（千葉大学審査学位論文）

ルテニウム触媒閉環メタセシスを用いるインドール類合成法の開発

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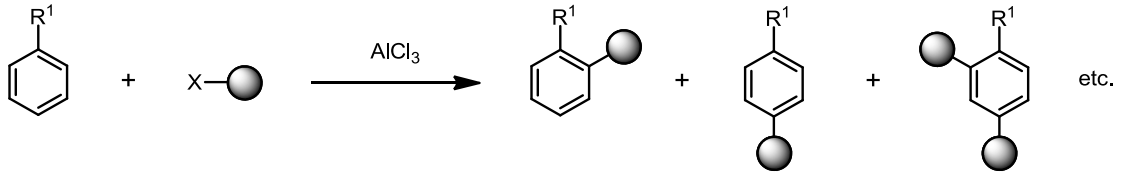
第一章

序論

置換芳香族化合物は、学術的ならびに工業的な観点から非常に重要な合成ターゲットとして挙げられる。特に多様な官能基が選択的に導入されている多置換芳香族化合物は医薬、農薬、機能性材料などの分野において幅広く利用されており、効率的な多置換芳香族化合物合成法の開発は極めて重要な意義を持つ。

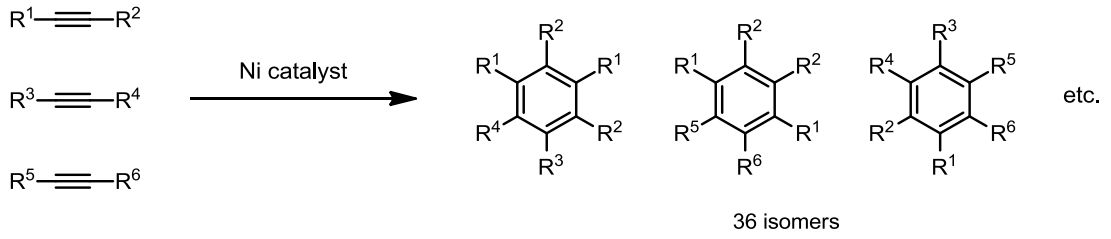
置換芳香族化合物の合成法としては既存の芳香環に対して新たな置換基を導入する手法が一般的であり、その中でも特に芳香族求電子置換反応は最も基本的かつ必須の変換反応として位置づけられる。しかし、望みの位置に選択的に置換基を導入することが時として困難であり、例えば、Friedel-Crafts 反応のような反応では反応条件が厳しい上に、複数の置換基が導入されてしまうなどの問題が避けられない(Scheme 1.1)[1]。

Scheme 1.1



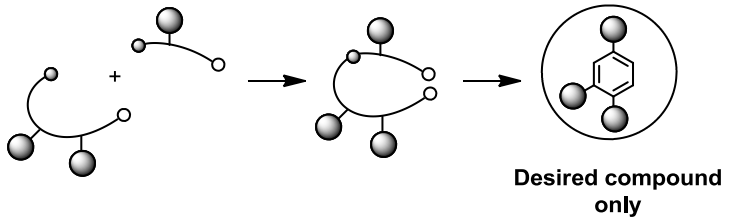
また、置換芳香族化合物を得る別の方法として、Reppe 反応などのアルキンの三量化反応があるが、本反応も目的外の異性体が数多く生成してしまうという欠点がある(Scheme 1.2)[2]。

Scheme 1.2



一方、それらの置換芳香族化合物合成法とは異なる手法として鎖状基質から芳香環そのものを構築するアプローチが考えられる(Scheme 1.3)。この手法では置換基をあらかじめ望みの位置に導入した鎖状基質を閉環/芳香族化させるため、上で述べた手法で問題となっていたような位置異性体の副生を全く伴わない選択的な置換芳香族化合物の合成が可能となる。

Scheme 1.3 Construction of aromatic compounds via cyclization of acyclic compounds.

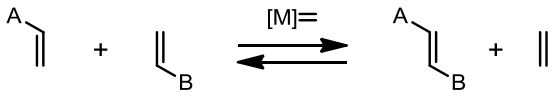


当研究室ではこのアプローチに基づき、ルテニウム触媒閉環メタセシスを閉環反応に用いる置換芳香族化合物の新たな合成手法の開発に取り組んできた[3]。

ここでメタセシス反応、特にオレフィンメタセシスについて述べておく。有機合成化学において効率的な炭素 - 炭素結合形成法の開発は最も重要な課題の一つであり、現在も活発に研究が行なわれている。そうした中で、近年オレフィンメタセシスは飛躍的な発展を遂げてきている[4]。2005 年には Yves Chauvin, Robert H. Grubbs, Richard R. Schrock に対し「有機合成におけるメタセシス反応を用いた手法の開発」の業績によってノーベル化学賞が与えられ、メタセシスの発展が有機合成化学に対して非常に大きな影響を与えたことが示された。

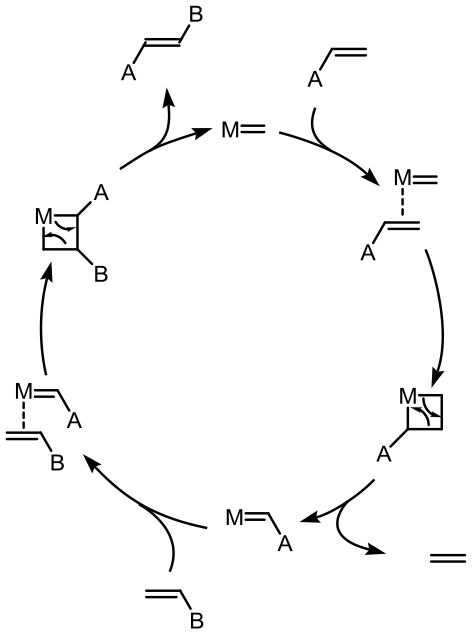
このオレフィンメタセシスとは、二種類のオレフィン間で炭素 - 炭素二重結合の組み換えが起こり新たなオレフィンが生成する反応のことである(Scheme 1.4)。

Scheme 1.4 Olefin metathesis reaction.



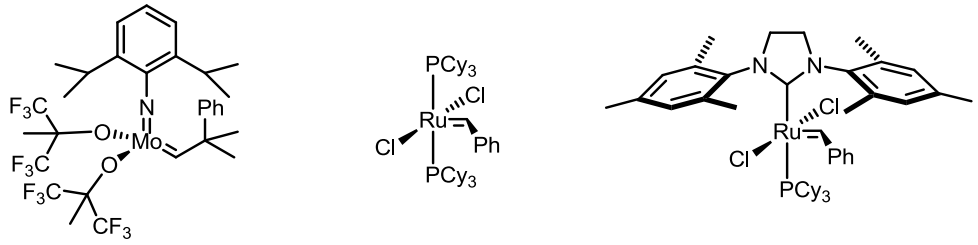
オレフィンメタセシスの反応機構は Scheme 1.5 のように考えられている。まず系中で生じた金属－炭素二重結合を持つ化学種であるメタルアルキリデン化学種が、オレフィンに対して付加環化し、メタロシクロブタンを形成する。次に逆付加環化過程を経てメチレン基の交換を行う。ここで、メタルアルキリデン化学種が再生し、触媒的に反応が進行する。この反応機構は Yves Chauvin によって提唱された[5]。

Scheme 1.5　Mechanism of olefin metathesis.



一般的にオレフィンメタセシスに利用される触媒としては、モリブデンアルキリデン錯体である Schrock 型カルベン錯体 **1** やルテニウムベンジリデン骨格を有する第一世代 Grubbs 触媒 **2**、またこのものに更に改良を加えた第二世代 Grubbs 触媒 **3** などを挙げることができる(Figure 1.1)。

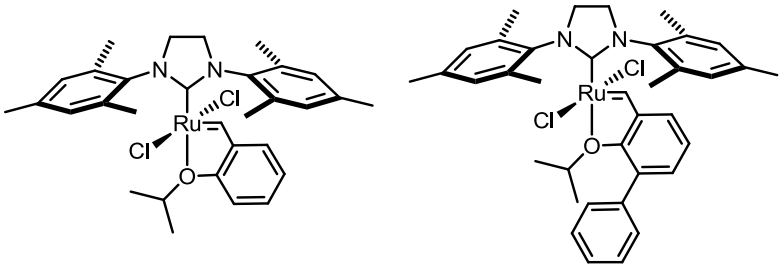
Figure 1.1



1　　**2**　　**3**

さらにこれらの触媒のほかにも、活発な触媒改良の研究によって多様なアルキリデン触媒が開発されてきている。代表的なものとしては Amir H. Hoveyda による Hoveyda-Grubbs 触媒 **4**[6]、Siegfried Blechert による Hoveyda-Blechert 触媒 **5**[7] などが挙げられる(Figure 1.2)。これらの触媒は、Grubbs 触媒では進行し難い電子不足オレフィンや特異な基質の反応に対して有効であることが知られている。

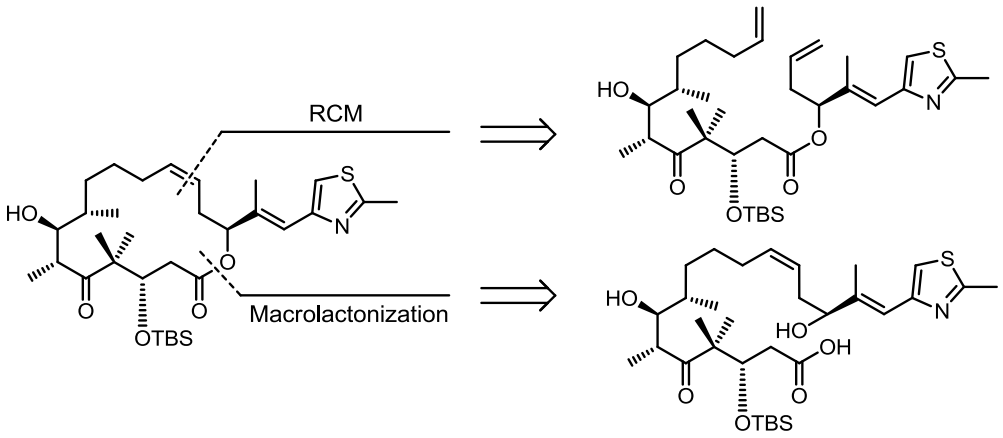
Figure 1.2



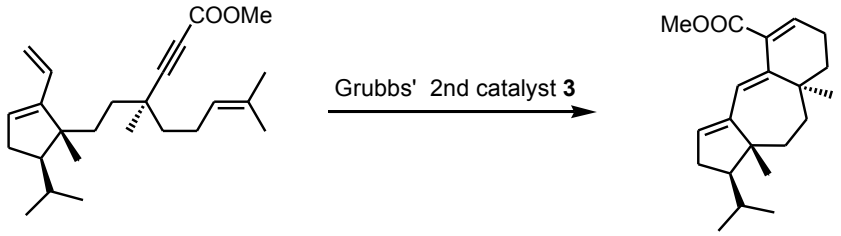
4 **5**

オレフィンメタセシスには交差メタセシス CM（Cross Metathesis）や高分子合成に応用されている開環メタセシス重合 ROMP[8]（Ring Opening Metathesis Polymerization）などのいくつかの形が存在するが、有機合成化学の分野では閉環オレフィンメタセシス RCM（Ring Closing Olefin Metathesis）が最も頻繁に用いられている。例えば、従来マクロライドなどの大環状化合物を合成する方法は山口法などのマクロラクトン化法が代表的なものであったが、RCM を用いることで全く異なるアプローチによる大環状化合物合成が可能となった(Scheme 1.6)[9]。この際、他の官能基の分解は起こらず、また、副生成物はエチレンガスのみであり反応系から容易に除去され悪影響を及ぼさないなど、RCM は精密有機合成を行う際にも価値が高いことが分かる。また、複数の反応点でメタセシスを起こすことで環状化合物を一挙に構築することも可能であり、Scheme 1.7 の例では閉環エンインメタセシス(RCEM)とのタンデム反応を利用した環構築を行っている [10]。これらの閉環メタセシス反応によって天然物化合物の研究においても、目的物の逆合成解析の方法が多様化した。

Scheme 1.6



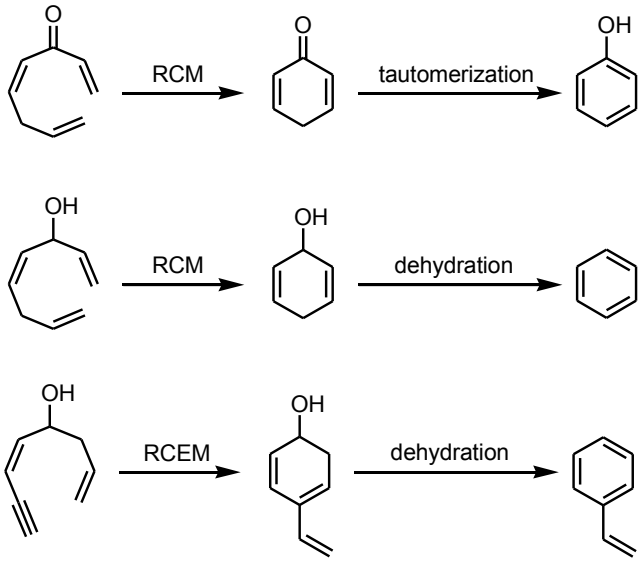
Scheme 1.7



以上のように、閉環メタセシス反応は強力な炭素-炭素不飽和結合形成反応であり且つ極めて優れた官能基選択性をもつ。また、副生するエチレンガスは反応系に影響を及ぼしにくく、調製、保存、取り扱いが容易なルテニウム触媒も開発されているなど、閉環反応に閉環オレフィンメタセシスを利用することは多くの利点をもち、より多様な置換基をもつ芳香族化合物の合成を可能にするものと期待される。

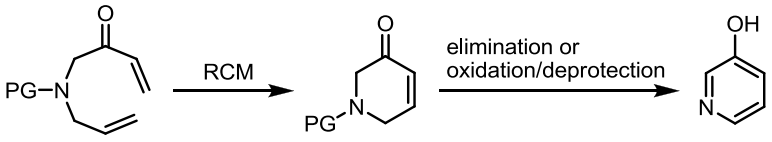
当研究室ではこの閉環メタセシスによる閉環と続く芳香族化の手法を用いて、これまでにフェノール、ベンゼン、スチレンといった様々な芳香族化合物合成を達成してきている(Scheme 1.8)[11]。

Scheme 1.8



また、含窒素ヘテロ環芳香族化合物である 3-ヒドロキシピリジンの合成も達成している(Scheme 1.9) [12]。

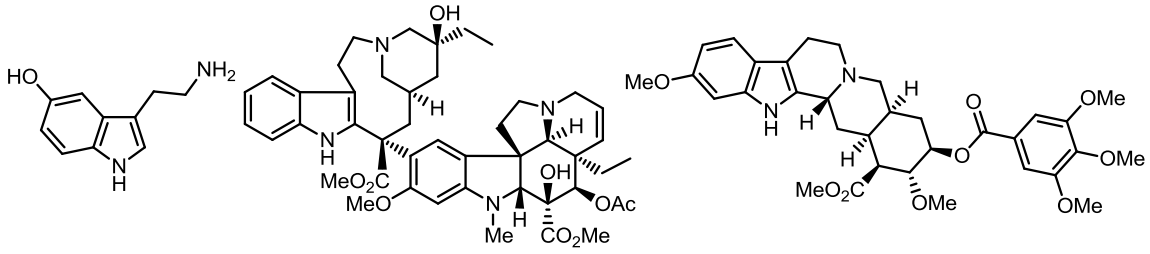
Scheme 1.9



このように本手法によって様々な置換芳香族化合物の合成法が開発されてきたが、複素環芳香族化合物合成の例は未だ限られていた。複素環芳香族化合物は生理活性物質や機能性材料など様々な分野において幅広く用いられており、我々の生活において多くの重要な役割を果たしていることに鑑みて、本手法がより幅広い複素環芳香族化合物の合成へと展開されることが強く望まれる。そこで本研究では、複素環芳香族化合物の中でもその重要性から多くの注目を集めているインドール類に着目し、閉環メタセシスによる閉環と続く芳香族化の手法を用いた合成法の開発を目指した。

インドール類は、アミノ酸の一種であるトリプトファンや神経伝達物質であるセロトニン、天然物由来の種々のアルカロイド、香料、植物ホルモン、抗炎症剤や抗悪性腫瘍剤など、天然物・人工物を問わず様々な化合物に見られ、その生理活性や機能から農業・工業・医薬品業をはじめとする多くの分野において重要な役割を担っている(Figure 1.3)[13]。

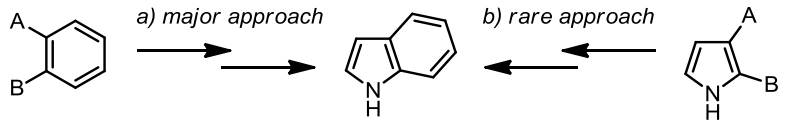
Figure 1.3　Useful materials containing indole skeleton.



このため、インドール骨格を構築するためにこれまでに多くの合成法が報告されてきており[14]、そのアプローチとしては大きく二つに分類することができる。その一つはベンゼン誘導体からピロール環を構築する手法(Scheme 1.10a)、もう一つはピロール誘導体からベンゼン環を構築する手法である(Scheme 1.10b)。両手法を比較すると、一般に C–N 結合の形成に比べ C–C 結合の形成が難しいために前者の手法に比べ後者の手法の報告例が極めて少なくなっている[15]。しかしながら、

アプローチの違いに応じて得られる化合物の種類や合成の容易さに違いが出てくることを考えれば、後者の手法がこれまで以上に注目されて然るべきであり、このアプローチに基づいた新たな合成手法を開発することは重要な意義をもつといえる。

Scheme 1.10　Two synthetic approaches to indole skeletons.



そこで本研究では、報告例が少なく且つメタセシスの強力な炭素-炭素結合能を活かすことができる後者のアプローチに基づき、閉環メタセシスを用いた炭素六員環構築によるインドール類の合成法を開発することとした。

以降の章において、第二章と第三章では六員環構築にRCM反応を用いた合成法について、第四章と第五章では六員環構築にRCEM反応を用いた合成法について述べる。

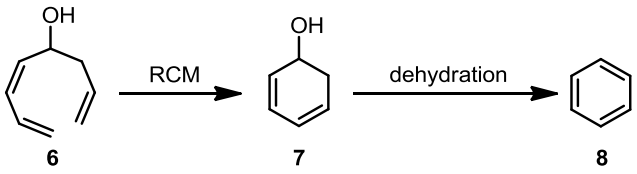
第二章

ルテニウム触媒閉環オレフィンメタセシスを用いるインドールの合成

第一節　インドールの合成戦略

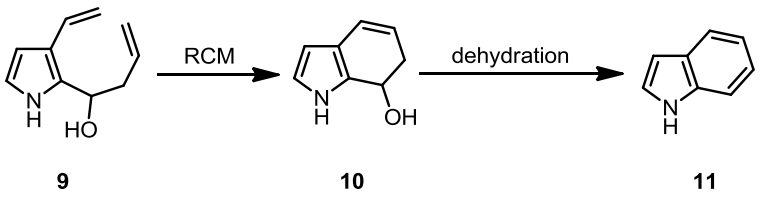
第一章で述べたように、近年、ルテニウム触媒閉環オレフィンメタセシス(RCM)を利用する芳香環構築法が芳香族化合物合成おける有効な合成戦略として浮上してきている [16–19]。当研究室もまたここ数年この分野において精力的に研究を行ってきており、これまでに様々な芳香族化合物誘導体の合成を行ってきた。その中で、1,5,7-octatoriene-4-ols **6** に対し RCM/dehydration を適用することでベンゼン誘導体 **8** が得られることを報告している(Scheme 2.1) [20]。この合成法にはベンゼン環上に多様な置換基を柔軟かつ選択的に導入できるという利点がある。

Scheme 2.1　1,5,7-Octatriene-4-ols **6** give benzenes **8** after RCM/dehydration.



そこでこの手法を Scheme 1.10b のアプローチに基づくインドールの合成法へと利用することを試みた(Scheme 2.2)。本合成戦略では環化前駆体 **9** に対し RCM/dehydration を適用することでインドール誘導体 **11** が得られるものと考えられる。

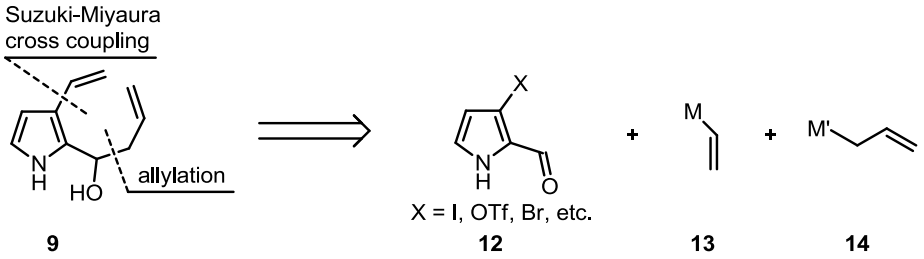
Scheme 2.2　Precursors **9** give indoles after RCM/dehydration.



ここで環化前駆体 **9** は基本的な三つの部位へと逆合成解析され得る(Scheme 2.3)。すなわち、2 位と 3 位にカルボニル基及びハロゲン等が導入されたピロール誘導体 **12** に対し、ビニル金属試薬 **13** を用いたカップリング反応及びアリル金属試薬 **14** を用いたアリル化を行うことで環化前駆体 **9** が得られるものと考えられる。各反応には穏やかな条件のものを選択し、種々の試薬を組み合わせることによって、柔軟かつ選択的に多様な置換基を導入できるものと期待される。例えば、カップリング反応には条件が穏やかで官能基選択性に優れた鈴木ー宮浦カップリング反応を用い、アリル化にはグリニャール試薬や、より穏やかな条件で反応するアリルボロン酸エステルなどを用いることで様々な官能基を導入することが可

能となるはずである。

Scheme 2.3　Retrosynthetic analysis of substrates **9**.



以上で述べた合成戦略に基づき、まず次節にて環化前駆体となるジエン基質の合成を行った結果を述べる。

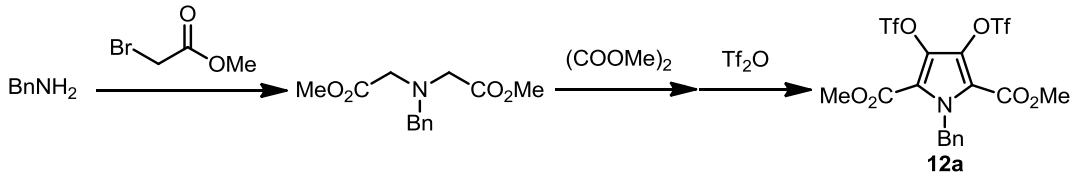
第二節　ピロール部位を有するジエン基質の合成

第一節で述べた合成戦略に従い、環化前駆体となる、ピロール部位を有するジエン基質 **9** の合成を試みた。

出発物質となるピロール **12** については容易に入手可能な市販品が無かったため、初めに **12** の合成に取り組んだ。目的のピロール **12** となり得る基質の合成を行っている種々の文献を検討した結果、二つの方法が利用可能であった(Schemes 2.4 and 2.5)。

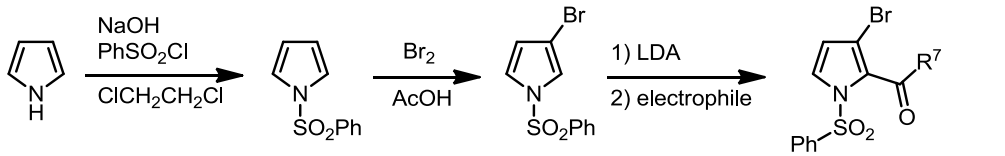
一例目では Hinsberg チオフェン合成 [21] をピロール環の構築に応用し、2 位にエステル、3 位にトリフルオロメタンスルホニル基が導入された対称なピロール基質 **12a** が得られる [22]。二例目では、リチオ化した 3-ブロモピロールと求電子試薬との位置選択的な反応によって 2 位にカルボニル基、3 位に臭素が導入されたピロール **12b** 及び **12c** が得られる [23]。

Scheme 2.4　Preparation of **12a**.



12a

Scheme 2.5　Preparation of **12b** and **12c**.



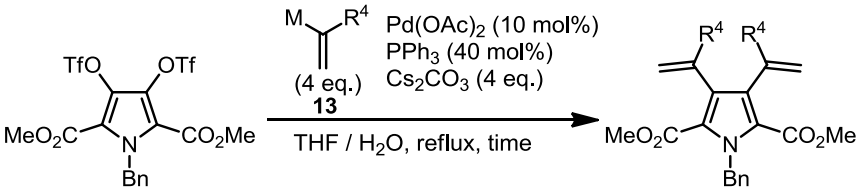
12b : R^7 = H

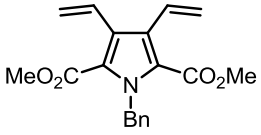
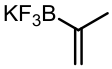
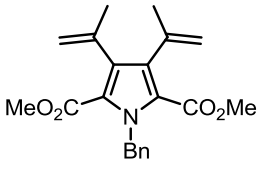
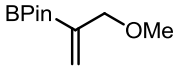
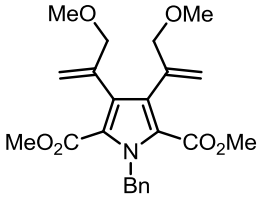
12c : R^7 = *p*-MeO-C_6H_4

このようにして得られる基質のうち、初めに **12a** を出発物質として環化前駆体 **9** の合成を試みた。Scheme 2.3 の逆合成に従い、まず **12a** に対して酢酸パラジウム、炭酸セシウム、トリフェニルホスフィンの存在下、THF/水の混合溶媒条件で鈴木‐宮浦カップリング反応を適用した(Table 2.1)。ここで、単純なビニルホウ素試薬 **13a** を用いて Pd 種と配位子との比率及び配位子の種類、塩基の種類、反応時間などについて検討を行った結果、$Pd(OAc)_2$ に対して 4 等量の PPh_3 を用いる触媒系で 2 日間 reflux させる条件が最適であった(Table 2.1, entry 1)。続いてこの反応条件で、ビニル上に他の置換基が導入されたホウ素試薬 **13b** 或いは **13c** を用いて鈴木‐宮浦カップリング反応の適用を試みた。しかしながら **13b** を用いた場合では反応が完全には進行せず、原料との分離が困難で、目的物のみを得ることができなかった(entry 2)。また、**13c** を用いた場合は黒色

固体が析出し、原料も分解してしまい、目的物を得ることができなかった(entry 3)。

Table 2.1 Application of Suzuki-Miyaura coupling to **12a**.

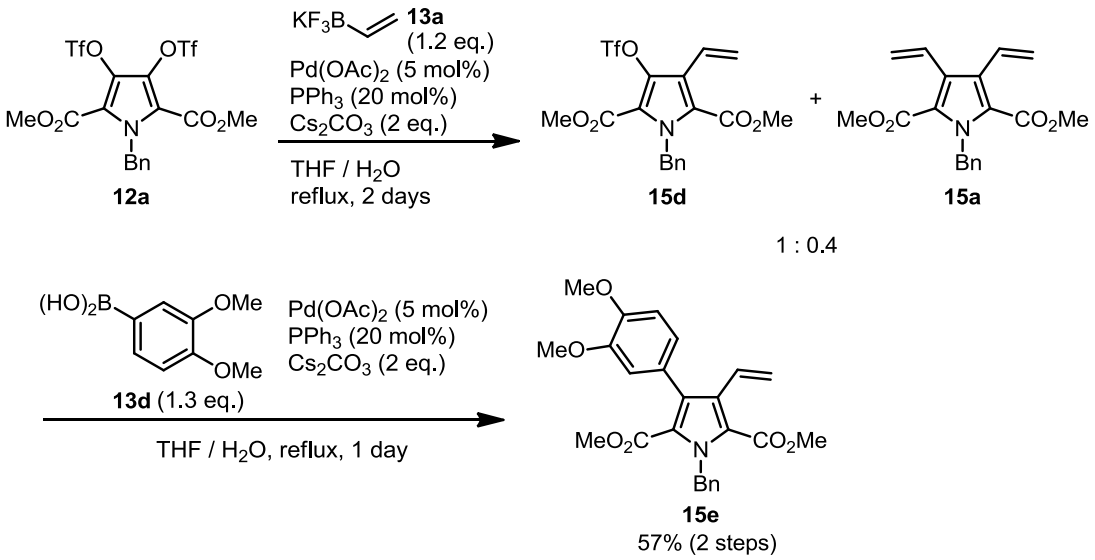


entry	13	time	17	yield (%)[a]
1	 **13a**	2 days	 **15a**	88
2	 **13b**	2 days	 **15b**	–[b]
3	 **13c**	21 h	 **15c**	–[c]

[a]Isolated yield. [b]Coupling reaction was not finished. Isolation of target compound was failed. [c]Coupling reaction did not occur and substrate was decomposed.

一方、**12a** の 3 位と 4 位でカップリングが行えることを利用し、**12a** を異なる二種類のホウ素試薬と順次カップリングさせることで、3 位と 4 位の一方にビニル基を他方にアリール基を導入した基質を合成することを試みた(Scheme 2.6)。Table 2.1 の結果から、二段階目のカップリング反応は進行しにくいことが分かるが、二段階目に、より反応性が高くかつ極性官能基が導入されたアリールホウ素試薬 **13d** を用いることで、目的の非対称なピロール基質 **15e** を良好な収率でかつ副生成物を混入させずに得ることができた。

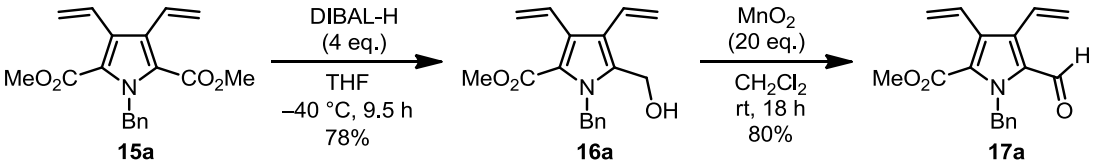
Scheme 2.6 Preparation of **15e** from **12a** by sequential Suzuki-Miyaura coupling.



