301.1416, found 301.1414; yellow oil

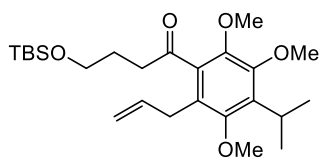
1-(2-allyl-4-isopropyl-3,5,6-trimethoxyphenyl)-4-((tert-butyldimethylsilyloxy)butan-1-ol (**292**)



A solution of Mg (135 mg, 5.55 mmol) and 1,2-dibromoethane (2 drops) in THF (2 mL) was stirred at 60 °C for 15 min, then cooled to rt, and a solution of $\text{Br}(\text{CH}_2)_3\text{OTBS}$ (665 mg, 2.78 mmol) in THF (2 mL) was added slowly at rt, and the mixture was stirred for 10 min at rt. Then the solution was stirred at 60 °C for 1 h, the solution of **267** (386.5 mg, 1.39 mmol) in THF (2 mL) was added at 0 °C, and the solution was stirred for another 2 h at room temperature. The solution was dissolved in AcOEt, sat. NH_4Cl aq. was added and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and sat. sodium chloride solution and dried over Na_2SO_4 . The solvent was removed in vacuum to leave a crude mixture, which was filtered through a short silica gel column (eluting with hexane/AcOEt = 20/1) to afford **292** (418 mg, 92%)

^1H -NMR (CDCl_3 , 400 MHz) δ : 0.05 (s, 6H), 0.89 (s, 9H), 1.33 (d, 6H, $J = 6.8$ Hz), 1.57-1.62 (m, 1H), 1.77-1.97 (m, 3H), 3.32-3.51 (m, 3H), 3.64 (s, 3H), 3.66-3.73 (m, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 4.74 (td, 1H, $J = 10.0, 3.6$ Hz), 5.00 (d, 1H, $J = 16.8$ Hz), 5.06 (d, 1H, $J = 10.0$ Hz), 5.91-6.01 (m, 1H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : -5.4, 18.3, 21.9, 22.2, 25.9, 26.1, 30.1, 30.5, 35.1, 59.8, 60.2, 62.3, 62.9, 71.1, 115.3, 125.0, 134.1, 135.0, 137.5, 148.5, 151.4, 152.2; IR (ATR) ν : 2930, 1410, 1245, 1031, 832, 754 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{44}\text{NaO}_5\text{Si}$, $[\text{M}+\text{Na}]^+$ 475.2856, found 475.2846; yellow oil

1-(2-allyl-4-isopropyl-3,5,6-trimethoxyphenyl)-4-((tert-butyldimethylsilyl)oxy)butan-1-one (293)



To an oven-dried 30 mL round-bottomed flask equipped with a stir bar was added 6 mL of CH₂Cl₂ and dimethyl sulfoxide (0.49 mL, 6.84 mmol), and the reaction mixture was cooled in a -78 °C. Oxalyl chloride (0.30 mL, 3.42 mmol) was added carefully, and the reaction stirred for 30 min at -78 °C, then **292** (772.9 mg) in CH₂Cl₂ (3 mL) was added, and the reaction mixture was stirred 30 min at -78 °C. Triethylamine (2.37 mL, 17.1 mmol) was added, and the reaction was allowed to warm to r.t. over 1 h. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and 1 M HCl (aq). The layers were separated, and the aqueous layer was extracted with EtOAc (×1). The combined organic layers were washed with sat. NaHCO₃ (aq), water, brine, dried over MgSO₄, and concentrated in vacuo. This crude mixture was filtered through a short silica gel column (eluting with hexane/AcOEt = 50/1) to afford **293** (624 mg, 81%)

¹H-NMR (CDCl₃, 400 MHz) δ: 0.06 (s, 6H), 0.89 (s, 9H), 1.33 (d, 6H, *J* = 7.2 Hz), 1.90 (tt, 2H, *J* = 7.2, 7.2 Hz), 2.85 (t, 2H, *J* = 7.2 Hz), 3.29 (d, 2H, *J* = 6.0 Hz), 3.39 (sept, 1H, *J* = 7.2 Hz), 3.66 (t, 2H, *J* = 7.2 Hz), 3.67 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.93 (d, 1H, *J* = 17.2 Hz), 5.00 (d, 1H, *J* = 10.4 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ: -5.4, 18.2, 21.9, 25.9, 26.2, 26.6, 31.0, 41.6, 60.1, 60.8, 62.2, 115.5, 124.1, 135.7, 136.2, 137.1, 145.9, 151.2, 152.5, 207.0; IR (ATR) ν: 2932, 1700, 1405, 1100, 1034, 835 cm⁻¹; HRMS (ESI) Calcd for C₂₅H₄₂NaO₅Si, [M+Na]⁺ 473.2699, found 473.2697; yellow oil

【論文目録】

本学位論文は下記の発表論文による。

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3. Amako, Y.; Hori, H.; Arai, S.; Nishida, A. *J. Org. Chem.* **2013**, *78*, 10763.
“Regioselective Hydronickelation of Allenes and Its Application to the Hydrocyanative Carbocyclization Reaction of Allene–Ynes and Bis-Allenens”

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4. ○Hiroto Hori, Yuka Amako, Koki Matsumoto, Shigeru Arai, Atsushi Nishida
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[2] 国内学会

1. ○天兒由佳、堀弘人、荒井秀、西田篤司、「ニッケル触媒によるアレンの位置及び立体選択的ヒドロシアノ化の開発と環化反応への応用」、第 44 回 複素環化学討論会、3O-02、(札幌市民ホール) 2014 年 9 月 (口頭発表)
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[3] 表彰等

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