このように**12a**から鈴木‐宮浦カップリング反応を適用して得ることができた基質**15a**及び**15e**に対し、今度は一方のエステルをアルデヒドへ変換し、アリル化を行うことを試みた。

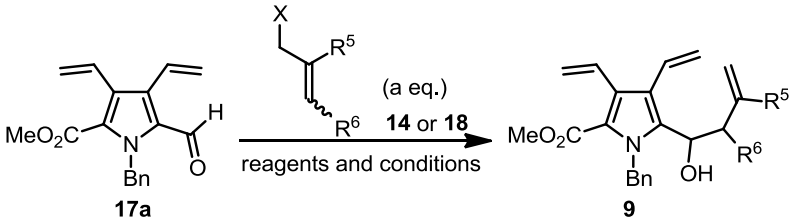
初めに、対称な基質 **15a** に対しては還元試薬に DIBAL-H を用い、反応温度および時間を検討して一方のエステルがアルコールに還元されたもの **16a** を主生成物として得た。続いて二酸化マンガンを用いて酸化することでアルデヒド **17a** へと変換した(Scheme 2.7)。

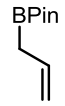
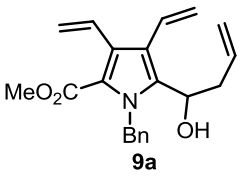
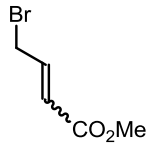
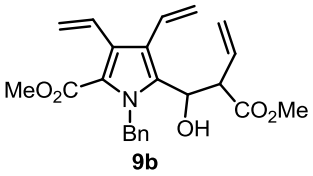
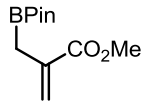
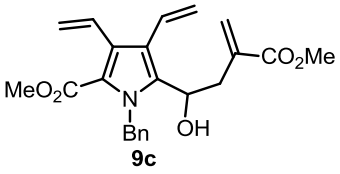
Scheme 2.7 Preparation of **17a** from ester **15a** by reduction with DIBAL-H and oxidation with MnO_2.



このアルデヒド**17a**に対し種々のアリル化試薬**14a**, **14b**, **18**等を用いてアリル化を行った(Table 2.2)。その結果、いずれの反応においても良好な収率で目的の生成物**9a-c**が得られた(entries 1-3)。

Table 2.2 Preparation of **9** from **17a** by allylation.

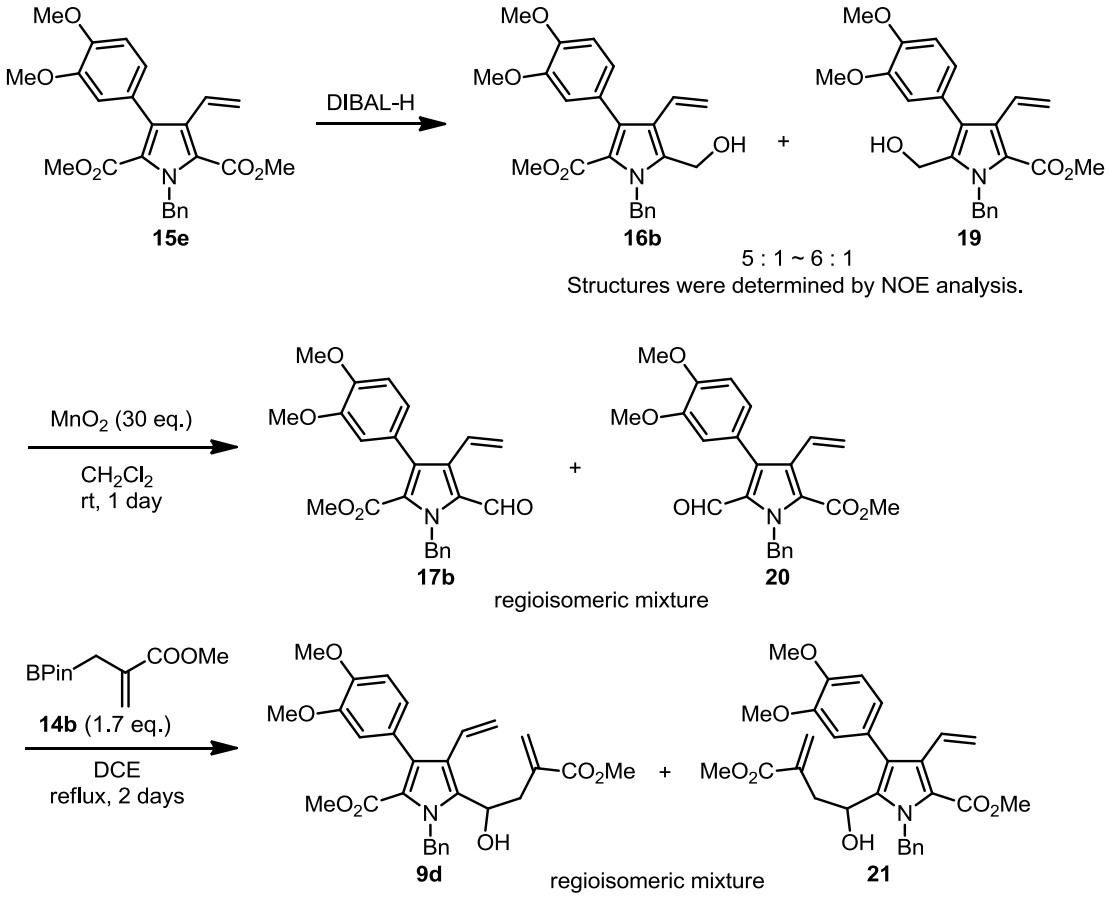


entry	**14** or **18**	a	reagents and conditions	**9**	yield (%)[a]
1	 **14a**	1.5	$ClCH_2CH_2Cl$ reflux, 1 day	 **9a**	95
2[b]	 **18**	2.0	$AlEt_2Cl$ (2.2 eq.) Zn (3 eq.) CuBr (0.1 eq.) THF, –20 °C, 13 h	 **9b**	80
3	 **14b**	1.7	$ClCH_2CH_2Cl$ reflux, 2 days	 **9c**	98

[a]Isolated yield. [b]A diastereomeric mixture of **9b** (0.57/0.43) was obtained.

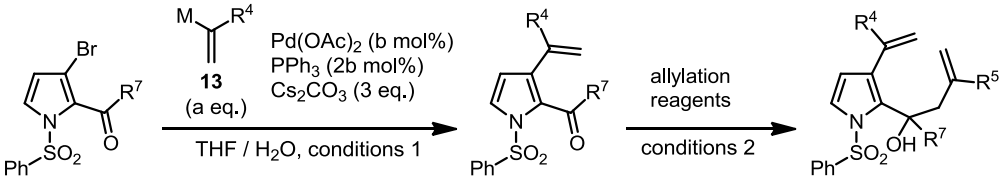
一方 **12a** から得られた非対称な基質 **15e** においても DIBAL-H によるエステルの部分還元を行った(Scheme 2.8)。レジオ選択的な還元を目指して反応温度および時間を検討したが、目的物 **16b** を単離するには至らなかった。この位置異性体混合物に対し、二酸化マンガンによる酸化によってアルデヒドへと変換した後アリル化を行うことで、環化前駆体 **9d** と異性体 **21** の混合物を得た。

Scheme 2.8 Preparation of **9d** from **15e** by reduction, oxidation, and allylation.

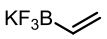
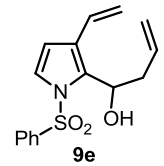
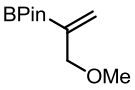
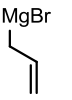
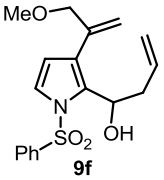
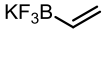
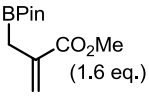
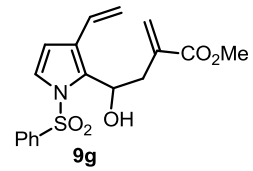
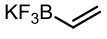
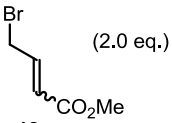
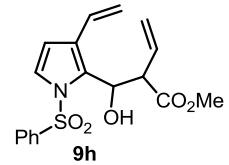
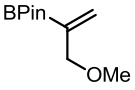
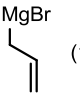
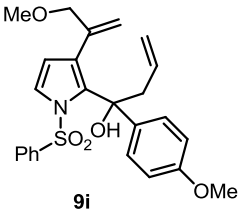
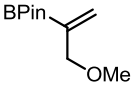
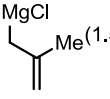
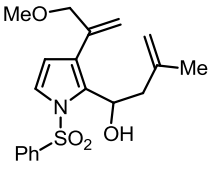


続いて Scheme 2.5 で得られる基質 **12b**, **c** を出発物質とする環化前駆体 **9** の合成を試みた。この場合も Scheme 2.3 の逆合成解析に従い、基質 **12b**, **c** に対して鈴木‐宮浦カップリング反応を適用したのち[24]、カルボニル基に対しアリル化を行うことで目的の環化前駆体 **9e-j** を得ることができた(Table 2.3)。**12a** に比べ **12b** は鈴木－宮浦カップリングの反応性が比較的良かったため、ホウ素試薬 **13c** を用いることができ、R^4 位への置換基導入が可能であった(entries 2 and 6)。また、種々のアリル化試薬を用いることで R^5, R^6 への置換基導入も可能であった(entries 3, 4, and 6)。さらに、2 位がアルデヒドではなくケトンの基質 **12c** に対しても同様の手法が適用でき良好な収率で R^7 に置換基が導入された環化前駆体 **9i** を得ることができた(entry 5)。

Table 2.3 Preparation of **9** from **12** by Suzuki-Miyaura coupling and allylation.



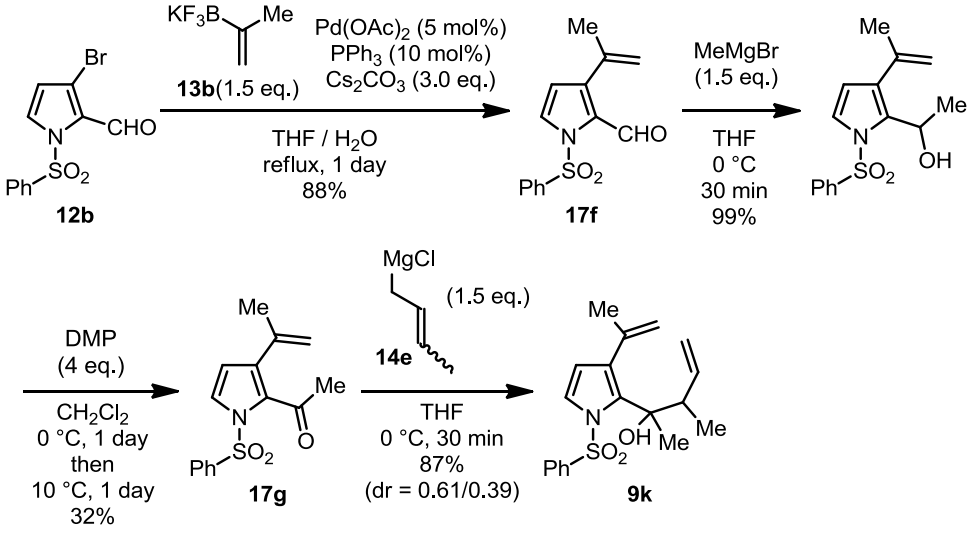
12 **17** **9**

entry	**12**	**13**	a	b	conditions 1	allylation reagents	conditions 2	**9**	yield (%)[a] (2 steps)
1	**12b**	 **13a**	1.5	5	reflux 1 day	 (1.2 eq.) **14a**	DCE reflux 1 day	 **9e**	17
2	**12b**	 **13c**	1.5	5	65 °C 4.5 h	 (1.5 eq.) **14c**	THF 0 °C 30 min	 **9f**	83
3	**12b**	 **13a**	1.5	5	reflux 1 day	 (1.6 eq.) **14b**	DCE reflux 1 day	 **9g**	79
4[b]	**12b**	 **13a**	1.5	5	reflux 1 day	 (2.0 eq.) **18** $AlClEt_2$ (2.2 eq.) Zn (3.0 eq.) CuBr (0.1 eq.)	DCE –20 °C 15 h	 **9h**	25
5	**12c**	 **13c**	2	10	reflux 2 days	 (1.5 eq.) **14c**	THF 0 °C 30 min	 **9i**	60
6	**12b**	 **13c**	1.5	5	65 °C 5 h	 (1.5 eq.) **14d**	THF 0 °C 30 min	 **9j**	67

[a]Isolated yield. [b]A diastereomeric mixture of **9h** (0.68/0.32) was obtained.

さらに、**12b** の鈴木カップリング後にアルデヒドをケトンへと変換し、その後アリル化するという経路で R^7 = Me の基質 **9k** を合成できたが、この際に置換基の小ささを利用して R^4, R^6, R^7 の三か所に置換基が導入された基質となるようにした(Scheme 2.9)。

Scheme 2.9　Preparation of **9k** from **12b**.



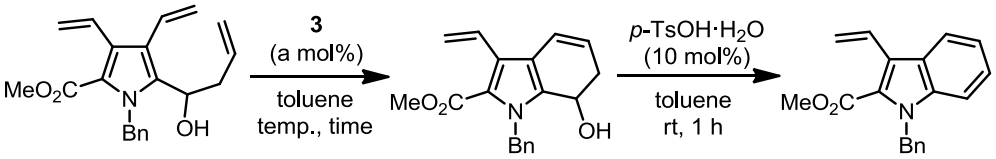
次節では、以上で得られた環化前駆体 **9a-k** に対する、閉環オレフィンメタセシスを用いたインドール合成について述べる。

第三節　閉環オレフィンメタセシスを用いるインドールの合成

前節で得られた環化前駆体 **9a-k** に対して閉環オレフィンメタセシス(RCM)による環化と脱水による芳香族化を行うことによってインドール合成を試みた。

初めに **9a** を用いて触媒量及び反応条件の検討を行った(Table 2.4)。第二世代 Grubbs 触媒 **3** を 1 mol%用いた場合では目的物は得られなかった(entry 1)。触媒量を 2.5 mol%、7.5 mol%に上げると中間体 **I** がそれぞれ 43%、89%以上の収率で得られてきた(entries 2 and 3)。触媒量 7.5 mol%で温度を室温に下げ反応時間を 12 時間に延ばすと **10a** が同程度の収率で得られ(entry 4)、単離した **10a** に対し脱水を行うと **9a** に対して 70%の収率で **11a** が得られた。以上の結果を踏まえ、触媒量が 7.5 mol%、反応時間が 12 時間の条件を最適条件とした。

Table 2.4　Optimization of RCM conditions for **9a**.



9a　　**10a**　　**11a**

entry	a	temp. (°C)	time (h)	yield of **10a** (%)[a]	yield of **39a** (%)[b]
1	1	80	2	-	-[c]
2	2.5	80	2	43	-
3	7.5	80	2	> 89	-
4	7.5	rt	12	> 84	70

[a]NMR yield by internal standard method. [b]Isolated yield. [c]Complex mixture was obtained. **11a** was not observed.

このようにして定めた反応条件を基準として、前節で得られた種々の環化前駆体 **9** に対し、RCM/脱水を行いインドール合成を行った(Table 2.5)。

初めに **9a** に対して Table 2.4 の entry 4 の条件で **10a** を単離せずに反応を行うと、73%の収率で対応するインドール **11a** が得られた(entry 1)。

R^6 にエステルが導入された場合、室温条件では反応が遅く、80 °C で反応を行うと原料は消失し、対応するインドール **11b** が得られたが収率は 53%と中程度にとどまった(entries 2 and 3)。

更に、RCM で組み替えの起こるオレフィン上の R^5 にエステルが導入された場合では反応温度を 100°C としてもインドール **11c** が 12%しか得られなかった(entry 4)。ここで、触媒量を倍の 15 mol%にすると収率もほぼ倍の 22%に上昇したことからこの基質を用いた RCM で

は触媒がすぐに失活してしまうものと考えられる(entry 5)。そこで、RCM の起こるオレフィン上に電子求引性の置換基が導入された基質に対して収率の向上が期待できる第二世代 Hoveyda-Grubbs 触媒 **4** を用いて反応を行ったが、収率は逆に低下する結果となった(entry 6)。

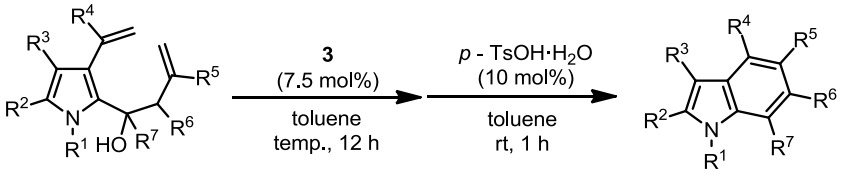
収率が低い原因として、R^2 と R^3 に導入されたエステルとオレフィンが触媒と錯形成し(Figure 2.1)、反応を阻害しているのではないかと考えたが、R^3 にオレフィンではなくアリールをもつ前駆体 **9d** に対して反応を行った場合でも収率は同程度であったため(entry 7)、この仮説は否定された。結局、収率が低い原因としては、R^2 と R^3 に同時に置換基が導入されているため嵩高くなり反応が進行しにくくなること、R^1 の置換基が電子供与性であるため窒素上の電子密度が高まり触媒を失活させやすくなること等が考えられる。

一方、**12b**, **c** から合成した環化前駆体に RCM/脱水の手法を適用した場合には概して高い反応性が見られた(entries 9-12 and 15)。六員環上に一つ以下の置換基が導入されたインドールを得る反応では良好又は高い収率となった(entries 8-11)。**11g** の合成に注目すると、同じく R^5 上にエステルの導入された前駆体 **11c** を用いた場合に比べて収率が大幅に向上しており(entry 10 vs. 4)、この結果は、上で述べた **11b-d** の収率が低下する原因に対する考察を支持している。

また、六員環上に二つの置換基を有するインドール **11i**、更には三置換であるインドール **11k** も高い収率で得ることができた(entries 12 and 15)。置換基の数が増えたにもかかわらず、予想に反して収率が低下せずむしろ向上する傾向を示したが、これは Thorpe–Ingold 効果によるものと考えられ[25]、本手法をより効果的なものにしている。

RCM の段階で四置換オレフィンが形成される必要のある基質 **11j** に適用した場合には、予想通り収率が大きく低下したが(entry 13)、触媒量を上げることで収率が向上した(entry 14)。

Table 2.5 Synthesis of indoles **11** by RCM/dehydration.



9 **11**

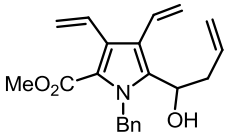
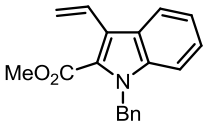
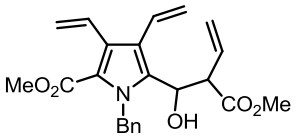
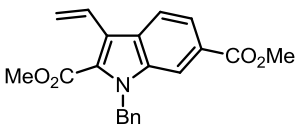
entry	**9**	temp. (°C)	**11**	yield (%)[a]
1	 **9a**	rt	 **11a**	73
2	 **9b**	rt	 **11b**	-[b]
3		80		53

Table 2.5 (continued)

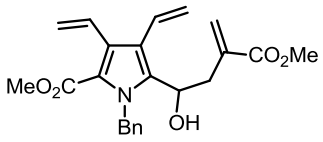
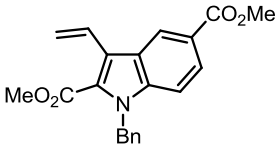
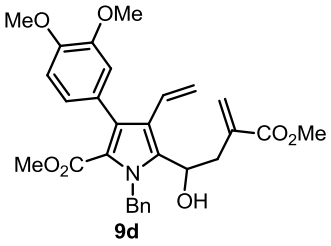
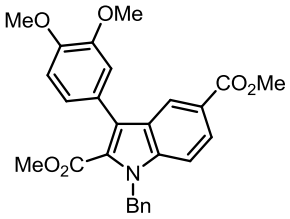
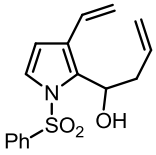
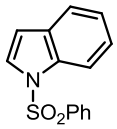
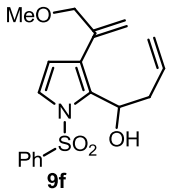
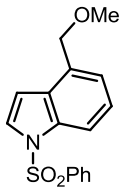
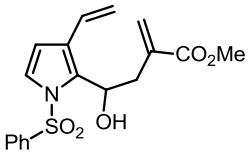
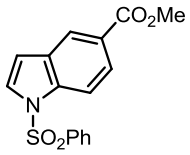
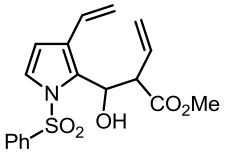
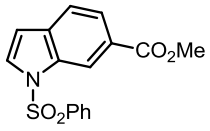
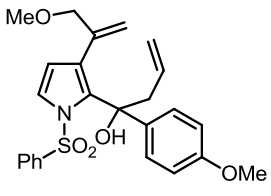
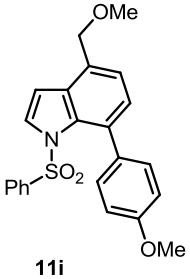
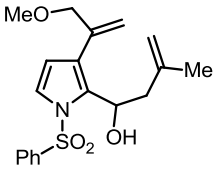
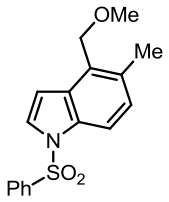
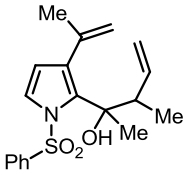
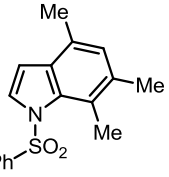
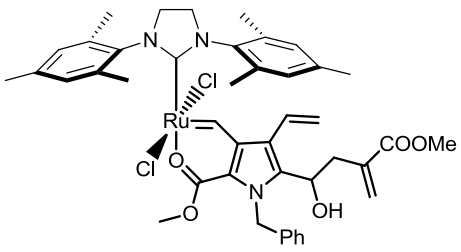
entry	9	temp. (°C)	11	yield (%)[a]
4	 **9c**	100	 **11c**	12
5[c]		100		22
6[d]		100		~7
7[e]	 **9d**	100	 **11d**	13
8	 **9e**	rt	 **11e**	98
9	 **9f**	80	 **11f**	93
10	 **9g**	80	 **11g**	70
11	 **9h**	80	 **11h**	81
12	 **9i**	80	 **11i**	>99

Table 2.5 (continued)

entry	**9**	temp. (°C)	**11**	yield (%)[a]
13		100		36
14[f]		100		66
	9j		**11j**	
15		80		93
	9k		**11k**	

[a] Isolated yield. [b] RCM reaction was very slow. [c] Catalyst **3** (15 mol%) was used. [d] Hoveyda-Grubbs' catalyst **4** (7.5 mol%) was used. [e] A mixture of regioisomers (**9d** : **21** = 2.00 : 0.35) was used. [f] The dehydration was carried out at 80 °C for 1.5 h.

Figure 2.1



22

plausible complex

第四節　結論

本章では、報告例の少ない Scheme 1.10b のアプローチに分類される、RCM/脱水を用いた炭素六員環構築を鍵反応とするインドール合成法を開発した。環化前駆体となるピロール環を有するジエン基質は鈴木-宮浦カップリングによるビニル化と有機金属試薬を用いたアリル化によって合成でき、種々の前駆体を合成できた。そして、得られた前駆体に RCM/脱水の手法を施すことで多様な置換基が複数導入されたインドール誘導体を選択的に合成することが可能であることを示せた。

RCM/脱水反応では、これまでの傾向と同じく電子求引性の置換基がオレフィンの近くにある基質や四置換オレフィンが形成される必要のある基質では収率が低下し、また、基質の R^1 から R^3 の置換基の影響も比較的大きかったが、一方で、構築される六員環上で置換基導入が可能な四か所のうち三か所に置換基が導入された誘導体を高収率で合成することもできるなど、予想より本手法が効果的な場合もあった。

第三章

閉環オレフィンメタセシスを用いる
インドール関連化合物合成への展開

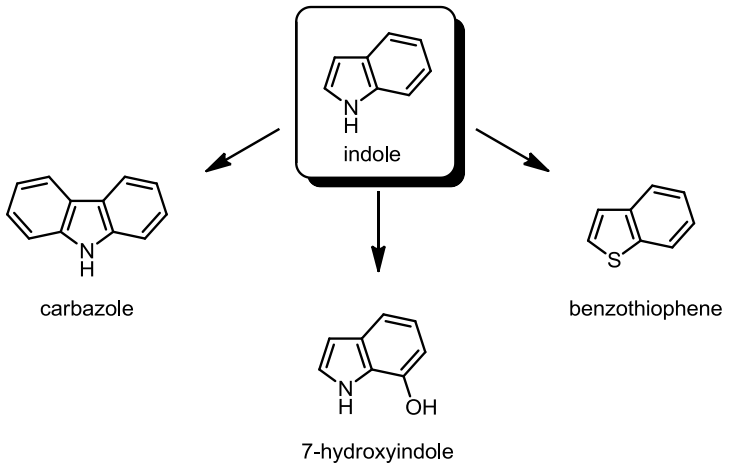
第一節　インドール関連化合物

第二章では、報告例の少ないアプローチである、閉環メタセシスを用いた炭素六員環構築によってインドールの合成を行うことができた。これによりこの手法がインドールと同様に複素五員環上に炭素六員環が縮環した構造を有する芳香族化合物の合成へと展開できるものと期待される。

本研究ではそのような化合物として、カルバゾール、7-ヒドロキシインドール、ベンゾチオフェンについて検討した(Scheme 3.1)。いずれの複素環芳香族化合物もインドール同様、従来は複素環を構築する合成法が一般的であり本手法を応用できればこれまでとは異なった経路による有用な合成手法を提示できるはずである。

以降の節より、第二節でカルバゾール、第三節で 7-ヒドロキシインドール、第四節でベンゾチオフェンについて各々検討した結果を述べる。

Scheme 3.1

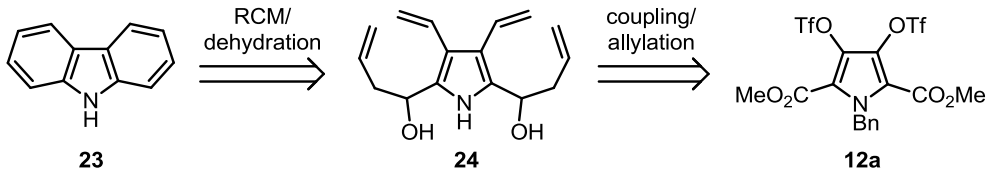


第二節　カルバゾール合成

カルバゾールはピロール環上に二つのベンゼン環が縮環した構造の化合物であり、種々の天然物アルカロイドに見られるとともに光電子材料にも用いられるなど多様な価値を生み出しうる複素環芳香族化合物の一つである[26]。

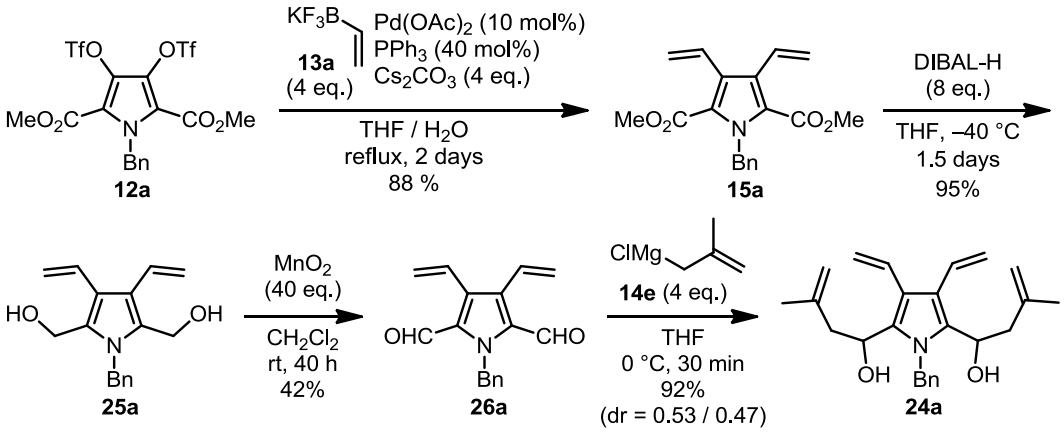
カルバゾール合成を行うためには、第二章でインドール合成の原料として用いた対称なピロール **12a** を出発物質とし、Scheme 3.2 の逆合成解析に示すような対称性を保ったクロスカップリング/アリル化の経路を経て、二つのベンゼン環を同時に構築すればよいと考えられる[27]。

Scheme 3.2　Retrosynthetic analysis of carbazoles **23**.



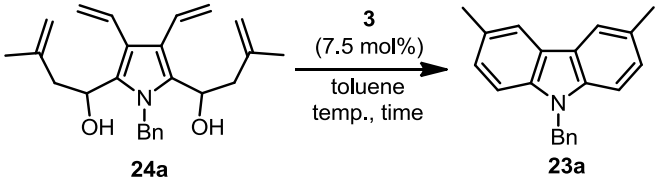
そこで、上記の合成戦略のもと、初めにカルバゾールの環化前駆体となるテトラエン基質 **24a** の合成を行った(Scheme 3.3)。インドール合成の場合と同様に **12a** から鈴木-宮浦カップリングによって得た **15a** に対して二つのエステル基の両方を還元/酸化によってホルミル基へと変換し、続いてアリル化を行うことによって目的のテトラエン基質 **24a** を得ることができた。ただし、ジオール **25a** からジアール **26a** への酸化において、酸化剤としては MnO_2 以外にも Dess-Martin Periodinane、TPAP、TEMPO 等を試し、Swern 酸化も試したがいずれも目的物が得られないか、痕跡量のみしか得られなかった。

Scheme 3.3　Preparation of **24a** from **12a** by coupling, reduction, oxidation and Allylation.



このようにして得たカルバゾールの環化前駆体 **24a** に対して RCM/脱水を施すことによりカルバゾール合成を試みた(Table 3.1)。室温条件では反応の進行が遅かったため(entry 1)、反応温度を 80 °C に上げたところ RCM 及びそれに続く自発的な脱水が素早く進行し、81%の高い収率で目的のカルバゾール **23a** の合成を達成することができた(entry 2)。

Table 3.1 Synthesis of carbazole **23a** by RCM/dehydration.



24a **23a**

entry	temp.	time	yield (%)[a]
1	rt	20 h	-[b]
2	80 °C	2 h	81%

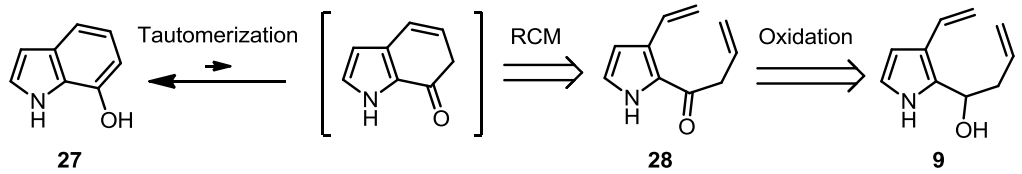
[a] Isolated yield. [b] RCM was not finished and substrate was recovered.

第三節　7-ヒドロキシインドール合成

RCM によるインドール合成において、環化前駆体としてピロール部位を有するジエンオン基質 **28** を用いると、RCM による環化の後に互変異性化による芳香族化が起こり、インドール上に水酸基が導入された 7-ヒドロキシインドール **27** が得られるものと期待される(Scheme 3.4)。芳香環上に導入された水酸基は、それ自身がアルコールとは異なる独特の性質を持つとともにトリフラート化することによりクロスカップリングに用いることもできるなど、導入することができれば生成物の有用性が大きく高まる官能基である。

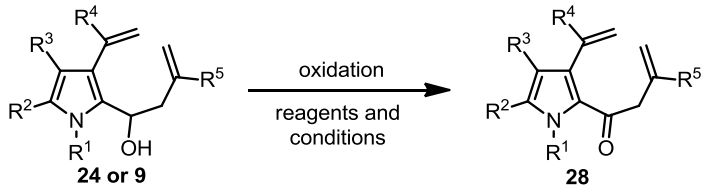
ここで、ピロール部位を有するジエンオン基質 **28** はインドール合成の環化前駆体 **9** を酸化することによって得られるものと考えられる。

Scheme 3.4　Retrosynthetic analysis of 7-hydroxyindoles **30**.



そこで、本章第二節で合成した **24a** 並びに第二章第二節で合成した **9a**, **9f** 及び **9g** に対して酸化を試みた(Table 3.2)。その結果、**9f**, **g** を DMP によって酸化することで対応する **32c**, **d** を得ることができた(entries 4 and 5)。

Table 3.2　Preparation of **28** from **24** or **9** by oxidation.



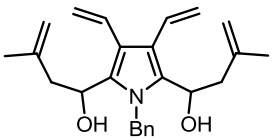
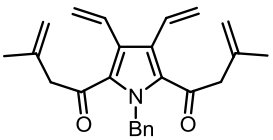
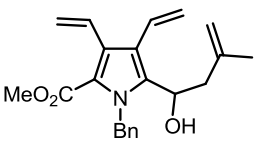
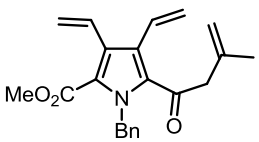
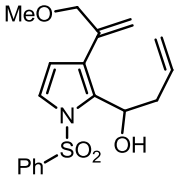
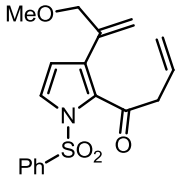
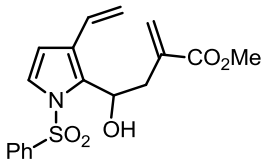
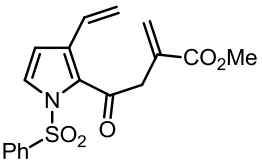
entry	alcohol	reagents and conditions	ketone	yield (%)[a]
1	 **24a**	DMP[b] CH_2Cl_2 0 °C, 15 h	 **28a**	0[c]
2		MnO_2[d] CH_2Cl_2 rt, overnight		-[e]
3	 **9a**	MnO_2 (20 eq.) CH_2Cl_2 rt, 19 days	 **28b**	0[f]

Table 3.2 (continued)

entry	alcohol	reagents and conditions	ketone	yield (%)
4	 **9f**	DMP (4 eq.) CH_2Cl_2 rt, 1 day	 **28c**	59
5	 **9g**	DMP (4 eq.) CH_2Cl_2 0 °C, 16 h	 **28d**	70

[a] Isolated yield. [b] DMP (4 eq.) was used, and DMP (2 eq.) was added after 3 h. [c] Almost substrate was decomposed. [d] MnO_2 (50 eq.) was used, and MnO_2 (20 eq.) and MnO_2 (10 eq.) were added after 1 h and 3.5 h, respectively. [e] Reaction was very slow and substrate was decomposed. [f] No reaction.

このようにして得た **28** に対して RCM/脱水を施すことで 7-ヒドロキシインドール **27** を良好な収率で合成することができた(Scheme 3.5)。ただし **28c** を用いた場合には、副生成物として **28c** のアリル部位の末端オレフィンが内部オレフィンへと異性化した **29** が得られてきた(Figure 3.1)。RCM 反応においては第二世代 Grubbs 触媒 **3** から副生する化学種によって異性化の副反応が起こる経路が報告されており [28]、基質 **28c** では RCM の反応性が下がるためにこのような副反応が起こるものと考えられる。

Scheme 3.5 Synthesis of 7-hydroxyindoles **27** by RCM/tautomerization.

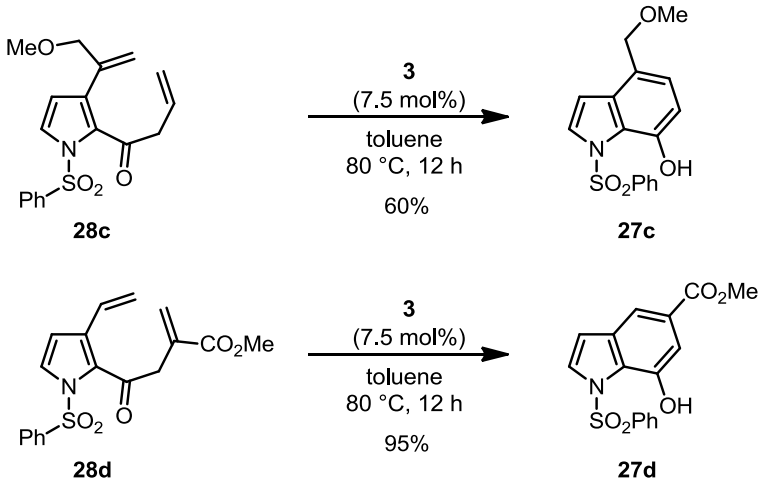
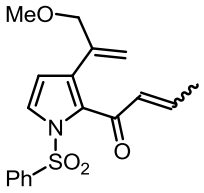


Figure 3.1 By-products **29** derived from **28c** by Ru catalyst **3**.



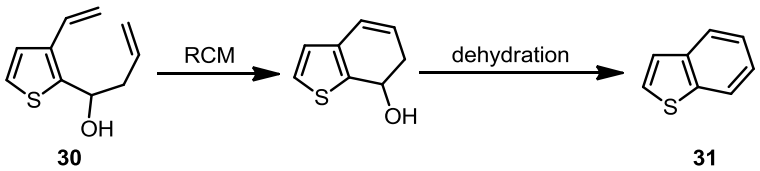
29

第四節　ベンゾチオフェン合成

ベンゾチオフェンはインドールの窒素が硫黄に置き換わった構造の化合物で、種々の天然物や薬理活性化合物に見出され、医薬品のみならず材料科学への応用も行われるなど重要な複素環式芳香族化合物の一つである。

このベンゾチオフェンの合成は、第二章で述べたインドール合成においてピロール環をチオフェン環に代えることで達成できると考えられる(Scheme 3.6)。

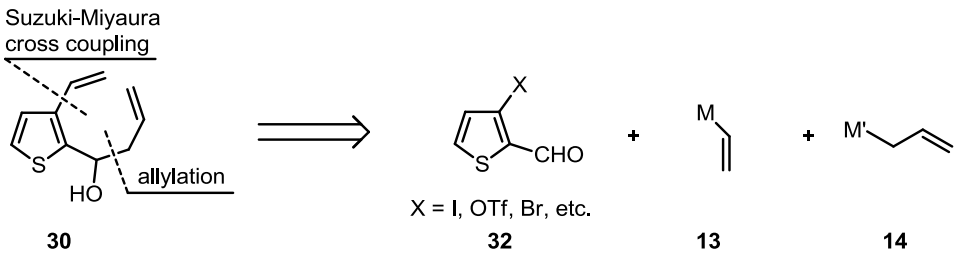
Scheme 3.6　Precursors **30** give benzothiophenes **31** after RCM/dehydration.



30　　**31**

そこで、環化前駆体となるチオフェン部位を有するジエン基質 **30** の合成を試みた。インドール合成の場合と同様に、環化前駆体 **30** は三つの部分へと逆合成解析できる(Scheme 3.7)。

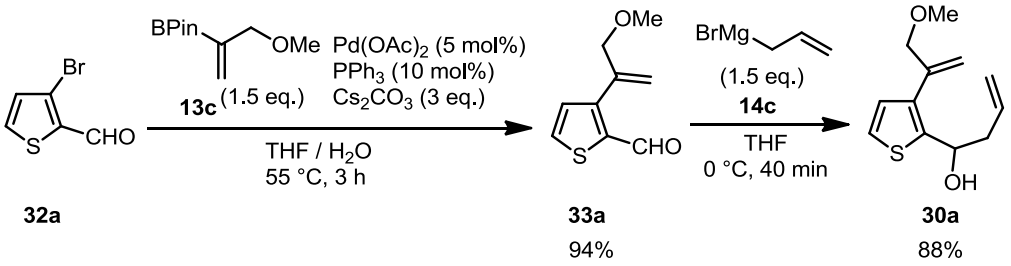
Scheme 3.7　Retrosynthesis of thiophene-containing dienes **30**.



30　　**32**　　**13**　　**14**

実際に行った合成経路を Scheme 3.8 に示す。出発物質となる基質 **32a** は市販されており容易に入手可能であった。そして、Scheme 3.7 の逆合成に従い、まず **32a** に対して酢酸パラジウム、炭酸セシウム、トリフェニルホスフィンの存在下、THF/水の混合溶媒条件でビニルボロン酸エステル **13c** を用いた鈴木‐宮浦カップリング反応を適用し、続いてグリニャール試薬 **14c** を用いたアリル化を行った。その結果、各反応は良好な収率で進行し、環化前駆体となる目的のジエン基質 **30a** を得ることができた。

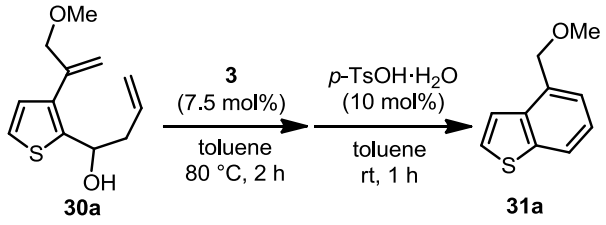
Scheme 3.8　Preparation of **30a** from **32a** by Suzuki-Miyaura coupling and allylation.



32a　**33a** 94%　**30a** 88%

このようにして得られた環化前駆体 **30a** に対し、RCM/脱水反応を適用しベンゾチオフェン合成を行った(Scheme 3.9)。RCM 反応、脱水反応共に円滑に進行し、目的のベンゾチオフェン誘導体 **31a** を良好な収率で得ることができた。

Scheme 3.9　Synthesis of benzothiophene **31a** by RCM/dehydration.



30a　**31a** 80%

ただし、ベンゼン環上に同じ置換基をもつインドール **11f** の合成の結果(Table 2.5, entry 9, 93% yield)と比較すると若干収率が低くなっている。これは、**11f** においては窒素原子上に電子吸引性の置換基が導入されているのに対し、ベンゾチオフェン **31a** や基質 **30a** の硫黄原子上には置換基は無く、このため相対的に電子密度が高くなっている硫黄原子上の孤立電子対が触媒に配位しやすくなり、触媒の失活が速まるためではないかと考えられる。

第五節　結論

本章では第二章でインドール合成に用いた手法をカルバゾール、7-ヒドロキシインドール、ベンゾチオフェンの各複素芳香環合成に応用できることを示すことができた。

カルバゾール合成では対称性を利用して、テトラエン基質を環化前駆体とし、ピロール上に同時に二つの炭素六員環を構築することで目的のカルバゾール誘導体を得た。7-ヒドロキシインドール合成では、六員環構築において RCM/脱水の手法を RCM/互変異性化にすることでインドールの 7 位に水酸基が導入された目的物を合成できた。ただし、基質によっては反応性が落ち、アリルの異性化という副反応が見られた。インドールの窒素にあたるヘテロ原子が硫黄となったベンゾチオフェン合成では、出発物質としてピロールの代わりにチオフェンの誘導体を用いることにより、期待した目的物を得ることができた。

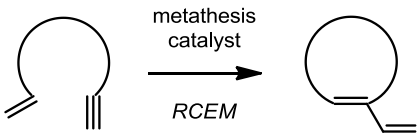
第四章

ルテニウム触媒閉環エンインメタセシスを用いる
4-ビニルインドールの合成

第一節　4-ビニルインドールの合成戦略

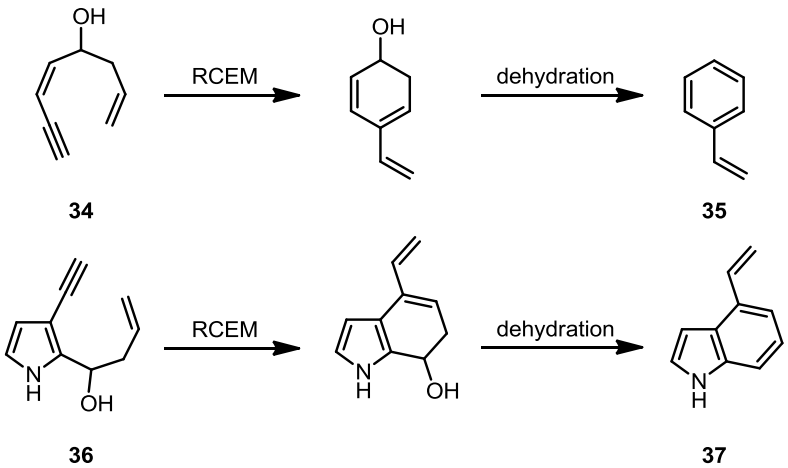
閉環エンインメタセシス(RCEM)反応は RCM 反応と同じく代表的な閉環メタセシス反応である。RCEM 反応では分子内のアルケンとアルキン間において Scheme 4.1 のような極めて独特の形式の反応が起こる[4d]。すなわち、二重結合と三重結合間で組み換えが起こり、新たに共役した二つの二重結合が形成される。この時、オレフィンメタセシスとは異なり形式上エチレンの放出はない。RCEM 反応は Grubbs 触媒においても進行することが見出されており、このため同触媒による RCM 反応同様、優れた官能基選択性や触媒の扱いやすさなどの利点を有する[29]。従って精密有機合成などにおける有用な手法となり得、実際、タンデム反応による複雑な反応の開発や天然物合成への応用なども行われている[30]。

Scheme 4.1　Ring-closing enyne metathesis (RCEM) reaction.



当研究室ではこの RCEM 反応を利用したスチレン合成を報告しており[31]、第二章のインドール合成で利用した RCM 反応の代わりに用いれば閉環と同時にビニル基が形成され、4-ビニルインドールが得られるものと考えられる(Scheme 4.2)。本手法で優れていると期待される点としては、反応条件が穏やかであることや、RCEM は理論上原子効率が 100%でアトムエコノミーであることなどが挙げられる。

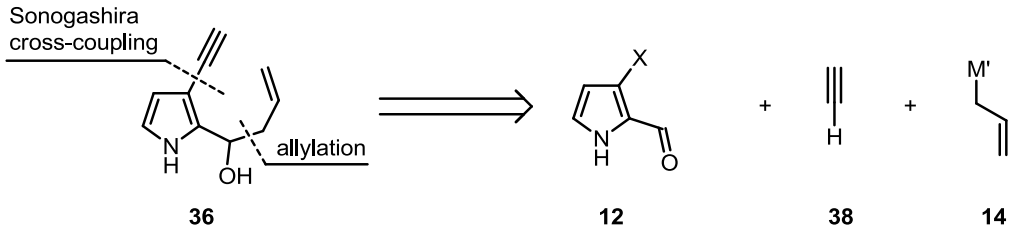
Scheme 4.2　Synthesis of **35** and **37** from **34** and **36**, respectively.



RCEM によって導入されるビニル基はエポキシ化やヒドロホウ素化、ジヒドロキシ化など様々な変換が可能な有用な官能基であり、得られる化合物は多様なインドール誘導体合成の中間体となり得ると期待される。このため、選択的に置換基を導入した 4-ビニルインドール合成法を開発することは有機合成上重要な意義をもつと言える。なお、現在のところ 4-ビニルインドール骨格を直接的に合成する一般的な方法は殆どなく [32]、その点においても 4-ビニルインドール合成法の開発の意義がある。

この合成で用いられる環化前駆体はエンイン基質となるが、この合成は、インドール合成の環化前駆体合成で用いた鈴木カップリングによるアルケンの導入を薗頭カップリングによるアルキンの導入に代えることで実現できる(Scheme 4.3)。

Scheme 4.3　Retrosynthesis of pyrrole-containing enynes **36**.



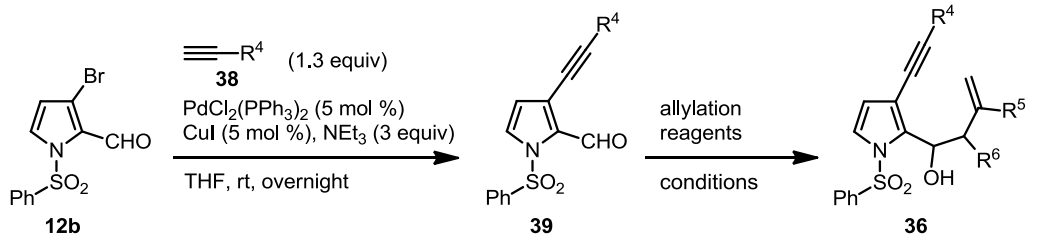
この合成戦略に基づき、まず次節にて環化前駆体となるエンイン基質の合成を行った結果を述べる。

第二節　ピロール部位を有するエンイン基質の合成

第一節で述べた合成戦略に従い、環化前駆体となる、ピロール部位を有するエンイン基質 **36** の合成を試みた。環化前駆体 **41** は Scheme 4.3 のように三つの部分へと逆合成解析される。従ってインドール合成と同じピロール誘導体 **12** を利用することができるため、第二章のインドール合成でも用いた基質 **12b** を出発物質として環化前駆体 **36** の合成を試みた。その結果を Table 4.1 に示す。基質 **12b** に対して薗頭カップリング反応を適用してアルキン **38** を導入したのち、アリル化を行うことで目的の環化前駆体 **36a-h** を得ることができた。薗頭カップリング反応の適用に関しては、ほとんどの基質でおおむね良好に反応が進行し、続くアリル化においてもおおむね良好な収率で生成物が得られた。ただし、**36f** に関しては、カラムクロマトグラフィーやリサイクル GPC による精製によっても除けない異性体 **41** が微量に混入した純度のまま次の反応に用いた(Figure 4.1)。

なお、詳しくは次節で述べるが、In を用いた **36d**, **36e** の合成(entries 4 and 5)ではα付加体がわずかに副生していると推測されるが、^{1}H NMR では確認できなかった。

Table 4.1　Preparation of **36** from **12b** by Sonogashira coupling and allylation.



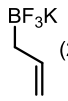
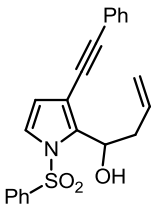
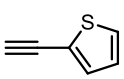
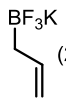
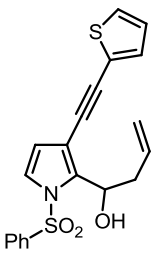
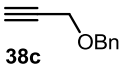
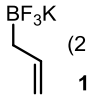
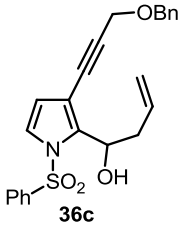
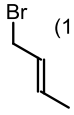
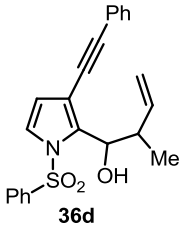
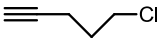
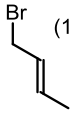
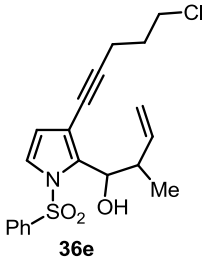
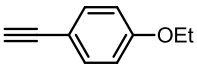
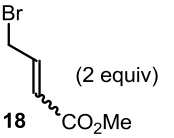
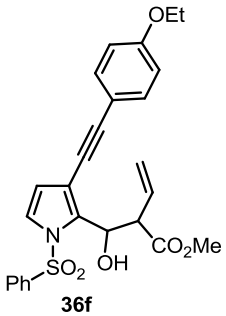
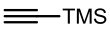
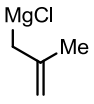
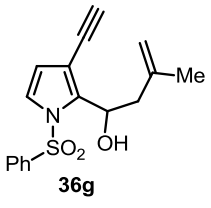
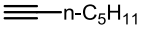
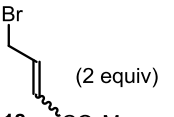
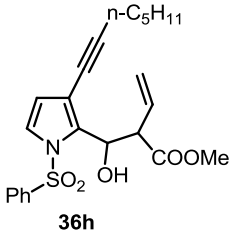
entry	**38**	yield of **39** (%)[a]	allylation reagents	conditions	**36**	yield of **36** (%)[a]
1	 **38a**	>99	 (2 equiv) **14f** ^{n}Bu$_4$NI (0.1 equiv)	CH_2Cl_2 / H_2O rt, ~1 h	 **36a**	97
2	 **38b**	95	 (2 equiv) **14f** ^{n}Bu$_4$NI (0.1 equiv)	CH_2Cl_2 / H_2O rt, ~1 h	 **36b**	93

Table 4.2 (continued)

entry	**38**	yield of **39** (%)[a]	allylation reagents	conditions	**36**	yield of **36** (%)[a]
3	 **38c**	57	 (2 equiv) **14f** $^{n}Bu_4NI$ (0.1 equiv)	CH_2Cl_2 / H_2O rt, ~1 h	 **36c**	92
4	 **38a**	–	 (1.5 equiv) **40** In (1.5 equiv)	DMF rt, 2 h	 **36d**	83[b] (2 steps)
5	 **38d**	94	 (1.5 equiv) **40** In (1.5 equiv)	DMF rt, 2 h	 **36e**	92[b]
6	 **38e**	>99	 (2 equiv) **18** $AlClEt_2$ (2.2 equiv) Zn (3.0 equiv) CuBr (0.1 eqquiv)	THF –20 °C 18 h	 **36f**	93
7	 **38f**	97	 (1.5 equiv) **14d**	THF –80 °C 2.5 h then K_2CO_3 (2.5 equiv) MeOH rt, 1 h	 **36g**	97
8	 **38g**	–	 (2 equiv) **18** $AlClEt_2$ (2.2 equiv) Zn (3.0 equiv) CuBr (0.1 equiv)	THF –20 °C 14 h	 **36h**	53 (2 steps)

[a] Isolated yield. [b] The existence of a trace amount of regioisomer was estimated, but it was not observed by ^1H NMR analysis (see the next section).

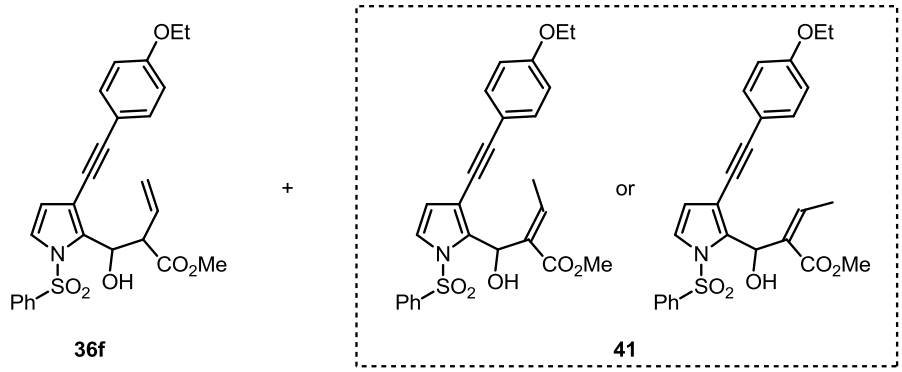
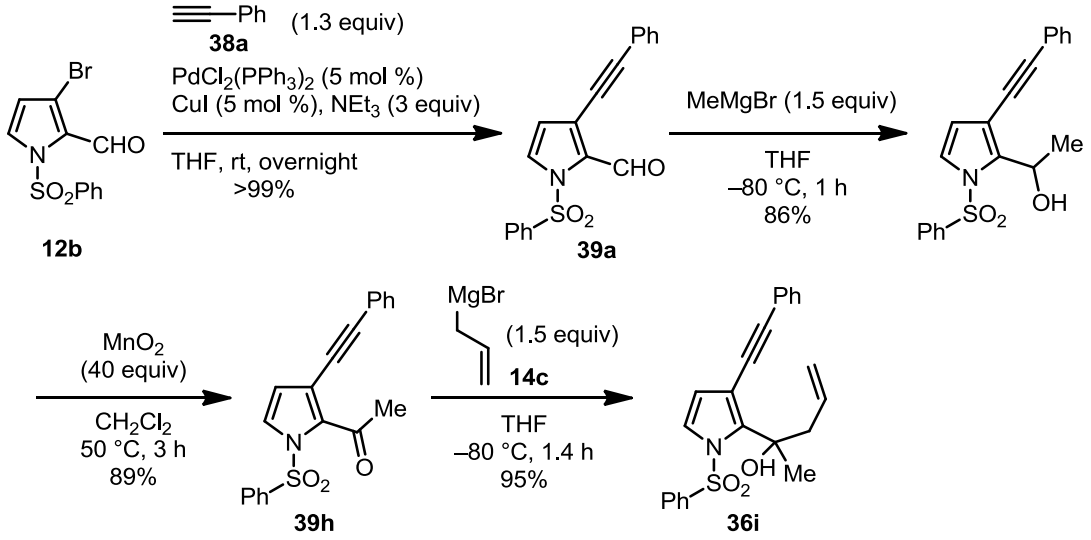


Fig. 4.1 Information about an isomer of **36f**.

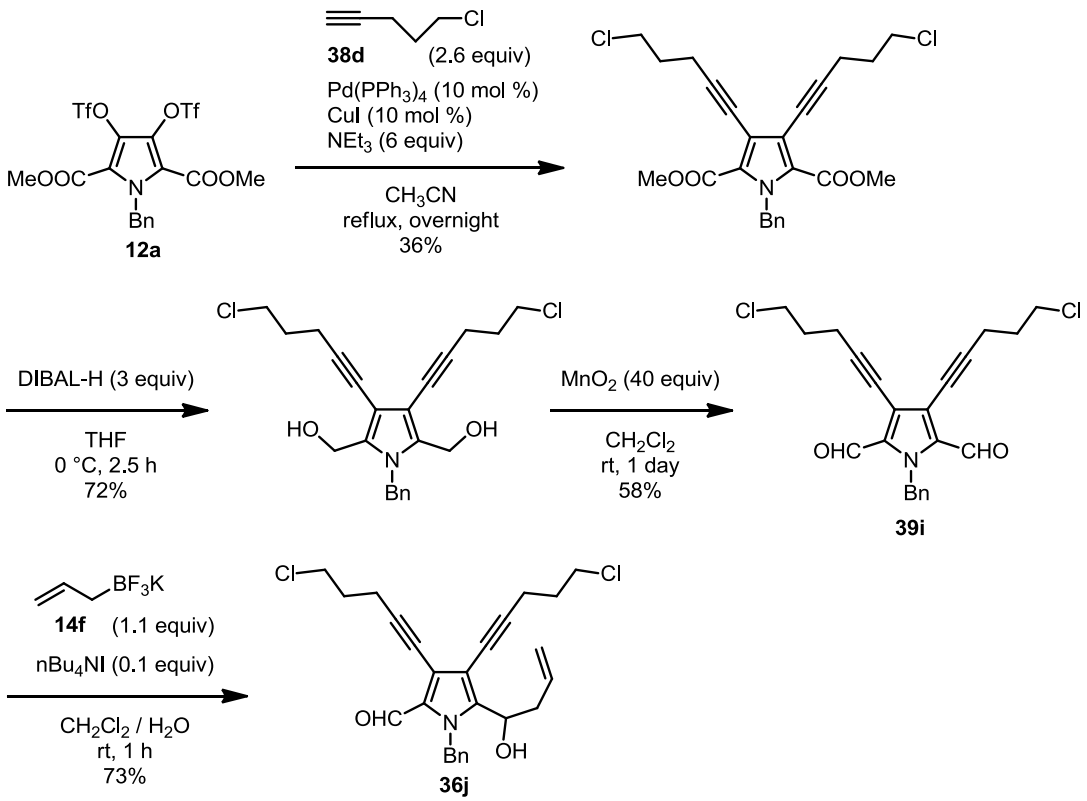
R[7]に置換基が導入された環化前駆体**36i**の合成は一度**39a**のアルデヒドをケトンへと変換した後にアリル化することで達成できた(Scheme 4.4)。

Scheme 4.4 Preparation of **36i** from **12b**.



一方、対称なピロール **12a** を出発物質として用いた環化前駆体合成も試みた(Scheme 4.5)。アルデヒドのアリル化の段階においてホウ素試薬の当量を調節することにより R[2],R[3]にアルデヒド及びアルキンを有したビニルインドール前駆体となり得るエンジイン化合物 **36j** を得ることができた。

Scheme 4.5 Preparation of **36j** from **12a**



次節では、以上で得られた環化前駆体 **36a-j** に対し、閉環エンインメタセシスを用いて 4-ビニルインドール合成を行った結果について述べる。

第三節　閉環エンインメタセシスを用いる 4-ビニルインドールの合成

前節で得られた環化前駆体**36**に対してRCEMによる環化と脱水による芳香族化を行うことによって4-ビニルインドール合成を試みた。

反応条件は、以前報告されているスチレン合成において窒素雰囲気下よりもエチレン雰囲気下の方が RCEM が進行やすいという結果を受け [31]、エチレン雰囲気下で反応を行うこととし、その他の条件はインドール合成で多く用いた条件を採用した。

初めに比較的置換基の少ない **36a** に RCEM/脱水の手法を適用したところ望みの 4-ビニルインドール **37a** を 99%収率で得ることができた(Table 4.2, entry 1)。ここで、窒素雰囲気下で反応を行うと収率 59%と大きく低下した(entry 2)。また、触媒量を 1 mol%まで下げた場合は収率がやや低下した(entry 3; 86%)。

続いて、entry 1 の条件のまま、**36a** と同じ位置に異なる置換基を持つ **36b** 及び **36c** に対しても反応を行うとそれぞれ良好な収率で対応する生成物が得られた(entries 4 and 5)。

R^6 または R^7 の位置に置換基がもう一つ導入された種々の環化前駆体に対しても本手法は適用でき、対応する多様なインドール誘導体 **36d-g** を中程度から良好な収率で合成できた(entries 6-9)。ただし、entry 11 の基質では中程度の収率で目的物 **36i** の生成が確認できるものの単離できなかった。これは電子求引性のエステル置換基があるために RCEM が遅くなってその分予期しない副反応が起きやすくなり、また、**37f** と比較して生成物に極性官能基が少なく、その分カラムなどでの分離が悪くなったためと推測される。実際、少量ながら **42** のような副生成物が得られた。これは環化前駆体のアルキン部位に二炭素付加したような構造であり、基質のアルキン部位と Ru 触媒そしてエチレンが反応して生成されるものと考えられ(Scheme 4.6; **36i**→[**A** or **B**]→**42**)、Ru 種とアリルのオレフィンとでアルキリデン錯体ができた後の環化の段階(**D**→**E**, **C**→**37i**)が遅くなっていることが窺える。

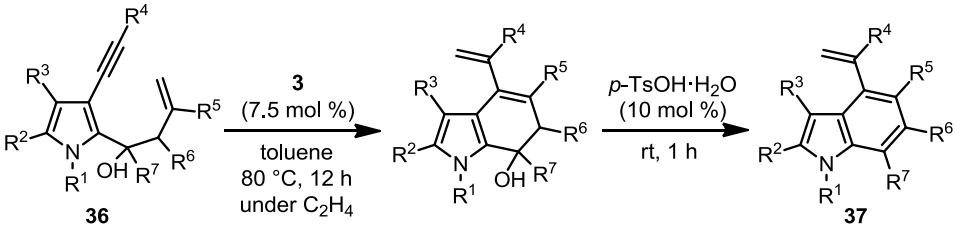
また、**37d**, **37e** の合成に関してはそれぞれ R^6 位がメチル基ではなく水素のビニルインドール **37a**, **37e'**が微量に混入してきた。これは環化前駆体合成時の In を用いたアリル化の段階において、期待されるγ付加とともにα付加もわずかに起こり、NMR では確認できなかったものの、これによる副生成物 **36d'**, **36e'**がそれぞれ微量に環化前駆体に混入してしまっていたためと考えられる(Schemes 4.7 and 4.8)。

一方、R^5 位にメチル基を持つ **36h** では全く RCEM が起こらない結果となった(entry 10)。これは、一般に四置換オレフィンが形成されるようなメタセシス反応が進行しにくい傾向がある為と考えられる。なお、以前に報告されている RCEM を用いたスチレン合成では、**36h** と同じ置換パターンの基質において低収率ながらも対応する生成物が得られている。

R^2, R^3 に官能基を持つ基質に対しても適用してみた(entry 12)。しかしながら低収率であり、原料が多く残存した。原因としてはピロール環上のすべての位置に置換基が導入されているため立体的に混み合うことや、電子供与的な置換基が結合した窒素上の電子の触媒への

悪影響、RCEM と関わらない官能基の配位による触媒活性低下の可能性などが挙げられる。

Table 4.2 Synthesis of 4-vinylindoles **37** by RCEM/dehydration.



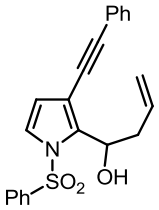
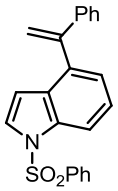
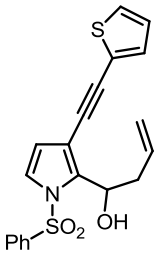
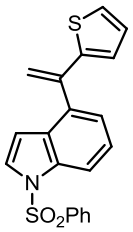
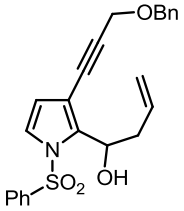
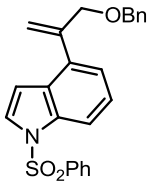
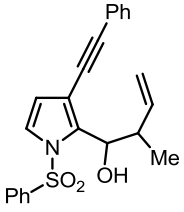
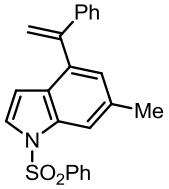
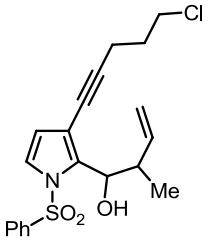
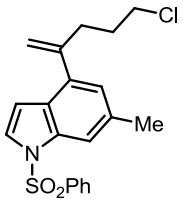
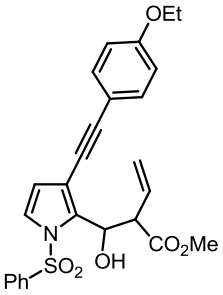
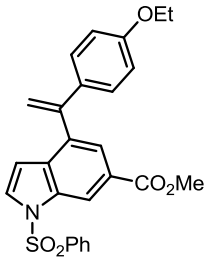
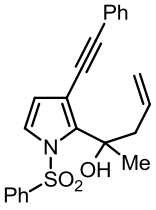
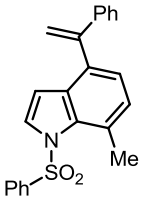
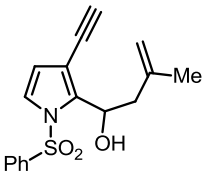
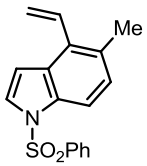
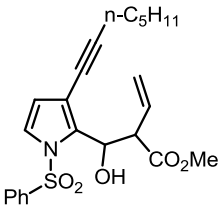
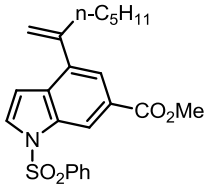
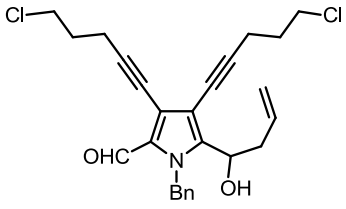
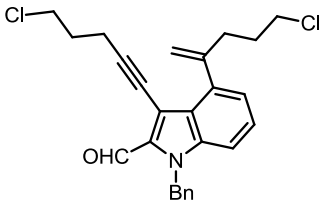
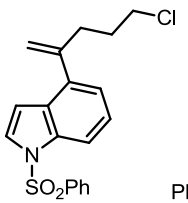
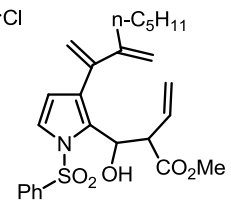
entry	substrate	product	yield (%)[a]
1	 **36a**	 **37a**	99
2[b]			59
3[c]			86
4	 **36b**	 **37b**	98
5	 **36c**	 **37c**	74
6[d]	 **36d**	 **37d**	85
7[e]	 **36e**	 **37e**	82

Table 4.2 (continued)

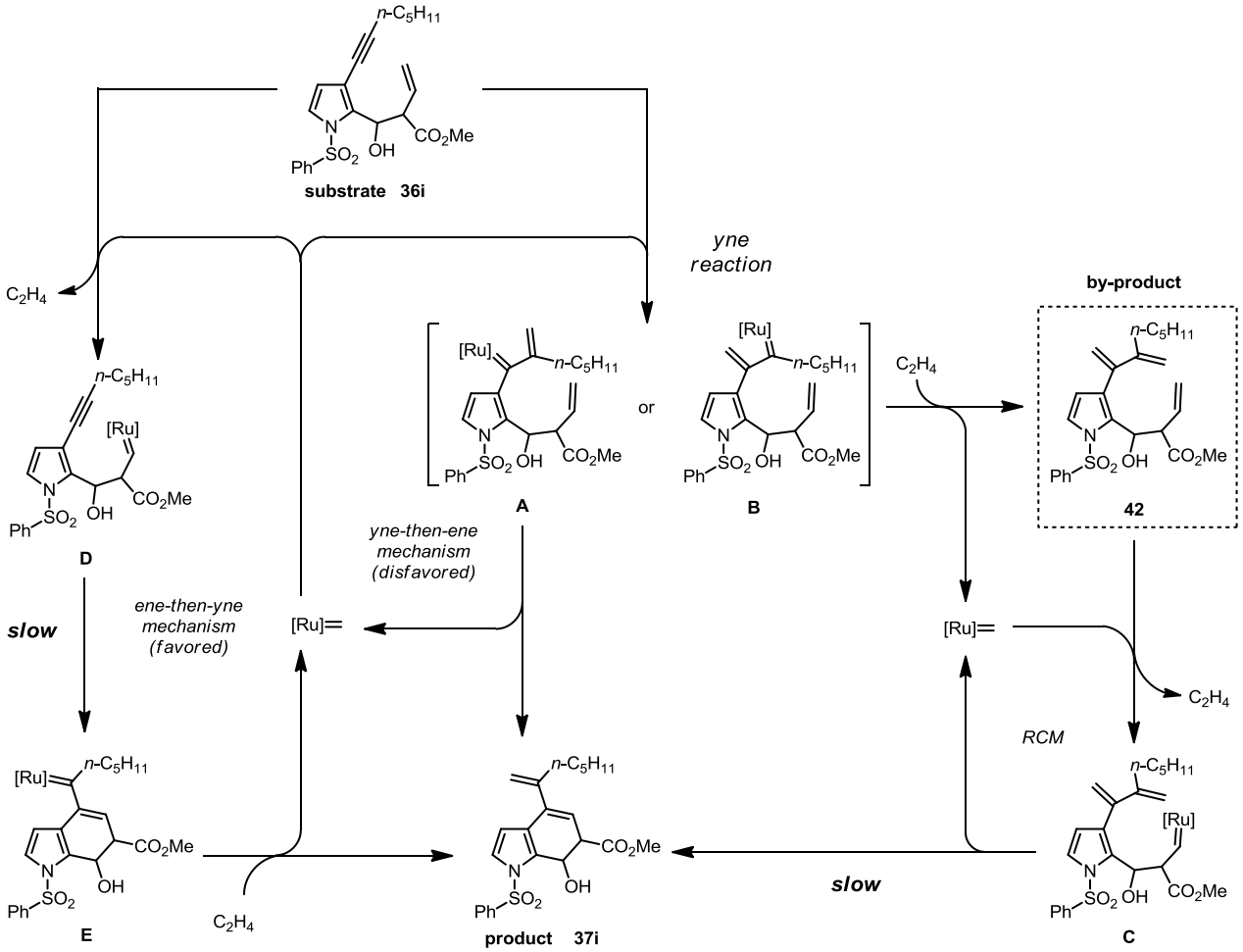
entry	substrate	product	yield (%)[a]
8[f]	 **36f**	 **37f**	67
9	 **36g**	 **37g**	97
10[g]	 **36h**	 **37h**	0
11[h]	 **36i**	 **37i**	~ 50
12[i]	 **36j**	 **37j**	13

[a] isolated yield. [b] The reaction was carried out under N_2 atmosphere. [c] The reaction was carried out wih 1 mol % of **3**.[d] **37a** was also obtained in 2% yield. [e] **37e'** was probably also obtained in 3% yield. [f] A mixture of **36f** and its regioisomer (1 / 0.014) was used as the starting material. [g] **36h** was recovered in 35% yield. [h] A mixture of **36i** and unknown compounds, 5% of **42**, and 2% of **36i** were obtained. [i] 72% of substrate was recovered.

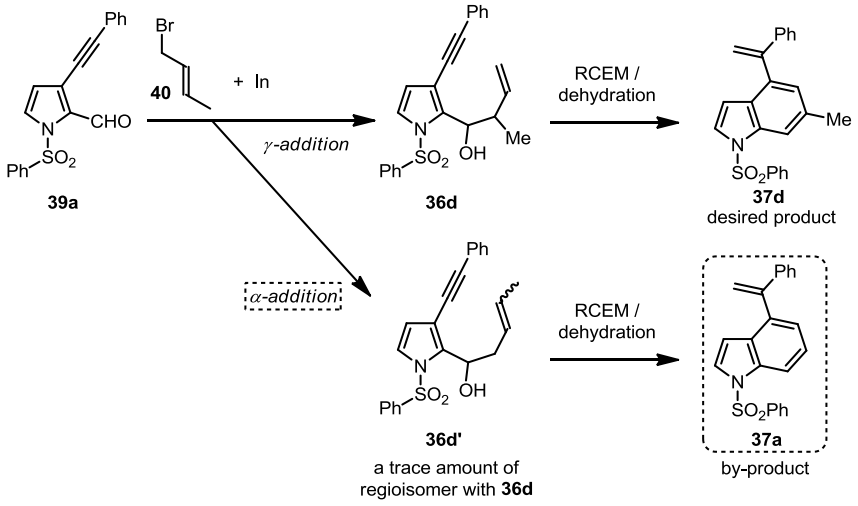

37e'


42

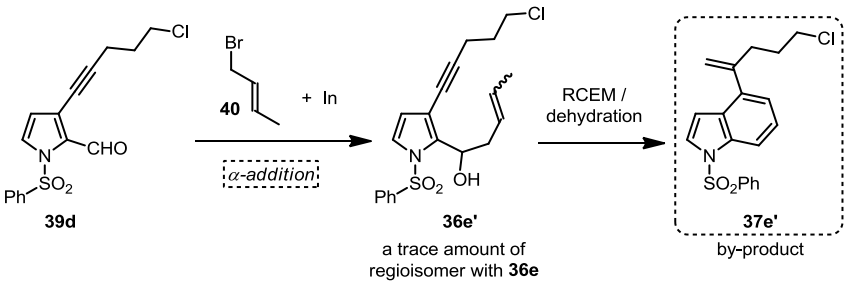
Scheme 4.6



Scheme 4.7



Scheme 4.8


Cl
CHO
N
SO2
Ph
39d
Br
40
+ In
α-addition
Cl
OH
36e'
a trace amount of
regioisomer with 36e
RCEM /
dehydration
Cl
SO2Ph
37e'
by-product

第四節　結論

本章では、第二章のインドール合成で用いた RCM 反応の代わりに RCEM 反応を用いることにより 4-ビニルインドールの合成を行った。環化前駆体となるエンイン基質合成はインドール前駆体合成で用いた鈴木-宮浦カップリングを薗頭カップリングに代えることで実現でき、多様な置換基を選択的に導入することができた。そして、得られたそれらの基質に対して RCEM/脱水の手法を用いることにより、容易には得難い 4-ビニルインドール誘導体を合成することができた。4-ビニルインドール上には多様な置換基を選択的に導入できることを示せ、また、ビニル基は種々の変換反応にふすことができるため本手法はこれまでとは異なるタイプの有用なインドール合成中間体を与え得ると期待される。そもそも緒論でも述べたように 4-ビニルインドールの一般的な合成法は殆どなく、インドール類合成における新たな手法を提示できたと言える。

RCEM/脱水反応の反応性の傾向としては、様々な置換基の位置や種類に対して概ね良好であったが、置換基が電子求引性であったり、四置換オレフィンの形成が必要であったりピロール環上の置換基が多い場合には低下する傾向があった。また、エチレンの効果については、以前のスチレン合成の報告から推測された通り、窒素雰囲気下よりもエチレン雰囲気下の方が収率が高い結果が得られた。

次章では 4-ビニルインドール構造を有するような他の芳香族化合物合成への本手法の展開を述べる。

第五章

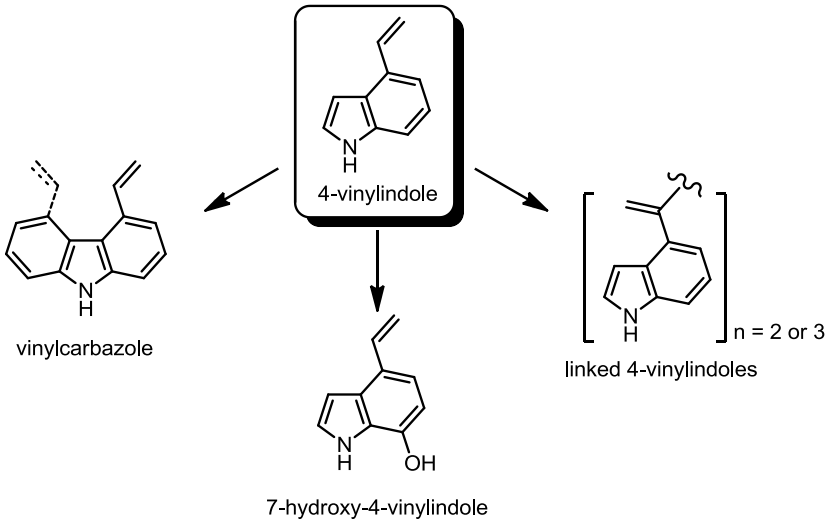
閉環エンインメタセシスを用いる
4-ビニルインドール関連化合物合成への展開

第一節　4-ビニルインドール関連化合物

第四章では閉環エンインメタセシスを利用することで、ビニル基の形成を伴う炭素六員環構築を鍵反応とする 4-ビニルインドール合成を達成した。これによって 4-ビニルインドール構造を有するような他の芳香族化合物の合成への展開が期待される。

本章ではそのような 4-ビニルインドール関連化合物合成への展開として、第二節では複数の 4-ビニルインドール部位を有する化合物、第三節ではビニルカルバゾール、第四節では 7-ヒドロキシ-4-ビニルインドールのそれぞれの合成について検討した結果を述べる (Scheme 5.1)。いずれの複素環芳香族化合物も 4-ビニルインドール同様、一般的な合成手法は殆ど開発されておらず、本手法を応用できればこれまであまり注目されてこなかった有用な化合物が合成できる可能性を示すことができる。

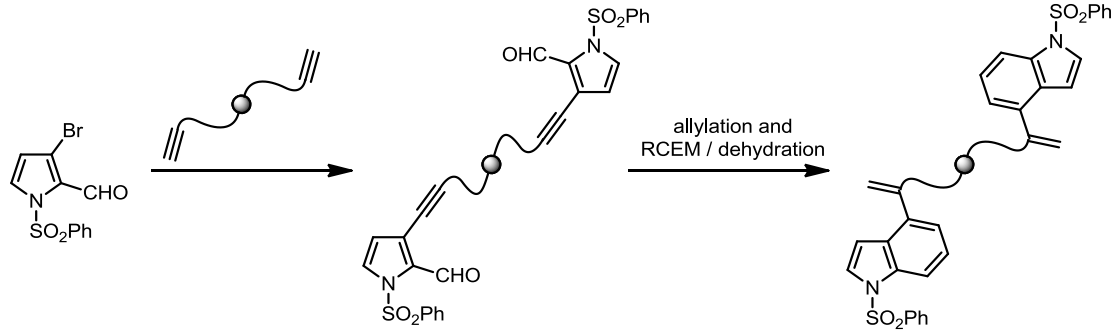
Scheme 5.1



第二節　複数の 4-ビニルインドール部位を有する化合物の合成

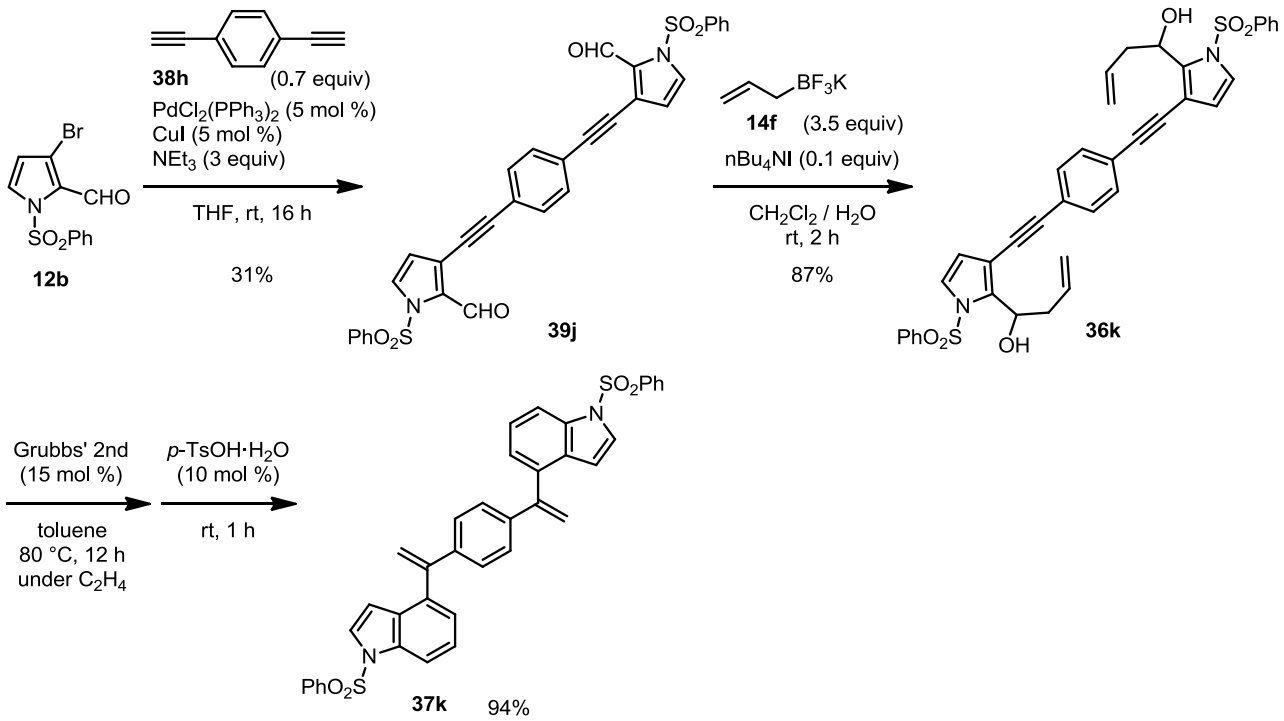
環化前駆体合成の薗頭カップリングの際に複数の末端アルキンを有する基質をカップリングパートナーとすれば、アルキン上に複数のピロールが導入された基質が得られ、これをアリル化し RCEM/脱水の手法を適用することで一分子内の複数の箇所で同時に 4-ビニルインドールが形成されたユニークな化合物が合成できると考えられる(Scheme 5.2)。

Scheme 5.2　Synthesis of linked 4-vinylindoles.

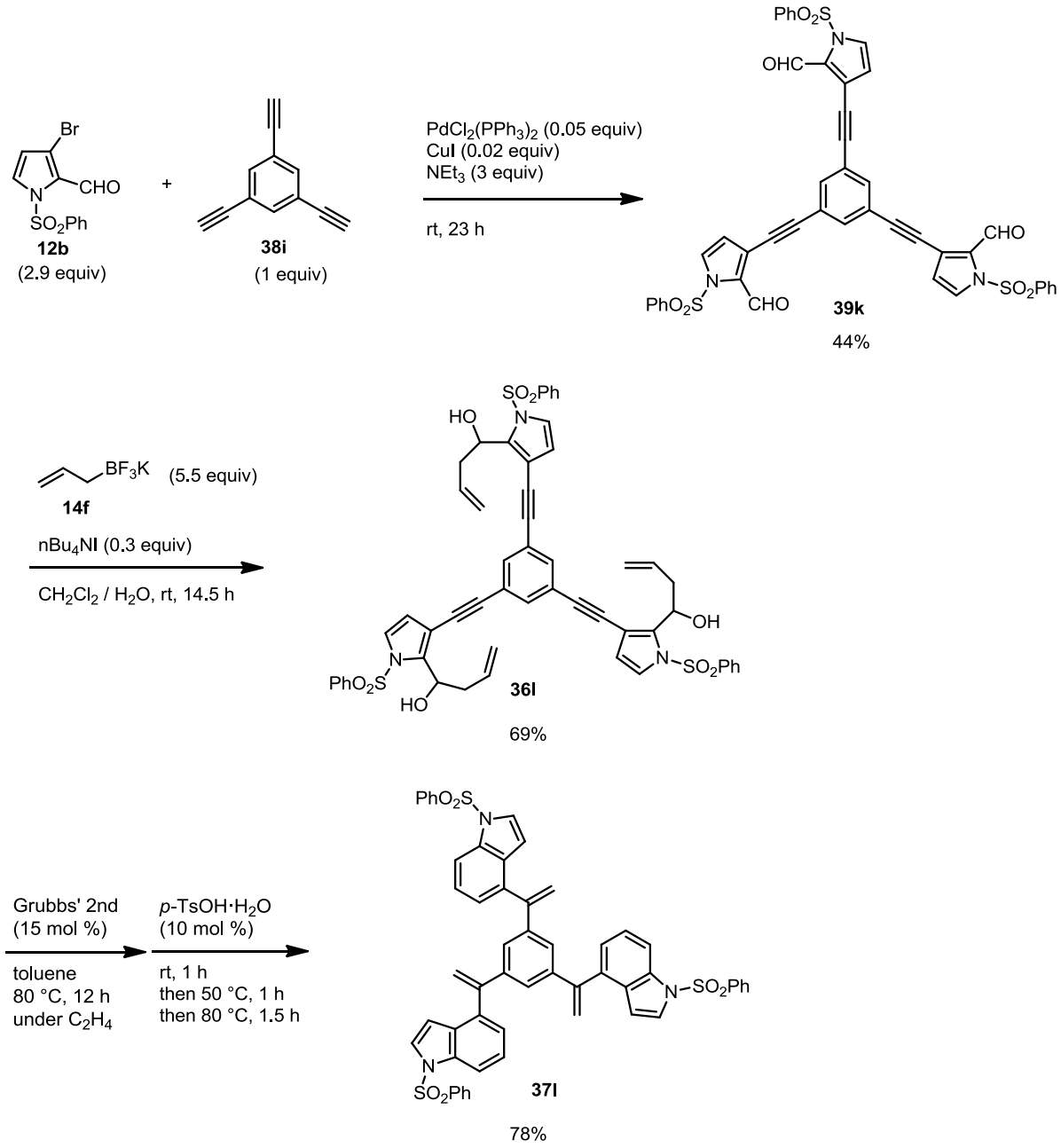


この方針に従い、ベンゼン環上に二つ或いは三つの末端アルキンを有する試薬 **38h** 及び **38i** をカップリング試薬として用いてそれぞれ合成を行った(Schemes 5.3 and 5.4)。

Scheme 5.3　Synthesis of **37k**.



Scheme 5.4 Synthesis of **37l**.



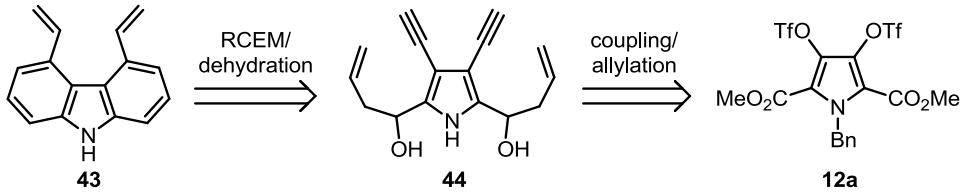
初めの薗頭カップリングの段階は、恐らくホモカップリングやポリマー化などの副反応及びカラムによる精製の難しさなどにより、中程度から低い収率にとどまってしまったが、アリル化の段階は良好な収率で進行した。そして、得られた基質に RCEM/脱水の手法を適用した結果、反応は円滑に進行し目的の化合物を良好な収率で得ることができた。

今回得られた化合物は複数の 4-ビニルインドールが架橋された構造をしており、本手法はポリマーの架橋剤や様々な機能性材料の合成へと応用できる可能性がある。

第三節　ビニルカルバゾール合成

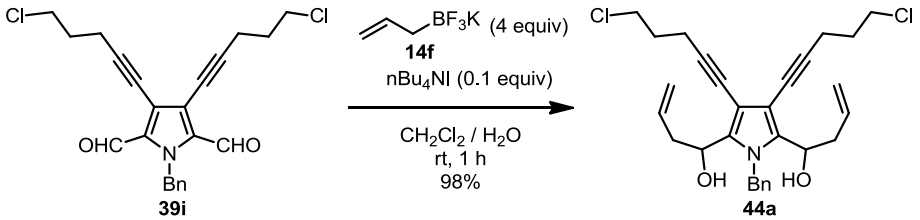
第一節でインドール合成の原料として用いた対称なピロール **12b** を出発物質とすれば、ピロール環に二つのスチレン環が縮合した 4,5-ジビニルカルバゾール **43** の合成も可能になると考えられる(Scheme 5.5)。

Scheme 5.5　Retrosynthetic analysis of 4,5-divinylcarbazoles **43**.



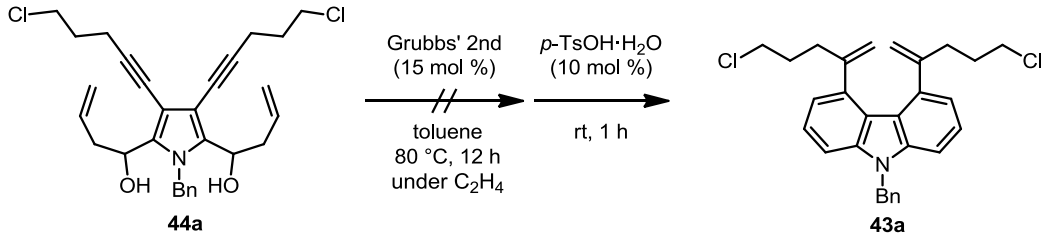
そこで、上記の合成戦略のもと、初めに 4,5-ジビニルカルバゾールの環化前駆体となるエンイン基質 **44** の合成を行った(Scheme 5.6)。4-ビニルインドール合成において **36j** 合成の中間体として用いた **39i** をアリル化することで目的の対称なエンイン基質 **44a** を得ることができた。

Scheme 5.6　Preparation of **44a** from **39i** by allylation.



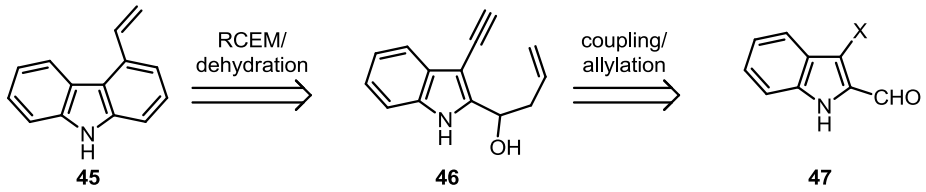
このようにして得た環化前駆体 **44a** に対して RCEM/脱水の手法を適用することにより 4,5-ジビニルカルバゾール合成を試みた(Scheme 5.7)。しかしながら、目的の化合物は得られなかった。これは、目的の生成物の立体が非常に混み合った形であることと、反応点となり得る複数のアルケン及びアルキン部位が近接した状態で存在し、複雑な副反応が起こったためと考えられる。これは合成設計上避けられないものであり、この手法でのビニルカルバゾール合成は難しいと判断した。

Scheme 5.7　Synthesis of 4,5-divinylcarbazole **43a** by RCEM/dehydration.



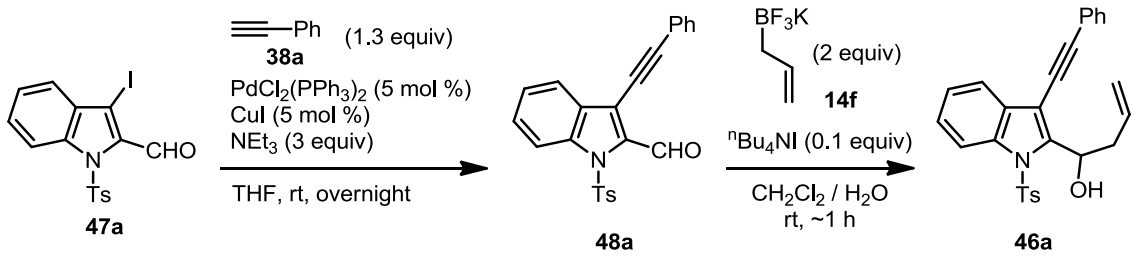
そこで、ビニル基が一つのみの非対称な 4-ビニルカルバゾールならば合成可能ではないかと考えた [27]。4-ビニルカルバゾールを合成するにはインドール誘導体 **47** が出発物質となる (Scheme 5.8)。

Scheme 5.8　Retrosynthetic analysis of 4-vinylcarbazoles **45**.



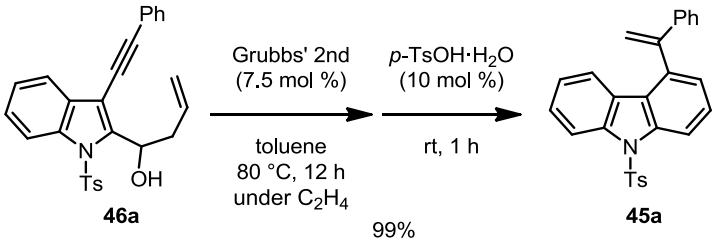
この合成戦略に従い、合成したインドール誘導体 **47a** に対し、薗頭カップリングとアリル化を行い、環化前駆体となる **46a** を得た(Scheme 5.9)。

Scheme 5.9　Preparation of **46a** from **47a** by Sonogashira coupling and allylation.



そして、この **46a** に対し RCEM/脱水の手法を適用したところ、高い収率で目的の 4-ビニルカルバゾール誘導体が得られた(Scheme 5.10)。

Scheme 5.10　Synthesis of 4-vinylcarbazole **45a** by RCEM/dehydration.

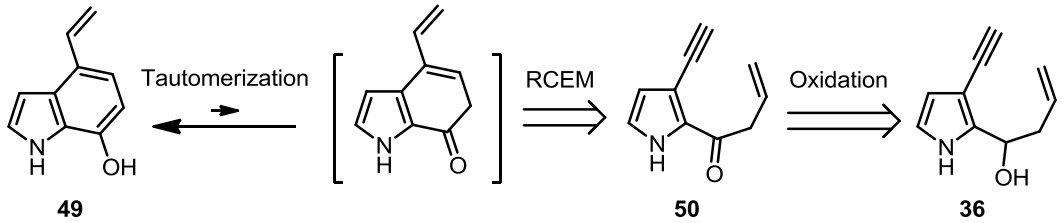


ジビニルカルバゾール合成とは対照的な結果となった理由としては、生成物のビニル基が一つのみで立体的な障害が少ないこと、環化前駆体の反応点が限られていること、窒素上の置換基が電子求引性のため窒素上の電子とルテニウム触媒との副反応が起こりにくくなるはずであることなど複数の要因が考えられ、この為に非常に円滑に目的の RCEM が進行したものと推測される。

第四節　7-ヒドロキシ-4-ビニルインドール合成

第三章第二節と同様に、環化前駆体としてアルコールではなくカルボニル基を有する基質 **50** を用いると、RCEM による環化と互変異性化による芳香族化によって 7-ヒドロキシ-4-ビニルインドール **49** が得られるものと期待される(Scheme 5.11)。7-ヒドロキシ-4-ビニルインドールはビニル基に加えて芳香族性水酸基を有するため、より有用な合成中間体となり得る。環化前駆体となるカルボニル基を有するエンイン基質 **50** は 4-ビニルインドール合成の環化前駆体 **36** を酸化することによって得られるものと考えられる。

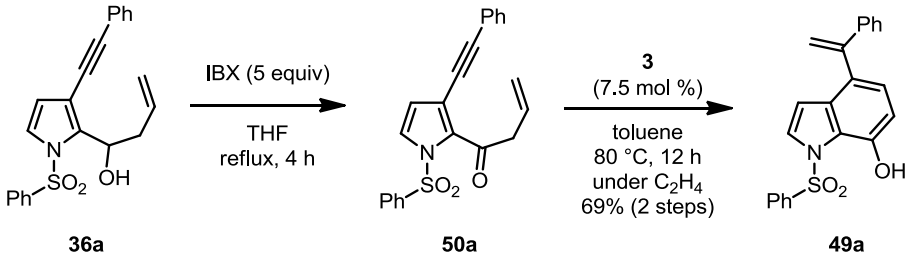
Scheme 5.11　Retrosynthetic analysis of 7-hydroxy-4-vinylindoles **49**.



そこで、第四章第二節で合成した **36a** に対して酸化を試みた。しかしながら、MnO_2 では酸化反応が進行せず、DMP を用いた酸化では副反応が起こるとともに workup 中に粗生成物が潰れていった。そこで、酸化時に酢酸を副生しない IBX を酸化剤として用いたところ数%の異性体が混じるものの他には副反応を起こさずに反応が進行した。なお、IBX が溶媒に殆ど溶けずに系が不均一系である方が良い結果を与えた。その後、異性体の除去を試みたが目的物が不安定であったため精製は濾過時にシリカゲルを通すだけとしそのまま次の RCEM 反応に用いた。

このようにして得た環化前駆体 **50a** に対し RCEM/互変異性化の手法を適用したところ良好な収率で目的の 7-ヒドロキシ-4-ビニルインドール **49a** を得ることができた(Scheme 5.12)。

Scheme 5.12　Synthesis of 7-hydroxy-4-vinylindole **57a** by oxidation and RCEM/tautomerization.



第五節　結論

本章では、第四章で 4-ビニルインドール合成に用いた手法を応用し、複数の 4-ビニルインドール部位を有する化合物、4-ビニルカルバゾール、7-ヒドロキシ-4-ビニルインドールの各化合物が合成できることを示すことができた。ただし、対称な 4,5-ジビニルカルバゾールの合成は困難であった。

複数の 4-ビニルインドール部位を有する化合物の合成では芳香環構築は問題なく進行し、その生成物のユニークさから、ポリマーの架橋剤や機能性材料の合成手法への利用が期待される。4-ビニルカルバゾール合成では、RCM/脱水の段階が非常に良好に進行したことから、この手法の広い一般性がうかがわれる。また、7-ヒドロキシ-4-ビニルインドール合成では RCEM/脱水の代わりに RCEM/互変異性化の手法を適用することで目的物を得た。環化前駆体を得る酸化反応に検討が必要であるものの、全体としては良好な収率で合成することができた。これによって得られる化合物はビニル基に加えて芳香族性水酸基が導入されるため合成上有用な中間体になり得ると期待される。更に、RCEM・互変異性化ともに分子量の変化がないためアトムエコノミーの観点からも優れた手法と言える。

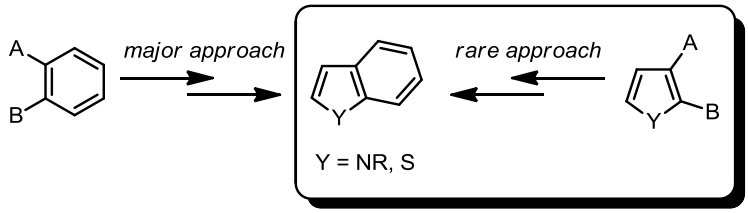
第六章

総括

本研究では、当研究室でこれまでに開発してきた閉環メタセシスを用いる新規芳香族化合物合成法に基づき、有用な複素環芳香族化合物であるインドール類の合成法の開発を行った。

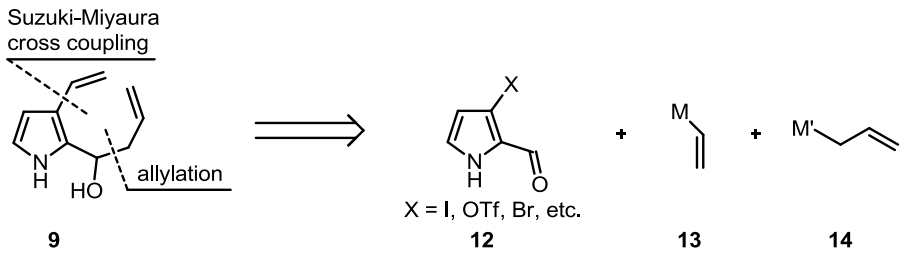
第一章で述べたように、重要な課題である置換芳香族化合物の合成において、近年、閉環メタセシスを用いた合成法の開発が盛んとなってきているが、当研究室では以前よりそのような手法の開発に取り組んできており、本研究においては、これまで開発してきた手法を、複素環芳香族化合物の中でも有用性の高いインドール類に着目し適用することを検討した。本手法は、インドール類の骨格を構築する多くの手法とは対照的に、炭素六員環をメタセシスによって形成するアプローチを採用している点に特に意義がある(Scheme 6.1)。このアプローチに基づき、第二章から第五章で実際に合成法の検討を行った。

Scheme 6.1　Two synthetic approaches to indole and benzothiophene skeletons.



第二章ではRCMを用いるインドール合成を検討した。環化前駆体合成は信頼性の高い鈴木カップリングと有機金属試薬によるアリル化を用いることで柔軟かつ選択的に種々の官能基を導入することが可能となった(Scheme 6.2)。

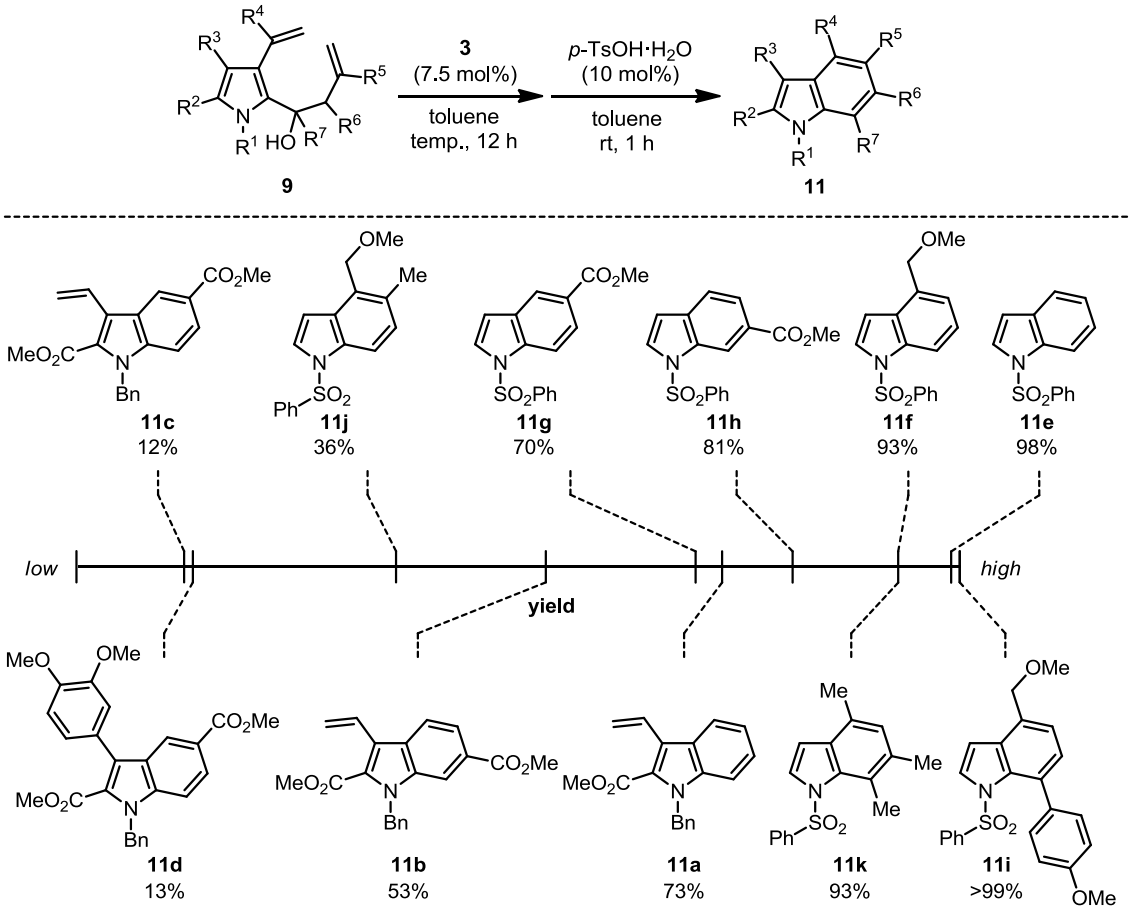
Scheme 6.2　Retrosynthetic analysis of subsrates **9**.



RCM/脱水の段階においては、**12a** から合成した環化前駆体に関しては反応性が低かったものの、**12b**, **c** から合成した基質を用いた場合には良好又は高い収率で反応が進行した。特

に鎖状部位に置換基の多い基質では Thorpe–Ingold 効果によって予想に反し高い収率で対応する化合物が得られ、本手法の有用性が高まった。ただし、四置換オレフィンが形成されるような合成では RCM の一般的な傾向から推測される通り反応が進行しにくかった (Scheme 6.3)。

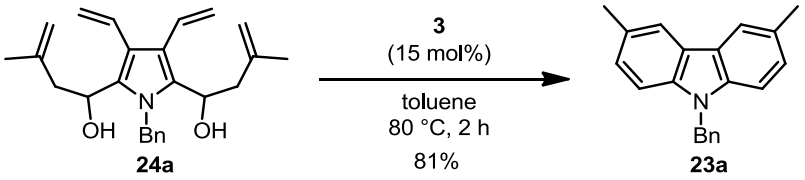
Scheme 6.3 Synthesis of indoles by RCM/dehydration.



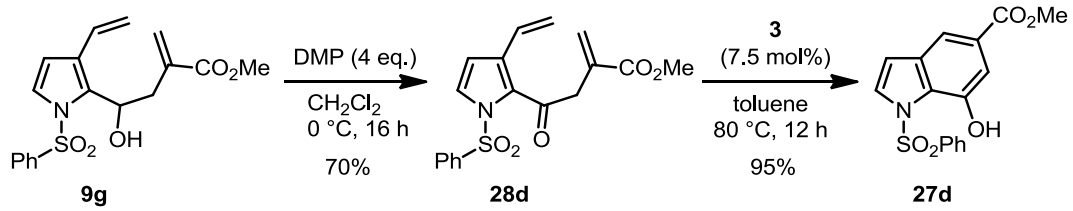
第三章では、第二章で開発したインドール合成を他の関連化合物合成へと応用することを試みた。対称なテトラエン基質を環化前駆体とすることでカルバゾールの合成へ、或いは環構築に RCM/脱水の代わりに RCM/互変異性化の手法を用いることによって 7-ヒドロキシインドールの合成へ、更にチオフェン環を有する環化前駆体を用いることで窒素の代わりに硫黄を含む複素芳香環であるベンゾチオフェンの合成へと展開できることを示した (Scheme 6.4)。

Scheme 6.4

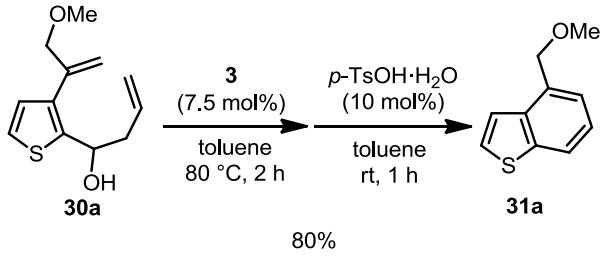
(a) Synthesis of carbazole by RCM/dehydration.



(b) Synthesis of 7-hydroxyindole by RCM/tautomerization.

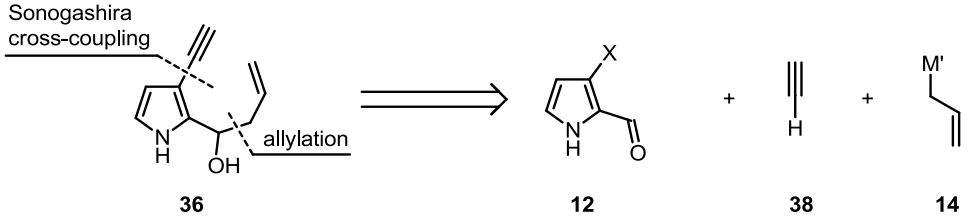


(c) Synthesis of benzothiophene by RCM/dehydration.



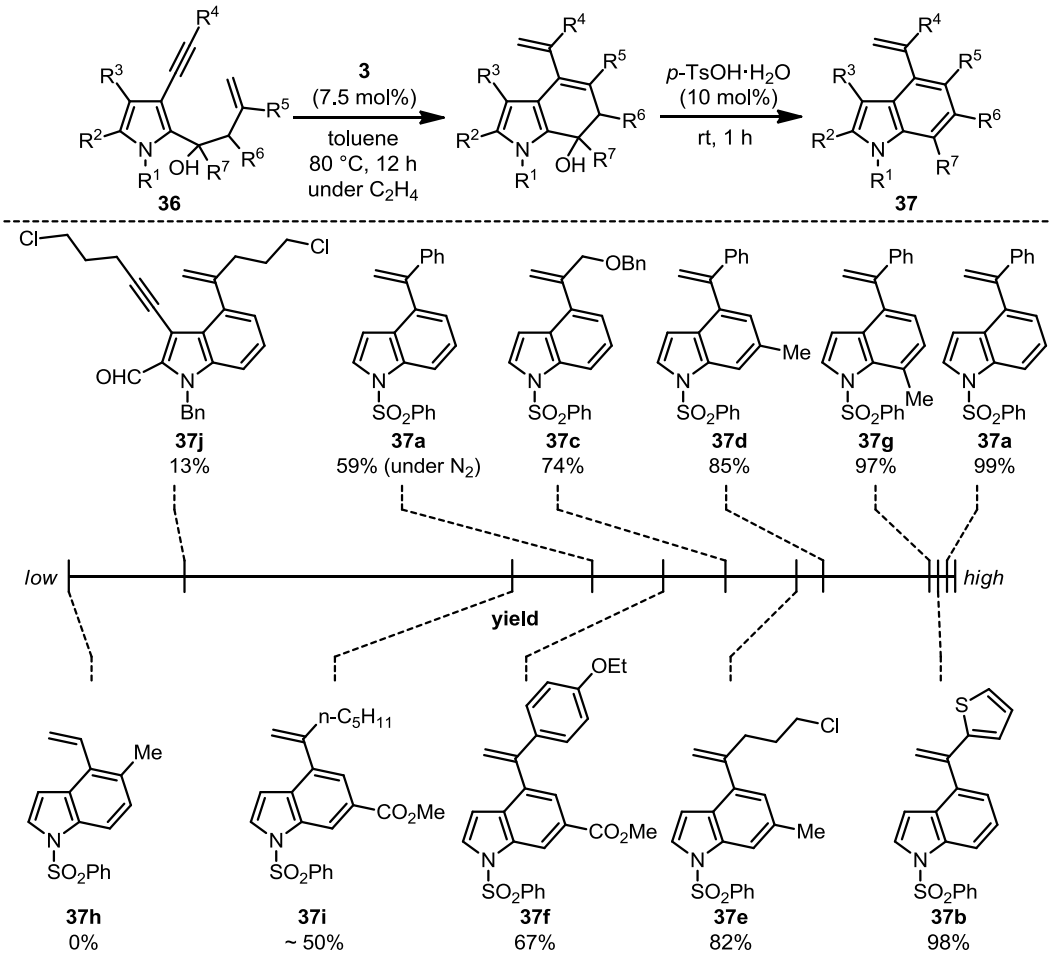
第四章では、閉環反応として RCM に代えて RCEM を用いることで 4-ビニルインドールの合成法の開発を試みた。環化前駆体合成はインドール合成における鈴木-宮浦カップリングを薗頭カップリングとしてアルキンを導入することで可能となった(Scheme 6.5)。

Scheme 6.5　Retrosynthetic analysis of subsrates **36**.



RCEM/脱水の段階においては多様な置換基が位置選択的に導入された生成物を得ることができた。以前のスチレン合成の報告を参考にして、反応はエチレン雰囲気下で行い、実際、窒素雰囲気下では収率が大幅に低下した。多くの基質において反応は円滑に進行したが、鎖状部分に電子求引性の置換基があると反応は遅くなる傾向が見られ、また、四置換オレフィンが形成されるような基質 **36h** や、**12a** から合成した基質 **36j** を用いた場合には反応が全く或いは殆ど進行しなかった(Scheme 6.6)。

Scheme 6.6　Synthesis of 4-vinylindoles by RCEM/dehydration.

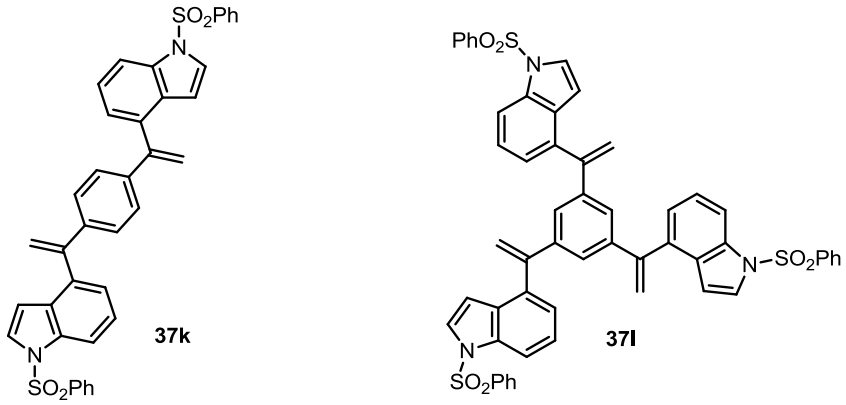


第五章では、第四章で開発した 4-ビニルインドール合成を他の関連化合物合成へと応用することを試みた。一分子内に複数の 4-ビニルインドール部位を有する基質や、非対称なビニルカルバゾールの合成に応用することができた。ただし対称なジビニルカルバゾールの合成は難しかった(Schemes 6.7a and 6.7b)。また、RCEM/互変異性化の手法を用いることで 7-ヒドロキシ-4-ビニルインドールの合成も可能であった(Scheme 6.7c)。この手法は RCEM、互変異性化ともに分子量の変化がないためアトムエコノミーの観点から優れている。また、

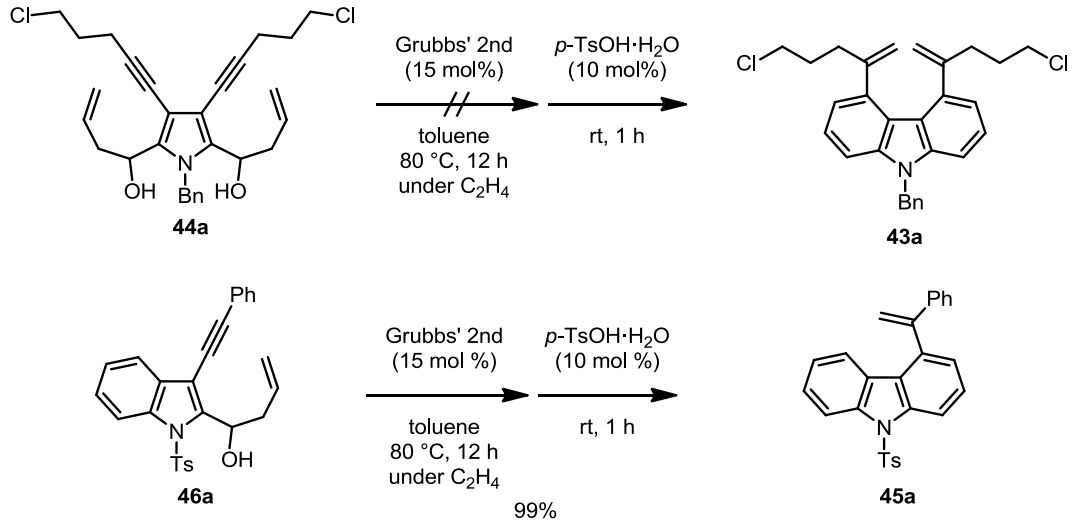
ビニル基並びにフェノール性水酸基はともに様々な変換反応に用いることができ、これらを選択的に導入できたことは意義のあることと言える。

Scheme 6.7

(a)

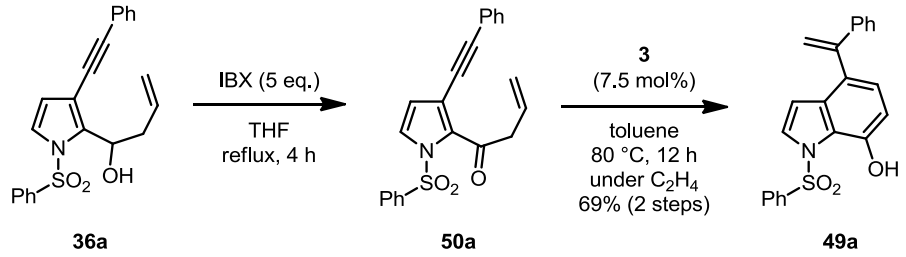


(b) Synthesis of vinylcarbazole by RCEM/dehydration.



Scheme 6.7 (continued)

(c) Synthesis of 7-hydroxy-4-vinylindole by RCEM/tautomerization.



36a **50a** **49a**

以上のように本研究では、ルテニウム触媒閉環オレフィンメタセシス並びに閉環エンインメタセシスを利用して炭素六員環側を構築することで多様な置換基が複数導入されたインドール類を選択的に合成するという新たな方法論を提示することができた。これにより、これまでは合成の難しいと考えられてきた芳香族化合物に対してこれまでとは異なる戦略によって合理的に合成設計を行える可能性が拓かれた。

今後は、本手法をベンゾフランやキノリンをはじめとする他の重要な複素環芳香族化合物の合成へ応用するなど更なる展開が期待される。

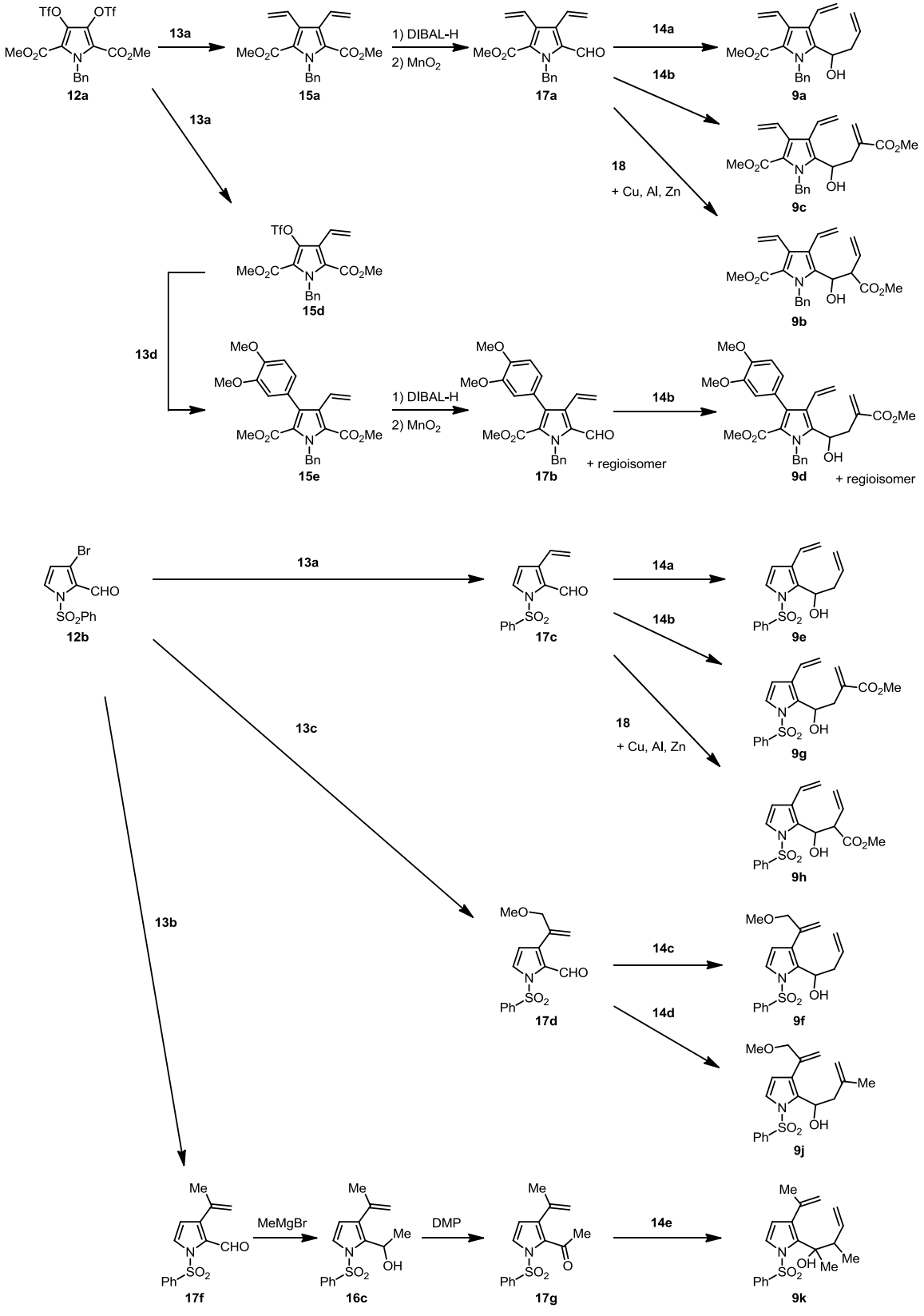
実験の部

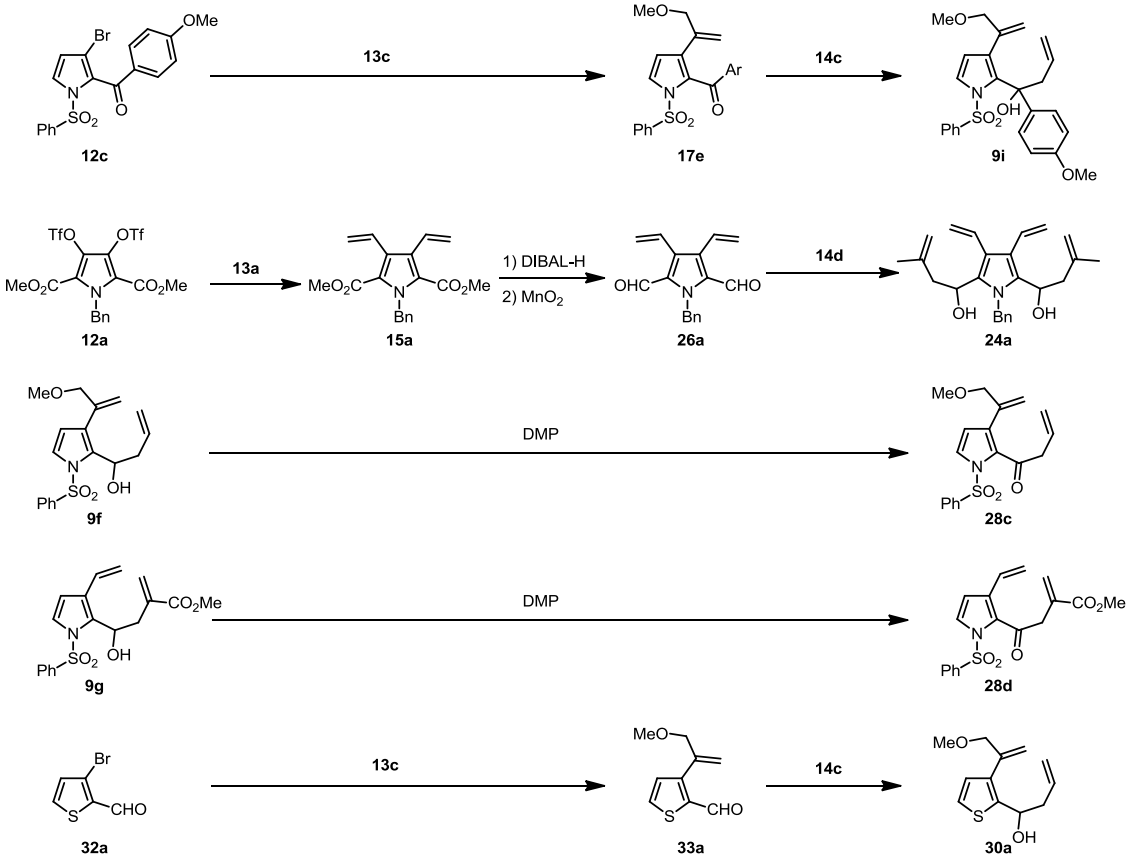
第二章 及び 第三章

General. All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or glove box techniques under prepurified argon. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), ECA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), LA-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) and ECS-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) at Chemical Analysis Center, Chiba University. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. High-resolution mass spectra were recorded on Thermo Fisher Scientific Exactive Orbitrap mass spectrometers at Chemical Analysis Center, Chiba University.

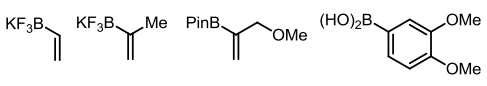
Materials. THF and Et_2O were distilled from sodium benzophenone-ketyl under nitrogen prior to use. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2 under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. Toluene was distilled from sodium benzophenone-ketyl under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. Ruthenium complex $(PCy_3)(Imes)Cl_2Ru{=}C(H)Ph$ (**3**) [33, 34] was prepared according to the reported procedures. Pyrroles **12a**,[22] **12b**,[23] and **12c**[23] were prepared according to the reported procedures. Potassium vinyl trifluoroborate **13a**,[35] potassium isopropenyltrifluoroborate **13b**,[36] and vinylboronic acid pinacol ester **13c**[37] were prepared according to the reported procedures. MnO_2 was prepared according to the reported procedure.[38] Allylic metal reagents **14a**,[39] **14b**,[40] **14c**,[41] **14d**,[42] and **14e**[41] were prepared according to the reported procedures. Dess-Martin periodinane were prepared according to the reported procedures.[43] $Pd(OAc)_2$, PPh_3, Cs_2CO_3, 3,4-dimethoxyphenylboronic acid **13d**, diisobutylaluminium hydride solution, methyl 4-bromocrotonate **18**, diethylaluminum chloride solution, zinc dust, copper bromide, methylmagnesium bromide (3.0 M solution in Et_2O), and *p*-toluenesulfonic acid monohydrate were used as received.

Summary of the Preparation of Substrates



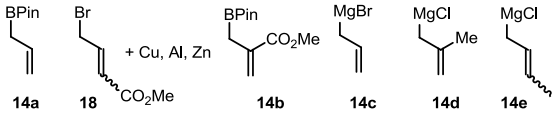


Suzuki-Miyaura coupling reagents



13a 13b 13c 13d

allylation reagents

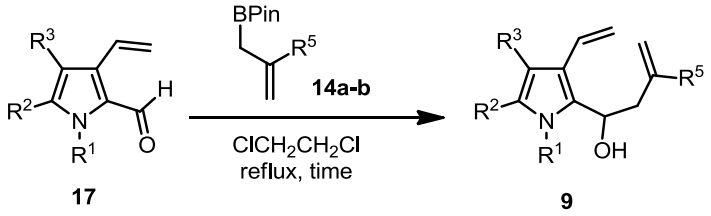


14a 18 14b 14c 14d 14e

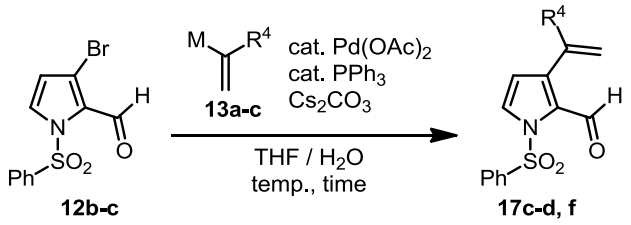
General Procedures.

General procedure A: **DIBAL-H reduction.** Diisobutylaluminium hydride (ca. 1 M solution in hexane) was added dropwise to a solution of ester **15** in THF (0.1 M) at –78 °C. The mixture was warmed up to a certain temperature and stirred for several hours. Then the mixture was treated with saturated potassium sodium tartrate (Rochelle salt) solution at the same temperature. The mixture was warmed up to 0 °C and stirred for 30 min. After extraction with EtOAc three or four times, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give alcohol **16** or **25a**.

General procedure B: MnO_2 oxidation. MnO_2 was added in one portion to a solution of alcohol **16** or **25a** in CH_2Cl_2 at room temperature under air. The mixture was stirred at the same temperature and then was filtered through Celite. The residual solid was washed thoroughly with CH_2Cl_2 and the filtrate was concentrated under reduced pressure to give aldehyde **17** or **26a**.

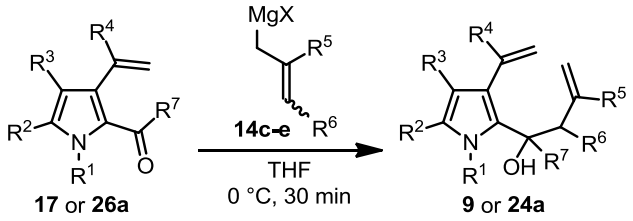


General procedure C: Allylation with allylboronic acid ester. To a stirred solution of aldehyde **17a-c** in 1,2-dichloroethane was added allylboronic acid pinacol ester **14a-b** at room temperature. The reaction mixture was refluxed for 1 day. After cooling to room temperature, the mixture was quenched by addition of saturated aqueous NH_4Cl solution and stirred for 10 min. The mixture was quenched again by addition of saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 three times. The organic layers were combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **9**.



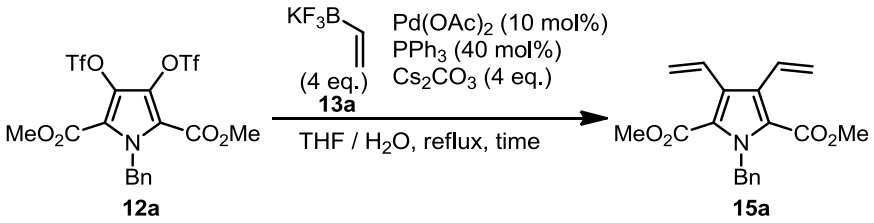
General procedure D: Suzuki-Miyaura coupling. A mixture of **13a-c** (1.5 eq.), $Pd(OAc)_2$ (5

mol%), PPh_3 (10 mol%), Cs_2CO_3 (3 eq.), and 3-bromopyrrole **12b-c** (1 eq.) in THF (0.05 M for **12b-c**) and water (1/5 (v/v) for THF) was heated and stirred. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography to give 3-vinylpyrrole **17c-d**, **f**.



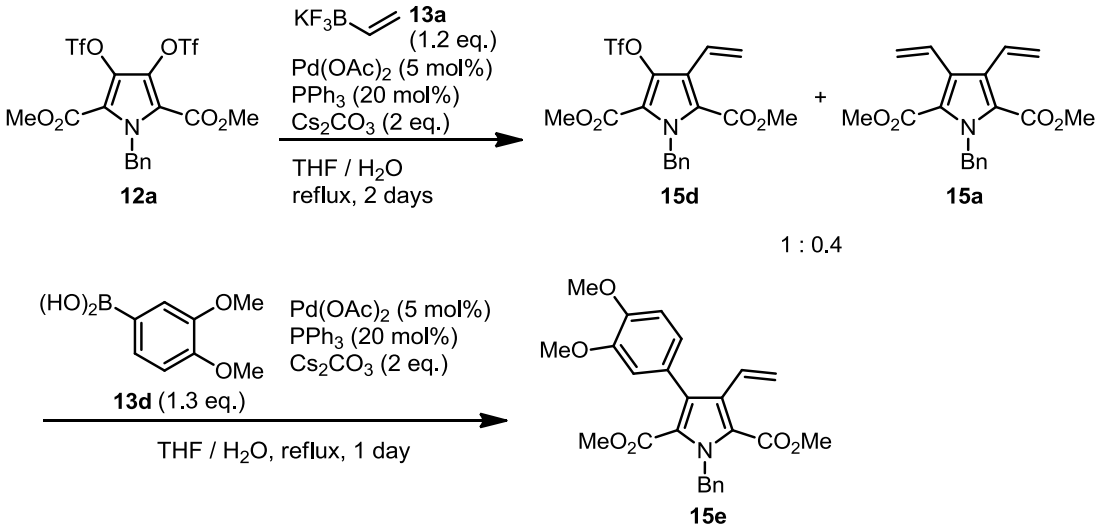
General procedure E: Allylation with allyl Grignard reagent. To a stirred solution of **17** or **26a** in THF (0.1 M) was added allyl Grignard reagent **14c-e** at 0 °C (salt-ice bath) and the reaction mixture was stirred for 30 min. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution at 0 °C, warmed to room temperature, extracted with EtOAc three times, and washed with brine. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **9** or **24a**.

Procedures for the Preparation of Dimethyl 1-benzyl-4-vinyl-1*H*-pyrrole-2,5-dicarboxylates 15.



Dimethyl 1-benzyl-3,4-divinyl-1*H*-pyrrole-2,5-dicarboxylate (15a); A mixture of **13a** (3.76 g, 28.1 mmol, 4.0 eq.), $Pd(OAc)_2$ (157.7 mg, 0.702 mmol, 0.10 eq.), PPh_3 (736.7 mg, 2.81 mmol, 0.40 eq.), Cs_2CO_3 (9.15 g, 28.1 mmol, 4.0 eq.), and pyrrole **12a** (3.99 g, 7.01 mmol, 1 eq.) in THF (141 ml, 0.05 M for **12a**) and water (28 ml, 1/5 (v/v) for THF) was refluxed for 2 days. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc four times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4.5/1) to give **15a** (2.01 g, 88% yield). m.p. 63-67 °C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.77 (s, 6H), 5.35 (dd, *J* = 11.5, 1.9 Hz, 2H), 5.41 (dd, *J* = 18.1, 1.9 Hz, 2H), 5.87 (s, 2H), 6.84 (dd, *J* = 18.1, 11.5 Hz, 2H), 6.95-6.99 (m, 2H), 7.16-7.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.71, 51.78, 118.93, 124.77, 126.13, 126.96, 127.06, 128.46, 129.22, 138.44, 162.07. HRMS (ESI) calcd for $C_{19}H_{19}NNaO_4$ (M^++Na) 348.1206, found 348.1197.

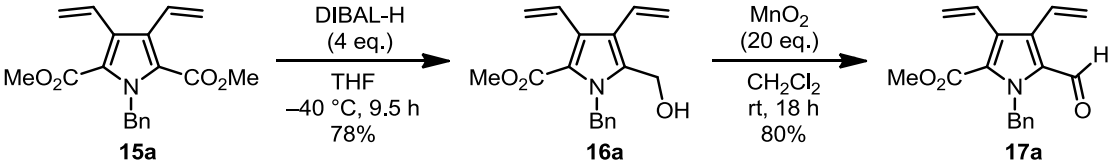


Dimethyl 1-benzyl-3-(3,4-dimethoxyphenyl)-4-vinyl-1*H*-pyrrole-2,5-dicarboxylate (15e); A mixture of **13a** (28.2 mg, 0.211 mmol, 1.2 eq.), $Pd(OAc)_2$ (1.98 mg, 0.0088 mmol, 0.050 eq.), PPh_3 (9.3 mg, 0.035 mmol, 0.20 eq.), Cs_2CO_3 (115.4 mg, 0.354 mmol, 2.0 eq.), and pyrrole **12a** (100.6 mg, 0.177 mmol, 1 eq.) in THF (3.5 ml, 0.05 M for **12a**) and water (0.7 ml, 1/5 (v/v) for THF) was refluxed for 2 days. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, washed with water followed by brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4.5/1) to give a mixture of **15d** and **15a**.

A mixture of **13d** (41.6 mg, 0.229 mmol, 1.3 eq. for **12a**), $Pd(OAc)_2$ (2.00 mg, 0.0089 mmol, 0.050 eq. for **12a**), PPh_3 (9.36 mg, 0.0357 mmol, 0.20 eq. for **12a**), Cs_2CO_3 (115.5 mg, 0.354 mmol, 2 eq. for **12a**), and **15d** (+ **15a**) in THF (3.5 ml 0.05 M for **12a**) and water (0.7 ml, 1/5 (v/v) for THF) was refluxed for 1 day. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, washed with water followed by brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4.5/1 to 2/1) to give **15e** (44.2 mg, 57% yield; 2 steps). m.p. 119-121 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.87 (dd, *J* = 18.0, 1.8 Hz, 1H), 5.05 (dd, *J* = 11.6, 1.8 Hz, 1H), 5.97 (s, 2H), 6.75-6.80 (m, 2H), 6.82-6.90 (m, 2H), 7.04 (d, *J* = 7.7 Hz, 2H), 7.21 (t, *J* =

7.4 Hz, 1H), 7.28 (t, J = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.67, 51.45, 51.74, 55.70, 55.84, 110.50, 113.45, 118.31, 122.44, 124.26, 125.65, 126.16, 127.01, 127.20, 127.55, 128.12, 128.42, 130.03, 138.55, 147.96, 148.28, 161.87, 161.91. HRMS (ESI) calcd for $C_{25}H_{25}NNaO_6$ (M^++Na) 458.1574, found 458.1564.

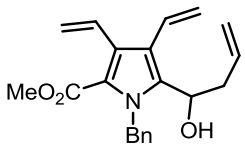
Procedure for the Preparation of Methyl 1-benzyl-5-formyl-3,4-divinyl-1*H*-pyrrole-2-carboxylate (17a).



Methyl 1-benzyl-5-formyl-3,4-divinyl-1*H*-pyrrole-2-carboxylate (17a); The reduction was carried out according to the general procedure A: Diisobutylaluminium hydride (1.04 M, 18.4 mL, 19.1 mmol, 4 eq.) and **15a** (1.55 g, 4.77 mmol, 1 eq.) were used and the reaction was performed at –40 °C for 9.5 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **16a** (1.11 g, 78% yield).

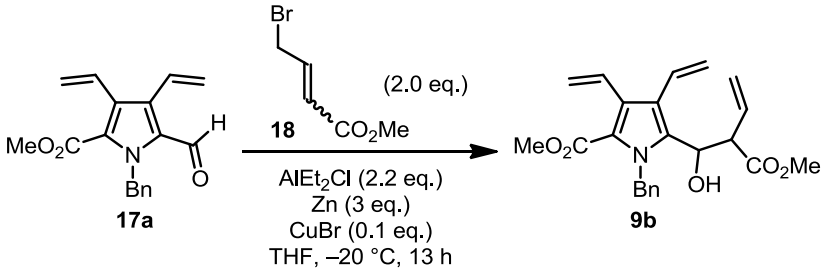
The oxidation was carried out according to the general procedure B; MnO_2 (234.1 mg, 2.69 mmol, 20 eq.), **16a** (39.7 mg, 0.134 mmol, 1 eq.) and CH_2Cl_2 (2.0 mL, 0.067 M for **16a**) were used and the reaction mixture was stirred for 18 h; The crude product of **17a** was used for next step without purification (31.7 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.42 (dd, J = 11.6, 1.9 Hz, 1H), 5.42 (dd, J = 17.6, 1.5 Hz, 1H), 5.48 (dd, J = 18.0, 1.5 Hz, 1H), 5.56 (dd, J = 11.0, 1.8 Hz, 1H), 6.07 (s, 2H), 6.77 (dd, J = 17.4, 11.3 Hz, 1H), 6.97 (dd, J = 17.7, 11.3 Hz, 1H), 7.00-7.04 (m, 2H), 7.16-7.31 (m, 3H), 9.85 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.48, 51.98, 119.35, 122.14, 126.09, 126.36, 127.06, 127.11, 127.97, 128.42, 128.64, 130.18, 133.82, 138.14, 161.64, 182.04. HRMS (ESI) calcd for $C_{18}H_{17}NNaO_3$ (M^++Na) 318.1101, found 318.1093.

Procedures for the Preparation of Methyl 1-benzyl-5-(1-hydroxybut-3-enyl)-4-vinyl-1*H*-pyrrole-2-carboxylates 9a-d.



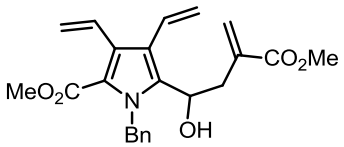
9a

Methyl 1-benzyl-5-(1-hydroxybut-3-enyl)-3,4-divinyl-1*H*-pyrrole-2-carboxylate (9a); The reaction was carried out according to the general procedure C; **17a** (549.8 mg, 1.86 mmol, 1 eq.), 1,2-dichloroethane (9.5 mL, 0.2 M for **17a**), and **14a** (471.9 mg, 2.81 mmol, 1.5 eq.) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) and remaining pinacol was removed under reduced pressure at 120 °C to give **9a** (596.9 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11-2.15 (m, 1H), 2.36 (dddt, *J* = 14.1, 6.5, 5.1, 1.2 Hz, 1H), 2.47-2.58 (m, 1H), 3.68 (s, 3H), 4.98-5.09 (m, 2H), 5.11 (ddd, *J* = 9.5, 5.1, 3.2 Hz, 1H), 5.25 (dd, *J* = 18.0, 1.9 Hz, 1H), 5.35 (dd, *J* = 11.4, 2.0 Hz, 1H), 5.35 (dd, *J* = 11.7, 2.0 Hz, 1H), 5.47 (dd, *J* = 18.1, 2.0 Hz, 1H), 5.71 (dddd, *J* = 17.6, 10.4, 8.0, 6.8 Hz, 1H), 5.85 (s, 2H), 6.68 (dd, *J* = 18.1, 11.5 Hz, 1H), 6.89 (d, *J* = 7.1 Hz, 2H), 7.08 (dd, *J* = 18.0, 11.7 Hz, 1H), 7.15-7.21 (m, 1H), 7.21-7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.11, 49.60, 51.11, 66.21, 117.79, 118.15, 118.22, 120.20, 120.24, 125.24, 126.73, 128.28, 128.47, 130.08, 130.50, 134.11, 137.05, 139.37, 161.80. HRMS (ESI) calcd for $C_{21}H_{23}NNaO_3$ (M^++Na) 360.1570, found 360.1559.



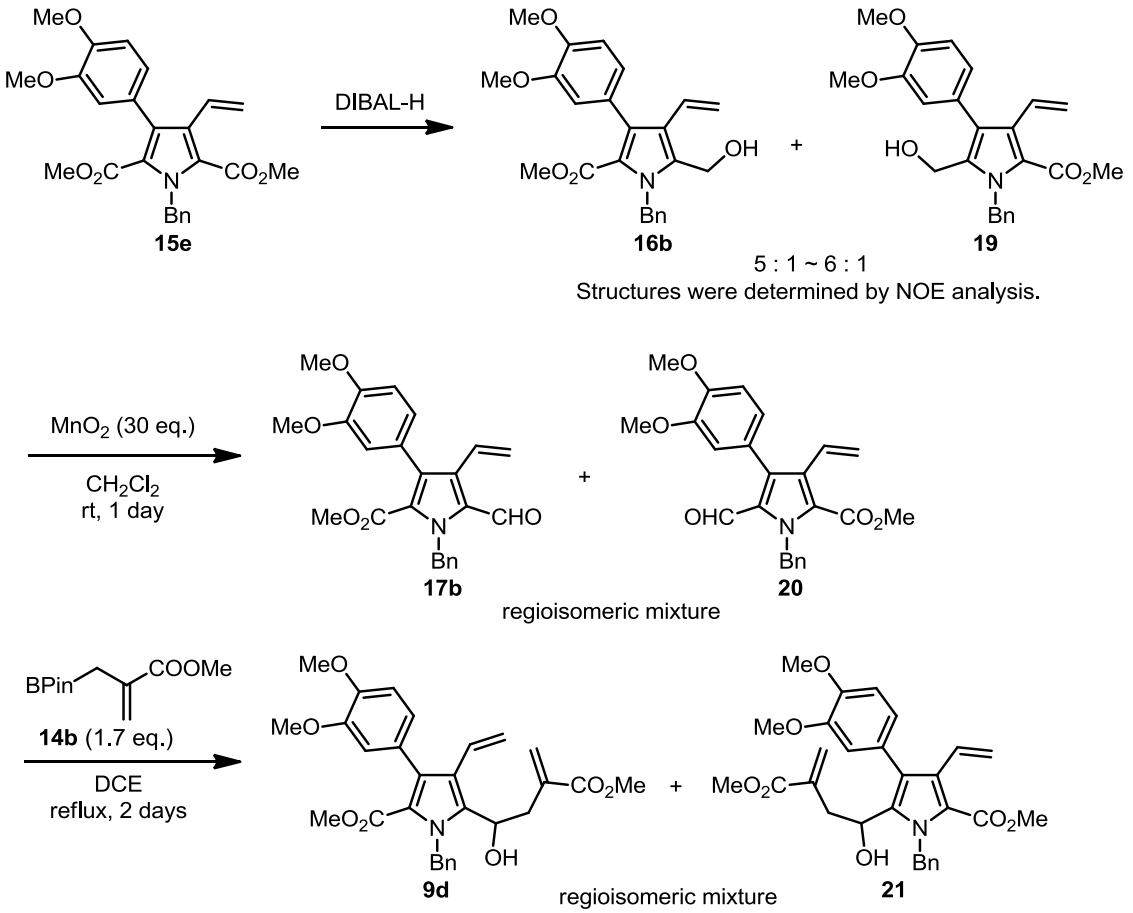
Methyl 1-benzyl-5-(1-hydroxy-2-(methoxycarbonyl)but-3-enyl)-3,4-divinyl-1*H*-pyrrole-2-carboxylate (9b)[44]; Diethylaluminum chloride (0.95 M solution in hexane, 1.57 mL, 1.49 mmol, 2.2 eq.) was added to a slurry of zinc dust (133.3 mg, 2.04 mmol, 3.0 eq.) and copper bromide (9.72 mg, 0.0678 mmol, 0.10 eq.) in THF (27 mL) with stirring at 0 °C. The resulting mixture was cooled to –20 °C. A solution of methyl 4-bromocrotonate **18** (245 mg, 1.37 mmol, 2.0 eq.) and aldehyde **17a** (200.1 mg, 0.678 mmol, 1 eq.) in THF (5 mL) was added slowly to the mixture over 15 min at –20 °C. After stirring for 13 h at the same temperature, the reaction mixture was quenched by addition of pyridine (0.3 mL), well stirred, and poured into 1N hydrochloric acid. The mixture was warmed up to room temperature and filtered to remove remaining zinc dust. After extraction three times with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column

chromatography (hexane/EtOAc = 3/1) to give a diastereomeric mixture of **9b** (0.57/0.43) (213.2 mg, 80% yield). Data for the major diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (d, *J* = 3.1 Hz, 1H), 3.51 (s, 3H), 3.67-3.74 (m, 4H), 5.18-5.27 (m, 2H), 5.30 (d, *J* = 10.1 Hz, 1H), 5.34 (dd, *J* = 11.6, 1.8 Hz, 1H), 5.37 (dd, *J* = 11.3, 1.9 Hz, 1H), 5.46 (dd, *J* = 17.7, 1.8 Hz, 1H), 5.50 (dd, *J* = 18.0, 1.9 Hz, 1H), 5.61 (d, *J* = 16.5 Hz, 1H), 5.82-6.02 (m, 2H), 6.69 (dd, *J* = 17.7, 11.3 Hz, 1H), 6.95-7.07 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.46, 51.15, 51.95, 55.49, 66.64, 118.32, 118.56, 120.56, 120.93, 121.18, 125.64, 126.91, 128.37, 128.52, 129.94, 130.19, 132.78, 134.23, 138.92, 161.88, 171.47. Data for the minor diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.76 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.68-3.77 (m, 7H), 4.80 (dd, *J* = 17.1, 0.9 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 1H), 5.20-5.41 (m, 4H), 5.47 (dd, *J* = 18.0, 1.9 Hz, 1H), 5.48 (dd, *J* = 18.0, 2.2 Hz, 1H), 5.72 (d, *J* = 16.5 Hz, 1H), 5.85 (d, *J* = 16.8 Hz, 1H), 6.65 (dd, *J* = 18.0, 11.6 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 7.04 (dd, *J* = 18.0, 11.6 Hz, 1H), 7.17-7.23 (m, 1H), 7.23-7.31 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.40, 51.18, 52.19, 54.54, 67.00, 118.31, 118.88, 119.79, 120.55, 121.76, 125.73, 127.01, 128.22, 128.51, 129.94, 130.22, 130.80, 133.98, 138.59, 161.88, 173.13. HRMS (ESI) calcd for $C_{23}H_{25}NNaO_5$ (M^++Na) 418.1625, found 418.1612.



9c

Methyl 1-benzyl-5-(1-hydroxy-3-(methoxycarbonyl)but-3-enyl)-3,4-divinyl-1*H*-pyrrole-2-carboxylate (9c); The reaction was carried out according to the general procedure C; **17a** (450.2 mg, 1.52 mmol, 1 eq.), 1,2-dichloroethane (3.8 mL, 0.4 M for **17a**), and **14b** (591.1 mg, 2.61 mmol, 1.7 eq.) were used and the reaction mixture was refluxed for 2 days; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1) and remaining pinacol was removed under reduced pressure at 150 °C to give **9c** (592.6 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (dd, *J* = 14.1, 3.7 Hz, 1H), 2.68 (d, *J* = 3.4 Hz, 1H), 2.77 (dd, *J* = 14.0, 9.8 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 5.22 (dt, *J* = 9.5, 3.7 Hz, 1H), 5.32-5.41 (m, 3H), 5.44-5.52 (m, 2H), 5.84 (d, *J* = 16.8 Hz, 1H), 5.90 (d, *J* = 16.5 Hz, 1H), 6.17 (s, 1H), 6.65-6.76 (m, 1H), 6.92 (d, *J* = 7.7 Hz, 2H), 7.07 (dd, *J* = 17.7, 11.6 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.76, 49.41, 51.09, 52.05, 65.93, 117.97, 118.17, 120.21, 120.29, 125.36, 126.76, 128.31, 128.51, 128.61, 130.10, 130.43, 136.59, 137.05, 139.33, 161.85, 167.79. HRMS (ESI) calcd for $C_{23}H_{25}NNaO_5$ (M^++Na) 418.1625, found 418.1625.



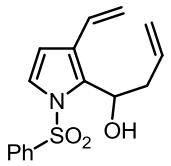
Methyl 1-benzyl-3-(3,4-dimethoxyphenyl)-5-(1-hydroxy-3-(methoxycarbonyl)but-3-enyl)-4-vinyl-1*H*-pyrrole-2-carboxylate (9d); The reduction step was carried out according to the general procedure A; Diisobutylaluminium hydride (1.02 M, 8.31 mL, 8.47 mmol, 6 eq.) and **15e** (614.9 mg, 1.41 mmol, 1 eq.) were used and the reaction was performed at –50 °C for 4 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1 to 1/1) to give a mixture of **16b** and **19** (1 : 0.17) (246 mg, 43% yield).

The oxidation step was carried out according to the general procedure B; MnO_2 (2.28 g, 26.2 mmol, 30 eq.), a mixture of **16b** and **19** (1 : 0.18) (355.4 mg, 0.872 mmol, 1 eq.) and CH_2Cl_2 (8.7 mL, 0.1 M for a mixture of **16b** and **19**) were used and the reaction mixture was stirred for 1 day; A mixture of **17b** and **20** (1 : 0.16) (265 mg, 75% yield) was given; The crude product was used without further purification.

The allylation was carried out according to the general procedure C; the mixture of **17b** and **20** (1 : 0.16) (131.6 mg, 0.325 mmol, 1 eq.), 1,2-dichloroethane (0.81 mL, 0.4 M for the mixture of **17b** and **20**), and **14b** (127.0 mg, 0.562 mmol, 1.7 eq.) were used and the reaction mixture was stirred for 2 days. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 1/1) to give a mixture of **9d** and **21** (1 : 0.18) (145 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63

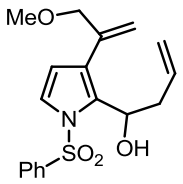
(dd, J = 14.4, 3.4 Hz, 1H), 2.71 (br s, 1H), 2.81 (dd, J = 14.4, 9.8 Hz, 1H), 3.44 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.96 (dd, J = 18.1, 1.8 Hz, 1H), 5.05 (dd, J = 10.9, 1.8 Hz, 1H), 5.20 (dd, J = 9.6, 3.0 Hz, 1H), 5.50 (s, 1H), 5.80 (d, J = 16.9 Hz, 1H), 5.91 (d, J = 16.9 Hz, 1H), 6.19 (d, J = 1.4 Hz, 1H), 6.64 (dd, J = 18.1, 11.7 Hz, 1H), 6.79-6.91 (m, 3H), 7.02 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.93, 49.02, 50.87, 52.14, 55.69, 55.81, 66.24, 110.26, 113.52, 116.21, 120.40, 122.40, 125.50, 125.53, 126.91, 128.47, 128.53, 128.60, 128.86, 131.57, 136.48, 136.68, 139.12, 147.65, 148.01, 162.05, 167.88. HRMS (ESI) calcd for $C_{29}H_{31}NNaO_7$ (M^++Na) 528.1993, found 528.1988.

Procedures for the Preparation of 1-Benzenesulfonyl-2-(1-hydroxybut-3-enyl)-3-vinyl-1*H*-pyrroles 9e-k.



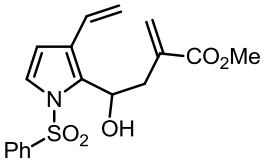
9e

1-(1-(Phenylsulfonyl)-3-vinyl-1*H*-pyrrol-2-yl)but-3-en-1-ol (9e); The coupling reaction was carried out according to the general procedure D; **12b** (200.3 mg, 0.638 mmol) and **13a** were used and the reaction mixture was refluxed for 1 day; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/2 to toluene only) to give corresponding 3-vinylpyrrole **17c**. Then, the allylation was carried out according to the general procedure C; **17c**, 1,2-dichloroethane (3.2 mL, 0.2 M for **12b**), and **14a** (130.2 mg, 0.775 mmol, 1.2 eq. for **12b**) were used; The crude product was purified twice by silica-gel column chromatography (first: hexane/toluene/EtOAc = 1/10/0.4, second: hexane/toluene/EtOAc = 1/10/0.3) to give **9e** (34.4 mg, 17% yield; 2 steps). **9e** was found to be somewhat unstable. Therefore, **9e** was used immediately to next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38-2.46 (m, 1H), 2.43 (d, J = 5.3 Hz, 1H), 2.61 (dddt, J = 14.2, 8.9, 7.8, 0.9 Hz, 1H), 5.02-5.09 (m, 2H), 5.16 (dd, J = 11.0, 1.4 Hz, 1H), 5.20 (dt, J = 8.9, 5.3 Hz, 1H), 5.46 (dd, J = 17.8, 1.4 Hz, 1H), 5.68 (dddd, J = 17.2, 10.6, 7.6, 6.9 Hz, 1H), 6.48 (d, J = 3.4 Hz, 1H), 6.90 (dd, J = 17.6, 11.0 Hz, 1H), 7.25-7.27 (m, 1H), 7.49-7.54 (m, 2H), 7.62 (tt, J = 7.6, 1.8 Hz, 1H), 7.77-7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.21, 66.39, 109.79, 114.34, 118.18, 123.56, 126.57, 126.90, 128.15, 129.50, 132.51, 133.96, 134.08, 139.31. HRMS (ESI) calcd for $C_{16}H_{17}NNaO_3S$ (M^++Na) 326.0821, found 326.0813.



9f

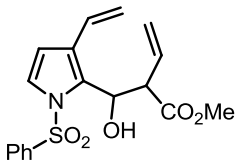
1-(3-(3-Methoxyprop-1-en-2-yl)-1-(phenylperoxythio)-1*H*-pyrrol-2-yl)but-3-en-1-ol (9f); The coupling reaction was carried out according to the general procedure D; **12b** (99.4 mg, 0.316 mmol) and **13c** were used and the reaction mixture was stirred at 65 °C for 4.5 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give corresponding 3-vinylpyrrole **17d**. Then, the allylation was carried out according to the general procedure E; **17d** and **14c** (0.52 M solution in Et_2O, 0.913 mL, 0.475 mmol, 1.5 eq. for **12b**) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1) to give **9f** (91.5 mg, 83% yield; 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (dt, *J* = 14.2, 6.9 Hz, 1H), 2.71 (ddd, *J* = 14.2, 8.2, 7.3 Hz, 1H), 3.32 (s, 3H), 3.33 (d, *J* = 8.2 Hz, 1H), 3.98-4.09 (m, 2H), 4.91-5.00 (m, 2H), 5.06 (td, *J* = 8.2, 6.4 Hz, 1H), 5.21 (t, *J* = 0.9 Hz, 1H), 5.41 (q, *J* = 1.8 Hz, 1H), 5.58 (ddt, *J* = 17.4, 10.1, 6.9 Hz, 1H), 6.19 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.50 (t, *J* = 8.2 Hz, 2H), 7.61 (tt, *J* = 7.8, 1.8 Hz, 1H), 7.78-7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.55, 58.16, 66.41, 75.78, 113.29, 117.23, 117.72, 123.23, 126.60, 127.86, 129.34, 133.29, 133.86, 134.44, 139.25, 139.39. HRMS (ESI) calcd for $C_{18}H_{21}NNaO_4S$ (M^++Na) 370.1084, found 370.1071.



9g

Methyl 4-hydroxy-2-methylene-4-(1-(phenylperoxythio)-3-vinyl-1*H*-pyrrol-2-yl) butanoate (9g); The coupling reaction was carried out according to the general procedure D; **12b** (200.3 mg, 0.638 mmol) and **13a** were used and the reaction mixture was refluxed for 1 day; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/1.5 to toluene only) to give corresponding 3-vinylpyrrole **17c**. Then, the allylation was carried out according to the general procedure C; **17c**, 1,2-dichloroethane (0.64 mL, 1.0 M for **12b**), and **14b** (231.7 mg, 1.02 mmol, 1.6 eq. for **12b**) were used; After quenching by saturated aqueous NH_4Cl solution, the mixture was stirred for 1 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2/1) and remaining pinacol was removed under reduced pressure at over 100 °C for 1 min to give **9g** (181.3 mg, 79% yield; 2 steps). **9g** was found to be somewhat unstable. Therefore, **9g** was used immediately to next reaction. When **9g** was used to the preparation of **28d**,

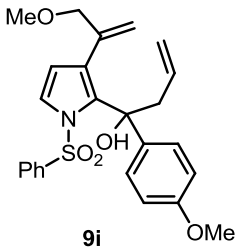
remaining pinacol was not removed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 14.2, 5.0 Hz, 1H), 2.97 (dd, *J* = 14.2, 9.0 Hz, 1H), 3.31 (d, *J* = 6.16 Hz, 1H), 3.76 (s, 3H), 5.15 (dd, *J* = 11.0, 0.9 Hz, 1H), 5.37 (dt, *J* = 8.7, 5.7 Hz, 1H), 5.44 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.63 (s, 1H), 6.20 (d, *J* = 0.9 Hz, 1H), 6.46 (d, *J* = 3.7 Hz, 1H), 6.88 (dd, *J* = 17.6, 11.0 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.77-7.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.65, 52.04, 66.39, 109.82, 114.36, 123.63, 126.46, 126.92, 127.92, 128.56, 129.37, 132.58, 133.83, 136.42, 139.15, 168.01. HRMS (ESI) calcd for $C_{18}H_{19}NNaO_5S$ (M^++Na) 384.0876, found 384.0869.



9h

Methyl 2-(hydroxy(1-(phenylsulfonyl)-3-vinyl-1*H*-pyrrol-2-yl)methyl)but-3-enoate (9h); The coupling reaction was carried out according to the general procedure D; **12b** (200.2 mg, 0.637 mmol) and **13a** were used and the reaction mixture was refluxed for 1 day; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/2 to toluene only) to give corresponding 3-vinylpyrrole **17c**. Then, allylation was carried out as follows.[13] Diethylaluminum chloride (0.95 M solution in hexane, 1.48 mL, 1.40 mmol, 2.2 eq. for **12b**) was added to a slurry of zinc dust (125.4 mg, 1.92 mmol, 3.0 eq. for **12b**) and copper bromide (9.14 mg, 0.0637 mmol, 0.10 eq. for **12b**) in THF (25.5 mL) with stirring at 0 °C. The resulting mixture was cooled to –20 °C. A solution of methyl 4-bromocrotonate **18** (229 mg, 1.28 mmol, 2.0 eq. for **12b**) and aldehyde **17c** in THF (5 mL) was added slowly to the mixture over 40 min at –20 °C. After stirring for 15 h at the same temperature, the reaction mixture was quenched by addition of pyridine (0.3 mL), well stirred, and poured into 1N hydrochloric acid. The mixture was warmed up to room temperature and filtered to remove remaining zinc dust. After extraction three times with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1) to give a diastereomeric mixture of **9h** (0.68/0.32) (56.6 mg, 25% yield; 2 steps). **9h** was used immediately to next reaction. Data for the major diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (d, *J* = 6.0 Hz, 1H), 3.59 (s, 3H), 3.79 (dd, *J* = 9.2, 6.9 Hz, 1H), 5.16 (dd, *J* = 10.9, 1.4 Hz, 1H), 5.19 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.4, 0.9 Hz, 1H), 5.44 (dd, *J* = 17.5, 1.4 Hz, 1H), 5.46 (t, *J* = 6.3 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 9.2 Hz, 1H), 6.46 (d, *J* = 3.8 Hz, 1H), 6.88 (dd, *J* = 17.5, 11.2 Hz, 1H), 7.24 (dd, *J* = 3.8, 0.6 Hz, 1H), 7.48-7.52 (m, 2H), 7.60 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.76-7.80 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.11, 56.48, 67.66, 110.09, 114.53, 120.91, 124.46, 126.51, 128.40, 128.54, 129.45, 129.59, 131.74, 133.95, 139.14, 172.59. Data for the minor diastereomer; ^{1}H NMR

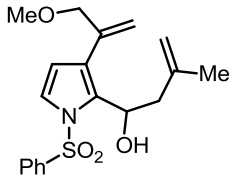
(500 MHz, $CDCl_3$) δ 3.19 (br s, 1H), 3.76 (s, 3H), 3.80 (t, *J* = 9.8 Hz, 1H), 4.86 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.88 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.21 (dd, *J* = 10.9, 1.2 Hz, 1H), 5.33 (ddd, *J* = 17.2, 10.3, 9.2 Hz, 1H), 5.47 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.53 (dd, *J* = 9.8, 6.6 Hz, 1H), 6.45 (d, *J* = 3.5 Hz, 1H), 6.81 (dd, *J* = 17.5, 10.9 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.48-7.53 (m, 2H), 7.58-7.63 (m, 1H), 7.81-7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.29, 57.00, 67.23, 109.93, 115.32, 119.58, 124.13, 126.76, 127.75, 128.34, 129.45, 129.79, 130.86, 134.01, 139.19, 173.03. HRMS (ESI) calcd for $C_{18}H_{19}NNaO_5S$ (M^++Na) 384.0876, found 384.0867.



9i

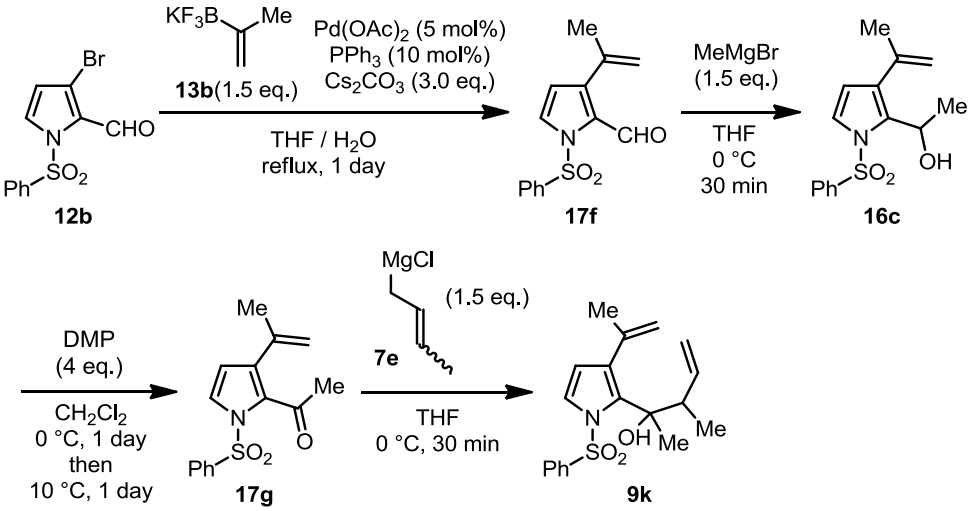
1-(4-Methoxyphenyl)-1-(3-(3-methoxyprop-1-en-2-yl)-1-(phenylperoxythio)-1*H*-pyrrol-2-yl)but-3-en-1-ol (9i); A mixture of **13c** (96.8 mg, 0.489 mmol, 2.0 eq.), $Pd(OAc)_2$ (5.53 mg, 0.0246 mmol, 10 mol%), PPh_3 (13.0 mg, 0.0495 mmol, 20 mol%), Cs_2CO_3 (248.5 mg, 0.763 mmol, 3.1 eq.), and **12c** (102.9 mg, 0.245 mmol, 1 eq.) in THF (4.9 mL, 0.05 M for **12c**) and water (0.98 mL, 1/5 (v/v) for THF) was refluxed for 2 days. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved in ether and treated with aqueous NH_4Cl solution. After stirring for over 1 h, saturated aqueous $NaHCO_3$ solution was added to the mixture. Then the mixture was extracted with ether three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give corresponding 3-vinylpyrrole **17e**. Then, the allylation was carried out according to the general procedure E; **17e** and **14c** (0.52 M solution in Et_2O, 0.508 mL, 0.264 mmol, 1.1 eq. for **12c**) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **9i** (67.1 mg, 60% yield; 2 steps). ^1H NMR (500 MHz, $CDCl_3$) δ 2.84 (ddd, *J* = 13.7, 7.5, 0.9 Hz, 1H), 3.27-3.35 (m, 1H), 3.35 (s, 3H), 3.75 (s, 3H), 3.94 (d, *J* = 13.3 Hz, 1H), 4.01 (d, *J* = 13.5 Hz, 1H), 4.57 (s, 1H), 4.87-5.00 (m, 2H), 5.11 (d, *J* = 0.7 Hz, 1H), 5.36 (q, *J* = 1.8 Hz, 1H), 5.58 (ddt, *J* = 17.2, 10.5, 7.6 Hz, 1H), 6.15 (d, *J* = 3.4 Hz, 1H), 6.54 (dt, *J* = 9.0, 3.0 Hz, 2H), 7.02 (dt, *J* = 8.9, 3.2 Hz, 2H), 7.12 (dq, *J* = 8.5, 1.1 Hz, 2H), 7.22-7.29 (m, 2H), 7.44 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.46, (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.38, 55.05, 58.35, 76.09, 76.29, 112.80, 114.27, 116.15, 118.27, 125.16, 126.09, 127.88, 128.19, 128.72, 132.74, 133.67, 136.07, 136.52, 139.51, 141.82,

158.48. HRMS (ESI) calcd for $C_{25}H_{27}NNaO_5S$ (M^++Na) 476.1502, found 476.1497.



9j

1-(3-(3-Methoxyprop-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)-3-methylbut-3-en-1-ol (9j); The coupling reaction was carried out according to the general procedure D; **12b** (100.0 mg, 0.318 mmol) and **13c** were used and the reaction mixture was stirred at 65 °C for 5 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1) to give corresponding 3-vinylpyrrole **17d**. Then, the allylation was carried out according to the general procedure E; **17d** and **14d** (0.67 M solution in THF, 0.713 mL, 0.477 mmol, 1.5 eq. for **12b**) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 2.5/1) to give **9j** (77.4 mg, 67% yield; 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 3H), 2.44 (dd, *J* = 14.2, 5.0 Hz, 1H), 2.77 (dd, *J* = 14.2, 9.6 Hz, 1H), 3.19 (d, *J* = 8.2 Hz, 1H), 3.34 (s, 3H), 3.99-4.09 (m, 2H), 4.71 (s, 1H), 4.78 (s, 1H), 5.19 (ddd, *J* = 9.6, 7.8, 5.0 Hz, 1H), 5.20-5.22 (m, 1H), 5.42 (q, *J* = 1.8 Hz, 1H), 6.20 (d, *J* = 3.7 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.48-7.54 (m, 2H), 7.61 (tt, *J* = 7.8, 1.8 Hz, 1H), 7.81-7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.09, 45.54, 58.15, 64.79, 75.68, 113.22, 113.38, 117.38, 123.25, 126.56, 127.65, 129.33, 133.67, 133.84, 139.24, 139.41, 142.18. HRMS (ESI) calcd for $C_{19}H_{23}NNaO_4S$ (M^++Na) 384.1240, found 384.1229.



3-methyl-2-(1-(phenylsulfonyl)-3-(prop-1-en-2-yl)-1*H*-pyrrol-2-yl)pent-4-en-2-ol (9k); The coupling reaction was carried out according to the general procedure D; **12b** (150.5 mg, 0.479 mmol) and **13b** were used and the reaction mixture was refluxed for 1 day; The crude product was

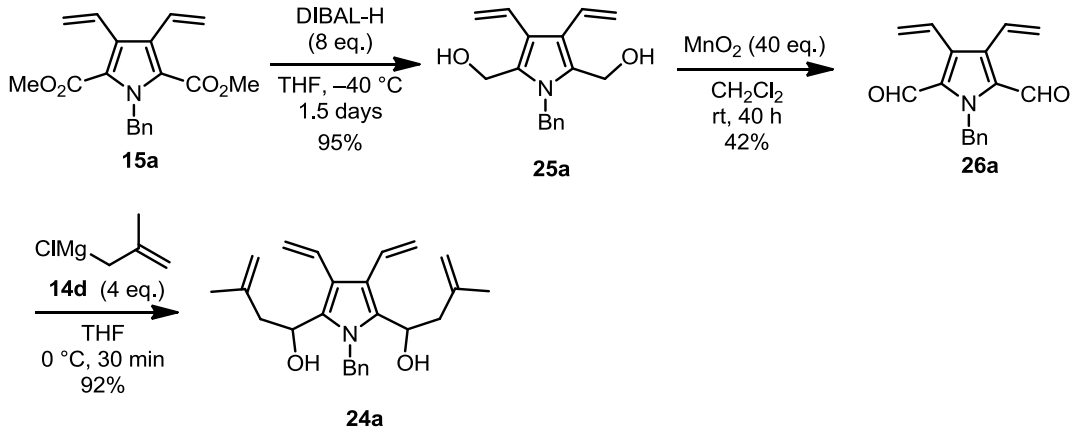
purified by silica-gel column chromatography (hexane/toluene = 1/5 to toluene only) to give corresponding 3-vinylpyrrole **17f** (116.5 mg, 88% yield).

To a stirred solution of **17f** (112.7 mg, 0.409 mmol) in THF (8.19 mL, 0.05 M) was added methylmagnesium bromide (3.0 M solution in Et_2O) at 0 °C (salt-ice bath) and the reaction mixture was stirred for 30 min. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution at the same temperature, warmed to room temperature, extracted with EtOAc three times, and washed with brine. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give **16c** (118.4 mg, 99% yield).

Dess-Martin periodinane (685.6 mg, 1.62 mmol, 4.0 eq.) was added to a solution of **16c** (117.6 mg, 0.403 mmol, 1 eq.) in dichloromethane (12.1 mL, 0.033 M) at 0 °C. The mixture was stirred for 1 day at 0 °C, then warmed up to 10 °C and stirred for additional 1 day. The mixture was diluted with ether, warmed up to room temperature, stirred for 5 min, and treated with 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1/1) solution. After extraction with ether three times, the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The crude product was purified twice by silica-gel column chromatography (first: hexane/EtOAc = 4.5/1, second: hexane/EtOAc = 5/1) to give **17g** (37.2 mg, 32% yield).

The allylation was carried out according to the general procedure E; **17g** (29.3 mg, 0.101 mmol) in THF (2.03 mL, 0.05 M) and **14e** (0.45 M solution in THF, 0.338 mL, 0.152 mmol, 1.5 eq.) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4.5/1) to give a diastereomeric mixture of **9k** (0.61/0.39) (29.1 mg, 87% yield). Data for the diastereomeric mixture; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.9 Hz, 3H (major)), 0.84 (d, *J* = 6.9 Hz, 3H (minor)), 1.44 (s, 3H (minor)), 1.47 (s, 3H (major)), 1.96-1.99 (m, 3H (major) and 3H (minor)), 3.04 (quint, *J* = 7.2 Hz, 1H (major)), 3.23 (quint, *J* = 6.9 Hz, 1H (minor)), 3.56 (s, 1H (minor)), 3.68 (s, 1H (major)), 4.83 (q, *J* = 1.1 Hz, 1H (minor)), 4.85 (q, *J* = 1.1 Hz, 1H (major)), 4.87-4.95 (m, 2H (major)), 5.06-5.13 (m, 1H (major) and 3H (minor)), 5.63 (ddd, *J* = 17.1, 10.3, 8.0 Hz, 1H (major)), 5.77 (ddd, *J* = 17.4, 10.6, 7.1 Hz, 1H (minor)), 6.04 (d, *J* = 3.4 Hz, 1H (minor)), 6.05 (d, *J* = 3.5 Hz, 1H (major)), 7.37 (d, *J* = 3.4 Hz, 1H (major)), 7.38 (d, *J* = 2.9 Hz, 1H (minor)), 7.44-7.50 (m, 2H (major) and 2H (minor)), 7.53-7.59 (m, 1H (major) and 1H (minor)), 7.67-7.71 (m, 2H (major) and 2H (minor)). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.33, 14.67, 24.07, 25.35, 25.68, 26.74, 46.28, 47.08, 75.20, 75.53, 113.67, 113.86, 115.36, 116.24, 116.36, 116.64, 124.99, 125.55, 125.95, 126.02, 128.98, 130.82, 131.80, 133.21, 136.13, 136.43, 139.32, 139.85, 140.87, 141.44, 141.50. HRMS (ESI) calcd for $C_{19}H_{23}NNaO_3S$ (M^++Na) 368.1291, found 368.1284.

Procedure for the Preparation of 1,1'-(1-Benzyl-3,4-divinyl-1*H*-pyrrole-2,5-diyl)bis(3-methylbut-3-en-1-ol) (24a).



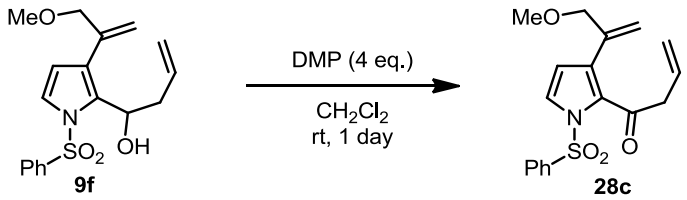
1,1'-(1-Benzyl-3,4-divinyl-1*H*-pyrrole-2,5-diyl)bis(3-methylbut-3-en-1-ol) (24a); The reduction step was carried out according to the general procedure A; Diisobutylaluminium hydride (1.04 M, 17.7 mL, 18.4 mmol, 4 eq.) and **15a** (1.50 g, 4.61 mmol, 1 eq.) were used and the reaction mixture was stirred at –40 °C for 12 h. Due to incompletion of the reaction, additional diisobutylaluminium hydride (1.04 M, 17.7 mL, 18.4 mmol, 4 eq.) was added to the mixture. The resulting mixture was stirred for 1 day; After extraction with EtOAc, the organic layer was dried and concentrated without washing with brine; The residue was purified by silica-gel column chromatography (hexane/EtOAc = 1.5/1) to give **25a** (1.18 g, 95% yield).

The oxidation step was carried out according to the general procedure B; MnO_2 (1.29 g, 14.9 mmol, 40 eq.), **25a** (100.5 mg, 0.371 mmol, 1 eq.), and CH_2Cl_2 (7.4 mL, 0.05 M for **25a**) were used and the reaction mixture was stirred for 40 h; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give **26a** (41.4 mg, 42% yield).

The allylation was carried out according to the general procedure E; **14d** (0.67 M solution in THF, 2.66 mL, 1.78 mmol, 4 eq.) and **26a** (118.0 mg, 0.445 mmol, 1 eq.) were used; After the extraction with EtOAc, the organic layer was dried and concentrated without washing with brine; The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give a diastereomeric mixture of **24a** (0.53/0.47) (155 mg, 92% yield). **25a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (br s, 2H), 4.56 (s, 4H), 5.25 (dd, *J* = 11.3, 1.9 Hz, 2H), 5.38 (dd, *J* = 17.4, 1.9 Hz, 2H), 5.40 (s, 2H), 6.73 (dd, *J* = 17.7, 11.3 Hz, 2H), 6.96 (d, *J* = 7.4 Hz, 2H), 7.23-7.33 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.02, 53.90, 115.08, 120.20, 125.48, 127.31, 128.82, 129.32, 129.92, 138.26. HRMS (ESI) calcd for $C_{17}H_{19}NNaO_2$ (M^++Na) 292.1308, found 292.1299. **24a**-meso; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 6H), 1.99 (s, 2H), 2.15 (dd, *J* = 14.1, 3.7 Hz, 2H), 2.49 (dd, *J* = 14.1, 10.4 Hz, 2H), 4.70 (s, 2H), 4.81 (t, *J* = 1.6 Hz, 2H), 5.03 (dd, *J* = 10.4, 3.7 Hz, 2H), 5.23 (dd, *J* = 11.3, 2.2

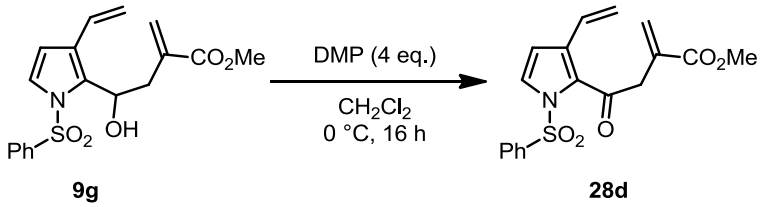
Hz, 2H), 5.29 (dd, *J* = 17.7, 2.2 Hz, 2H), 5.55 (s, 2H), 6.83 (dd, *J* = 17.7, 11.3 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 7.17-7.33 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.93, 45.44, 48.57, 64.56, 113.67, 115.31, 119.28, 125.56, 127.11, 128.69, 130.46, 131.40, 139.36, 142.39. HRMS (ESI) calcd for $C_{25}H_{31}NNaO_2$ (M^++Na) 400.2247, found 400.2234. **24a**-dl; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 6H), 2.03 (s, 2H), 2.17 (dd, *J* = 14.0, 3.4 Hz, 2H), 2.55 (dd, *J* = 14.1, 10.4 Hz, 2H), 4.70 (s, 2H), 4.80 (t, *J* = 1.6 Hz, 2H), 5.00 (dd, *J* = 10.4, 3.4 Hz, 2H), 5.24 (dd, *J* = 11.3, 2.2 Hz, 2H), 5.27 (dd, *J* = 18.0, 1.9 Hz, 2H), 5.36 (d, *J* = 17.7 Hz, 1H), 5.75 (d, *J* = 17.4 Hz, 1H), 6.85 (dd, *J* = 17.7, 11.3 Hz, 2H), 6.95 (d, *J* = 7.1 Hz, 2H), 7.18-7.32 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.79, 45.35, 48.47, 64.33, 113.63, 115.24, 119.37, 125.52, 127.10, 128.68, 130.56, 131.40, 139.31, 142.45.

Procedure for the Preparation of 1-(3-(3-Methoxyprop-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-3-en-1-one (28c).



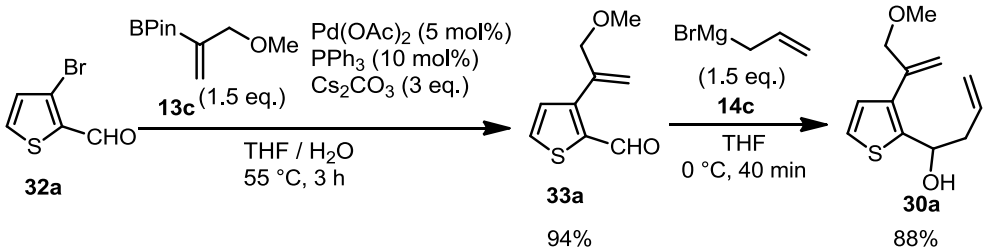
1-(3-(3-Methoxyprop-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-3-en-1-one (28c); Dess-Martin periodinane (398.4 mg, 0.939 mmol) was added to a solution of **9f** (81.2 mg, 0.234 mmol) in dichloromethane at 0 °C. After 10 min of stirring, the mixture was warmed up to room temperature and stirred for 1 day. The mixture was then diluted with ether, stirred for 5 min, and treated with 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1/1) solution. After extraction with ether three times, the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **28c** (47.7 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.59 (dt, *J* = 6.9, 1.4 Hz, 2H), 4.06 (s, 2H), 5.13 (d, *J* = 0.7 Hz, 1H), 5.13 (dq, *J* = 17.4, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.37 (q, *J* = 1.4 Hz, 1H), 5.96 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H), 6.28 (d, *J* = 3.24 Hz, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.54 (tt, *J* = 8.2, 1.6 Hz, 2H), 7.63 (tt, *J* = 7.6, 2.0 Hz, 1H), 7.99-7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.82, 58.25, 74.95, 112.20, 117.91, 118.83, 124.82, 127.81, 128.99, 130.30, 130.64, 130.74, 133.96, 137.96, 138.71, 194.95. HRMS (ESI) calcd for $C_{18}H_{19}NNaO_4S$ (M^++Na) 368.0927, found 368.0918.

Procedure for the Preparation of Methyl 2-methylene-4-oxo-4-(1-(phenylsulfonyl)-3-vinyl-1*H*-pyrrol-2-yl)butanoate (28d).



Methyl 2-methylene-4-oxo-4-(1-(phenylsulfonyl)-3-vinyl-1*H*-pyrrol-2-yl)butanoate (28d); Dess-Martin periodinane (324.4 mg, 0.765 mmol, 4.0 eq.) was added to a solution of **9g** (69.1 mg, 0.191 mmol, 1 eq.) in dichloromethane (5.7 mL, 0.033 M for **9g**) at 0 °C and stirred for 16 h. The mixture was then diluted with ether, warmed up to room temperature, stirred for 5 min, and treated with 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1/1) solution. After extraction with ether three times, the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **28d** (48.3 mg, 70% yield). **28d** was found to be somewhat unstable. Therefore, **28d** was used immediately to next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.90 (d, *J* = 0.7 Hz, 2H), 5.34 (dd, *J* = 11.0, 1.2 Hz, 1H), 5.59 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.78 (d, *J* = 1.2 Hz, 1H), 6.40 (d, *J* = 0.7 Hz, 1H), 6.46 (d, *J* = 3.4 Hz, 1H), 6.74 (dd, *J* = 17.6, 11.0 Hz, 1H), 7.32 (dd, *J* = 3.4, 0.7 Hz, 1H), 7.46-7.52 (m, 2H), 7.59 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.83-7.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.03, 52.10, 110.94, 118.24, 126.65, 127.31, 127.37, 129.04, 129.56, 130.80, 131.92, 133.73, 133.94, 138.30, 166.67, 192.18. HRMS (ESI) calcd for $C_{18}H_{17}NNaO_5S$ (M^++Na) 382.0720, found 382.0707.

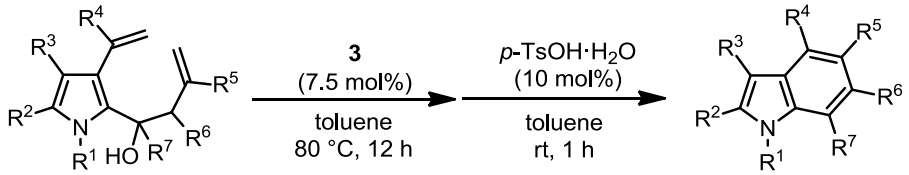
Procedure for the Preparation of 1-(3-(3-Methoxyprop-1-en-2-yl)thiophen-2-yl)but-3-en-1-ol (30a).



1-(3-(3-Methoxyprop-1-en-2-yl)thiophen-2-yl)but-3-en-1-ol (30a); The coupling reaction was carried out according to the general procedure D; **32a** (40.5 mg, 0.212 mmol) and **13c** were used

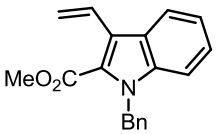
and the reaction mixture was stirred at 55 °C for 3 h; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/2 to toluene only) to give **33a** (36.2 mg, 94% yield). Then, the allylation was carried out according to the general procedure E; **33a** (36.2 mg, 0.199 mmol) and **14c** (0.74 M) were used and the reaction mixture was stirred for 40 min; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **30a** (39.4 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56-2.70 (m, 2H), 2.90 (s, 1H), 3.33 (s, 3H), 4.08 (d, *J* = 13.2 Hz, 1H), 4.15 (d, *J* = 12.6 Hz, 1H), 5.06 (t, *J* = 6.3 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.5 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.20 (d, *J* = 1.8 Hz, 1H), 5.44 (d, *J* = 1.7 Hz, 1H), 5.84 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H), 6.89 (d, *J* = 5.15 Hz, 1H), 7.21 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.17, 58.14, 67.02, 76.05, 117.23, 118.09, 123.63, 127.59, 134.34, 137.57, 140.59, 143.89. HRMS (ESI) calcd for $C_{12}H_{16}NaO_2S$ (M^++Na) 247.0763, found 247.0759.

Procedures for the Preparation of Indoles 11.



9 **11**

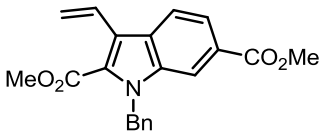
General procedure F: RCM/dehydration. To a solution of **9** (0.100 mmol, 1 eq.) in toluene (10 mL, 0.01 M) was added catalyst **3** (0.0075 mmol, 7.5 mol%) in one portion under nitrogen and the reaction mixture was stirred for 12 h at 80 °C. The reaction mixture was treated with *p*-toluenesulfonic acid (0.010 mmol, 10 mol%) and stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and purified by silica-gel column chromatography or PTLC on silica gel to give indole **11**.



11a

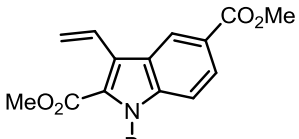
Methyl 1-benzyl-3-vinyl-1*H*-indole-2-carboxylate (11a); The reaction was carried out according to the general procedure F. **9a** (60.3 mg, 0.179 mmol) was used. The reaction was performed at room temperature and the crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give **11a** (37.9 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 5.50 (dd, *J* = 18.0, 1.6 Hz, 1H), 5.75 (s, 2H), 5.87 (dd, *J* = 18.0, 1.6 Hz, 1H),

7.02 (d, J = 7.3 Hz, 2H), 7.15-7.27 (m, 4H), 7.27-7.35 (m, 2H), 7.39 (dd, J = 18.0, 11.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.19, 51.72, 110.84, 116.80, 121.25, 122.11, 122.30, 124.81, 124.92, 125.67, 126.10, 127.09, 128.54, 130.07, 138.10, 139.08, 162.70. HRMS (ESI) calcd for $C_{19}H_{17}NNaO_2$ (M^++Na) 314.1152, found 314.1147.



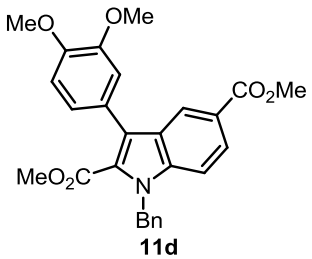
11b

Dimethyl 1-benzyl-3-vinyl-1*H*-indole-2,6-dicarboxylate (11b); The reaction was carried out according to the general procedure F. **9b** (46.9 mg, 0.119 mmol) was used. The crude product was purified by PTLC (hexane/EtOAc/Et_3N = 32/8/1) twice to give **11b** (21.9 mg, 53% yield). m.p. 130-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.92 (s, 3H), 5.54 (dd, J = 11.6, 1.6 Hz, 1H), 5.82 (s, 2H), 5.87 (dd, J = 18.0, 1.5 Hz, 1H), 6.99-7.04 (m, 2H), 7.19-7.20 (m, 3H), 7.34 (dd, J = 18.0, 11.6 Hz, 1H), 7.87 (dd, J = 8.6, 1.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 8.14 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.31, 51.98, 52.15, 113.10, 117.41, 121.83, 122.05, 126.08, 127.14, 127.33, 127.37, 128.13, 128.66, 129.54, 137.70, 138.34, 162.32, 167.39. HRMS (ESI) calcd for $C_{21}H_{19}NNaO_4$ (M^++Na) 372.1206, found 372.1194.



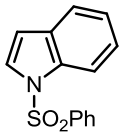
11c

Dimethyl 1-benzyl-3-vinyl-1*H*-indole-2,5-dicarboxylate (11c); The reaction was carried out according to the general procedure F. **9c** (39.5 mg, 0.100 mmol) was used. The reaction was performed at 100 °C and the crude product was purified by PTLC (hexane/EtOAc = 3/1) to give **11c** (4.1 mg, 12% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.94 (s, 3H), 5.58 (dd, J = 11.6, 1.2 Hz, 1H), 5.79 (s, 2H), 5.94 (dd, J = 18.0, 1.2 Hz, 1H), 7.02 (d, J = 7.0 Hz, 2H), 7.19-7.29 (m, 3H), 7.31-7.39 (m, 2H), 8.01 (dd, J = 8.9, 1.8 Hz, 1H), 8.77 (d, J = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.47, 51.94, 52.03, 110.60, 118.22, 123.37, 123.47, 124.53, 125.46, 126.00, 126.10, 126.59, 127.37, 128.68, 129.32, 137.52, 141.25, 162.38, 167.54. HRMS (APCI) calcd for $C_{21}H_{20}NO_4$ (M^++H) 350.1387, found 350.1377.



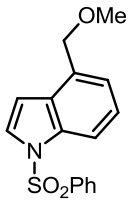
11d

Dimethyl 1-benzyl-3-(3,4-dimethoxyphenyl)-1*H*-indole-2,5-dicarboxylate (11d); The reaction was carried out according to the general procedure F. The reaction was performed with a mixture of **9d** and **21** (1:0.18) (**9d**: 34.18 mg, 0.0676 mmol) at 100 °C and the crude product was purified by PTLC (hexane/EtOAc = 3/1) to give a mixture of **11d** (4.0 mg, 13% yield) and **21**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H) 3.89 (s, 3H), 3.91 (s, 3H), 3.98 (s, 3H), 5.82 (s, 2H), 6.97-7.07 (m, 3H), 7.08-7.13 (m, 2H), 7.21-7.34 (m, 3H), 7.41 (d, *J* = 8.8 Hz, 1H), 8.02 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.36 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.48, 51.68, 51.98, 55.89, 55.97, 110.30, 110.45, 110.76, 113.60, 122.44, 122.66, 123.18, 125.01, 125.49, 126.07, 126.30, 126.53, 126.58, 127.44, 128.72, 137.58, 140.49, 148.39, 162.63, 167.51. HRMS (ESI) calcd for $C_{27}H_{25}NNaO_6$ (M^++Na) 482.1574, found 482.1570.



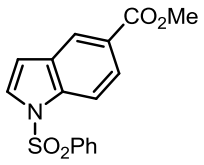
11e

1-(Phenylsulfonyl)-1*H*-indole (11e); The reaction was carried out according to the general procedure F. **9e** (33.5 mg, 0.110 mmol) was used. The reaction was performed at room temperature and the crude product was purified by PTLC (hexane/EtOAc = 3/1) to give **11e** (28.0 mg, 98% yield). m.p. 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 3.9, 0.7 Hz, 1H), 7.22 (td, *J* = 7.3, 1.2 Hz, 1H), 7.31 (td, *J* = 8.5, 1.4 Hz, 1H), 7.38-7.44 (m, 2H), 7.48-7.54 (m, 2H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.85-7.89 (m, 2H), 8.00 (dd, *J* = 8.4, 0.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.21, 113.48, 121.39, 123.34, 124.61, 126.26, 126.70, 129.21, 130.71, 133.76, 134.80, 138.21. HRMS (ESI) calcd for $C_{14}H_{11}NNaO_2S$ (M^++Na) 280.0403, found 280.0397.



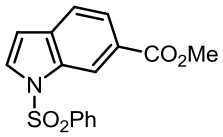
11f

4-(Methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole (11f); The reaction was carried out according to the general procedure F. **9f** (34.7 mg, 0.0999 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 2/1) to give **11f** (27.9 mg, 93% yield). m.p. 119-121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.64 (s, 2H), 6.80 (dd, *J* = 3.7, 0.9 Hz, 1H), 7.19 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.42 (tt, *J* = 8.0, 1.7 Hz, 2H), 7.51 (tt, *J* = 7.5, 1.7 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.88 (dq, *J* = 7.8, 1.4 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.26, 72.74, 107.51, 113.11, 122.88, 124.48, 126.24, 126.73, 129.22, 129.58, 130.81, 133.80, 134.94, 138.18. HRMS (ESI) calcd for $C_{16}H_{15}NNaO_3S$ (M^++Na) 324.0665, found 324.0658.



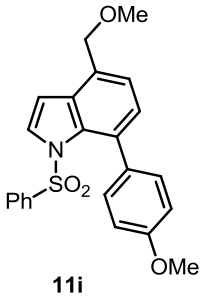
11g

Methyl 1-(phenylsulfonyl)-1*H*-indole-5-carboxylate (11g); The reaction was carried out according to the general procedure F. **9g** (48.0 mg, 0.133 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 2/1) to give **11g** (29.2 mg, 70% yield). m.p. 161-163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.37 (d, *J* = 3.7 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 3.7 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 8.01 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 8.26 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.11, 109.54, 113.15, 123.74, 125.47, 125.84, 126.73, 127.48, 129.37, 130.46, 134.12, 137.27, 137.92, 167.07. HRMS (ESI) calcd for $C_{16}H_{13}NNaO_4S$ (M^++Na) 338.0457, found 338.0454.



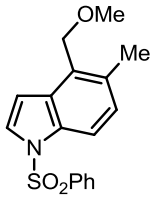
11h

1-(Phenylsulfonyl)-1*H*-indole-6-carboxylate (11h); The reaction was carried out according to the general procedure F. **9h** (35.8 mg, 0.0991 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 2/1) to give **11h** (25.5 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.70 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.43-7.48 (m, 2H), 7.55 (tt, *J* = 7.5, 1.7 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 3.7 Hz, 1H), 7.89-7.95 (m, 3H), 8.69-8.71 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.24, 108.98, 115.20, 121.12, 124.51, 126.54, 126.79, 129.17, 129.39, 134.07, 134.28, 134.36, 137.97, 167.15. HRMS (ESI) calcd for $C_{16}H_{13}NNaO_4S$ (M^++Na) 338.0457, found 338.0447.



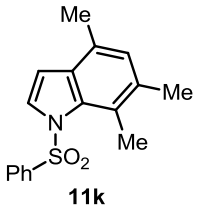
11i

4-(Methoxymethyl)-7-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (11i); The reaction was carried out according to the general procedure F. **9i** (34.7 mg, 0.0766 mmol) was used. The dehydration was carried out at 80 °C for 1.5 h and the crude product was purified by PTLC (hexane/EtOAc = 2.5/1) to give **11i** (31.2 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.85 (s, 3H), 4.67 (s, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 3.9 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.22-7.32 (m, 4H), 7.44 (tt, *J* = 6.9, 2.5 Hz, 1H), 7.76 (d, *J* = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.18, 58.17, 72.45, 107.95, 112.73, 123.40, 126.28, 128.62, 129.36, 130.10, 130.57, 130.68, 132.06, 132.76, 133.04, 133.89, 138.30, 158.66. HRMS (ESI) calcd for $C_{23}H_{21}NNaO_4S$ (M^++Na) 430.1084, found 430.1079.



11j

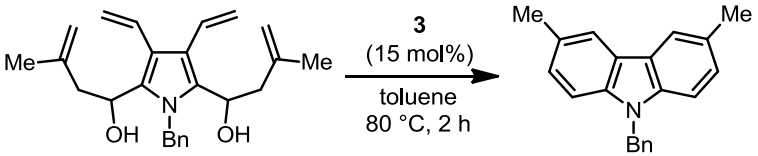
4-(Methoxymethyl)-5-methyl-1-(phenylsulfonyl)-1*H*-indole (11j); The reaction was carried out according to the general procedure F. **9j** (39.0 mg, 0.108 mmol) was used. The reaction was performed at 100 °C and the crude product was purified by PTLC (hexane/EtOAc = 2.5/1) to give **11j** (12.1 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.38 (s, 3H), 4.64 (s, 2H), 6.80 (dd, *J* = 3.9, 0.7 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.38-7.44 (m, 2H), 7.51 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.54 (d, *J* = 3.9 Hz, 1H), 7.82-7.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.53, 58.31, 69.29, 107.79, 113.04, 126.32, 126.71, 127.37, 127.90, 129.18, 131.21, 132.14, 133.41, 133.73, 138.21. HRMS (ESI) calcd for $C_{17}H_{17}NNaO_3S$ (M^++Na) 338.0821, found 338.0810.



11k

4,6,7-trimethyl-1-(phenylsulfonyl)-1*H*-indole (11k); The reaction was carried out according to the general procedure F. **9k** (29.1 mg, 0.0877 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 5/1) to give **11k** (24.5 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 6.65 (d, *J* = 3.7 Hz, 1H), 6.89 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.51 (tt, *J* = 7.4, 0.8 Hz, 1H), 7.63 (dd, *J* = 8.6, 0.8 Hz, 2H), 7.67 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.71, 17.98, 20.78, 107.90, 121.17, 126.39, 127.30, 127.33, 129.03, 129.32, 130.77, 133.30, 134.11, 136.17, 139.60. HRMS (ESI) calcd for $C_{17}H_{17}NNaO_2S$ (M^++Na) 322.0872, found 322.0870.

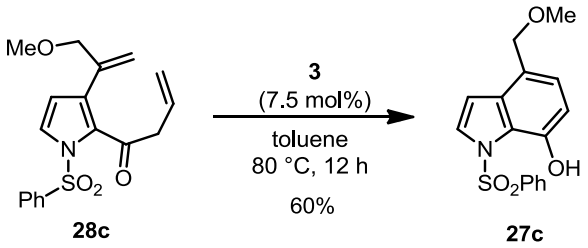
Procedure for the Preparation of 9-Benzyl-3,6-dimethyl-9*H*-carbazole (23a).



24a **23a**

9-Benzyl-3,6-dimethyl-9*H*-carbazole (23a); To a solution of **24a** (29.7 mg, 0.0787 mmol) in toluene (8.0 mL, 0.01 M) was added 15 mol% catalyst **3** (10.0 mg, 0.0118 mmol) in one portion under nitrogen and the reaction mixture was stirred for 2 h at 80 °C. The reaction mixture was concentrated under reduced pressure and purified by silica-gel column chromatography (hexane/EtOAc = 5/1) to give carbazole **23a** (18.3 mg, 81% yield). m.p. 110-114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (s, 6H), 5.44 (s, 2H), 7.07-7.12 (m, 2H), 7.15-7.32 (m, 7H), 7.88 (d, *J* = 0.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.36, 46.54, 108.48, 120.28, 122.94, 126.34, 126.94, 127.29, 128.18, 128.69, 137.46, 139.19. HRMS (ESI) calcd for $C_{21}H_{20}N$ (M^++H) 286.1590, found 286.1586.

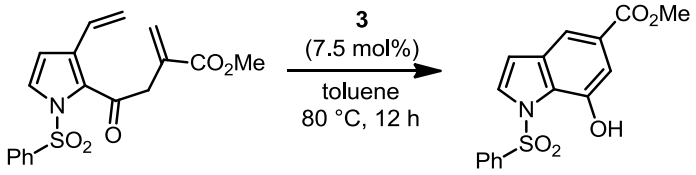
Procedure for the Preparation of 4-(Methoxymethyl)-1-(phenylsulfonyl)-1*H*-indol-7-ol (27c).



28c 27c

4-(Methoxymethyl)-1-(phenylsulfonyl)-1*H*-indol-7-ol (27c); To a solution of **28c** (43.2 mg, 0.124 mmol) in toluene (12 mL, 0.01 M) was added 7.5 mol% catalyst **3** (7.90 mg, 0.0093 mmol) in one portion under nitrogen and the reaction mixture was stirred for 12 h at 80 °C. The reaction mixture was concentrated under reduced pressure and purified by PTLC on silica gel (hexane/EtOAc = 2/1) to give 7-hydroxyindole **27c** (23.3 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 4.53 (s, 2H), 6.82 (d, *J* = 3.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.45 (tt, *J* = 7.3, 1.7 Hz, 2H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.55 (tt, *J* = 7.6, 2.0 Hz, 1H), 7.81 (dq, *J* = 8.5, 1.2 Hz, 2H), 8.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.96, 72.39, 110.19, 113.19, 122.26, 126.12, 126.88, 127.86, 129.52, 133.56, 134.18, 137.05, 144.31. HRMS (ESI) calcd for $C_{16}H_{14}NO_4S$ (M^-–H) 316.0649, found 316.0652.

Procedure for the Preparation of Methyl 7-hydroxy-1-(phenylsulfonyl)-1*H*-indole-5-carboxylate (27d).

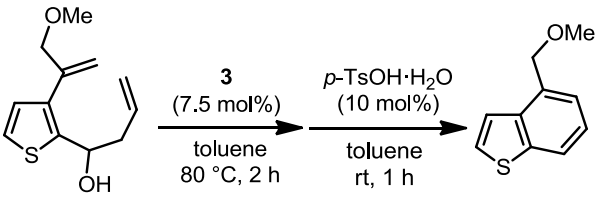


28d 27d

Methyl 7-hydroxy-1-(phenylsulfonyl)-1*H*-indole-5-carboxylate (27d); To a solution of **28d** (38.3 mg, 0.107 mmol) in toluene (10.7 mL, 0.01 M) was added 7.5 mol% catalyst **3** (6.80 mg, 0.00801 mmol) in one portion under nitrogen and the reaction mixture was stirred for 12 h at 80 °C. The reaction mixture was concentrated under reduced pressure and purified by PTLC on silica gel (hexane/EtOAc = 2/1) to give 7-hydroxyindole **27d** (33.7 mg, 95% yield). m.p. 148-151 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.73 (d, *J* = 3.7 Hz, 1H), 7.44-7.48 (m, 2H), 7.52 (d, *J* = 3.8 Hz, 1H), 7.56 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.79-7.83 (m, 2H), 8.75 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.18, 112.08, 114.55, 115.31, 125.53, 126.83,

127.90, 128.83, 129.61, 134.21, 134.41, 136.83, 114.07, 166.72. HRMS (ESI) calcd for $C_{16}H_{12}NO_5S$ (M^-–H) 330.0442, found 330.0442.

Procedure for the Preparation of 4-(Methoxymethyl)benzo[*b*]thiophene (31a).



30a **31a** 80%

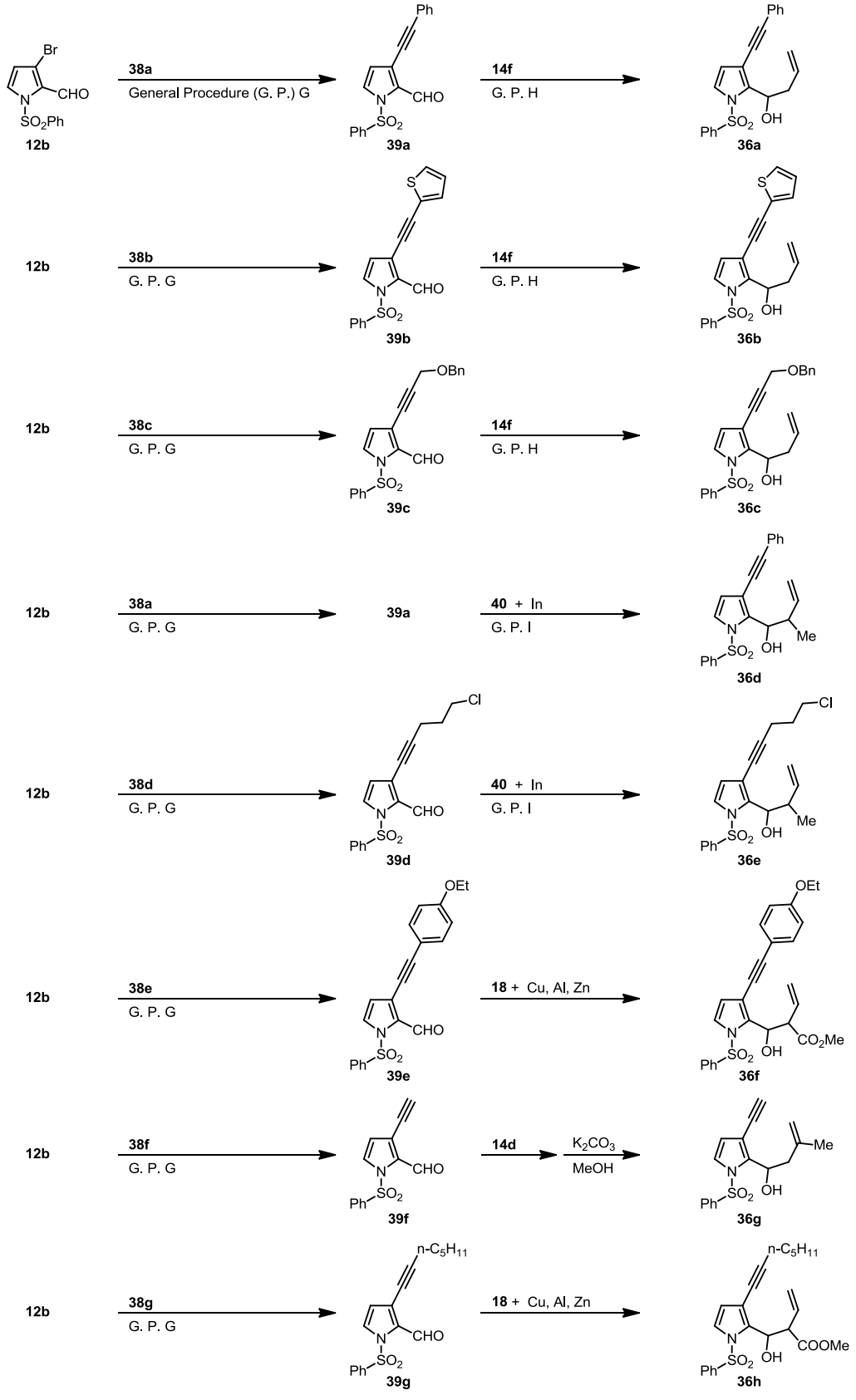
4-(Methoxymethyl)benzo[*b*]thiophene (31a); The reaction was carried out according to the general procedure F; **30a** (27.0 mg, 0.120 mmol) was used and the reaction mixture was stirred for 2 h; The crude product was purified by PTLC (hexane/EtOAc = 4/1) to give **31a** (17.2 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (s, 3H), 4.78 (s, 2H), 7.32 (d, *J* = 6.2 Hz, 1H), 7.32 (d, *J* = 2.7 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.52 (dd, *J* = 5.5, 0.7 Hz, 1H), 7.84 (ddd, *J* = 6.2, 2.8, 0.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.08, 73.44, 121.82, 122.20, 123.97, 126.58, 132.61, 138.23, 140.26. HRMS (ESI) calcd for $C_{10}H_{10}NaOS$ (M^++Na) 201.0345, found 201.0345.

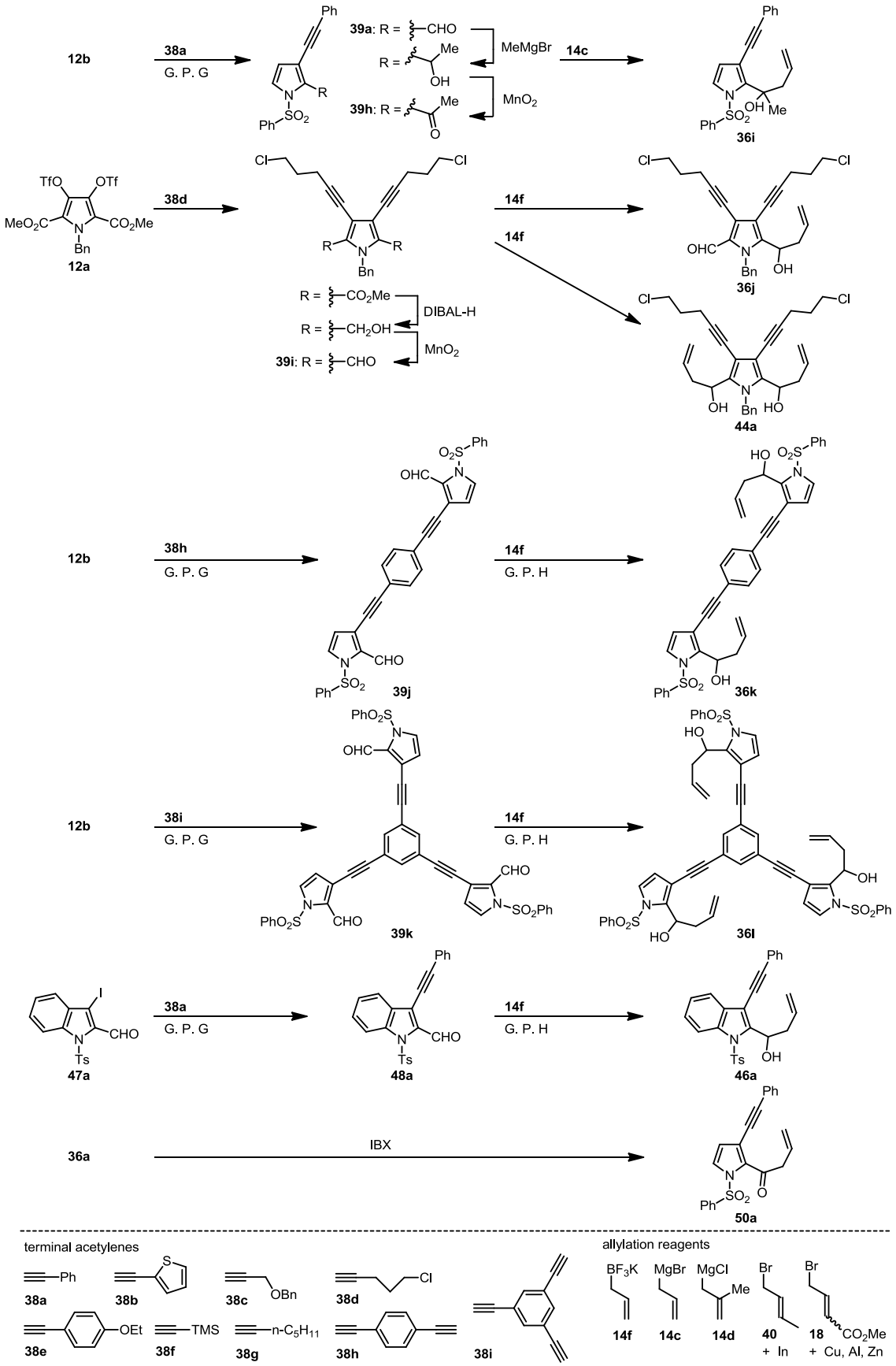
第四章 及び 第五章

General. All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or glove box techniques under prepurified argon. NMR spectra were recorded on a JEOL JNM ECA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) and ECS-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) at Chemical Analysis Center, Chiba University. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. High-resolution mass spectra were recorded on Thermo Fisher Scientific Exactive Orbitrap mass spectrometers at Chemical Analysis Center, Chiba University.

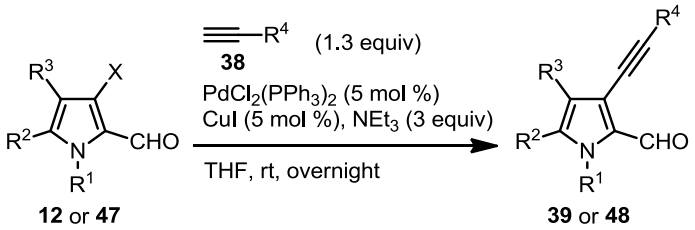
Materials. THF was distilled from sodium benzophenone-ketyl under nitrogen prior to use. Dichloromethane was distilled from CaH_2 under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. Toluene was distilled from sodium benzophenone-ketyl under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. Ruthenium complex $(PCy_3)(H_2Imes)Cl_2Ru=C(H)Ph$ (**3**)[33, 34] was prepared according to the reported procedures. Pyrrole **12a**[22] and **12b**[23] were prepared according to the reported procedure. Terminal acetylenes **38b**[45] and **38c**[46] were prepared according to the reported procedures. Terminal acetylenes **38a** and **38d-h** were used as received. Allylic metal reagents **14c**,[41] **14d**,[42] and **14f**[47] were prepared according to the reported procedures. MnO_2 was prepared according to the reported procedure.[38] IBX was prepared according to the reported procedures.[48] Dichlorobis(triphenylphosphine)palladium, triethyl amine, copper iodide, tetrabutylammonium iodide, indium powder, 1-bromo-2-butene **40**, methyl 4-bromocrotonate **18**, diethylaluminum chloride solution, zinc dust, copper bromide, methylmagnesium bromide (3.0 M solution in Et_2O), potassium carbonate, pyridine, and *p*-toluenesulfonic acid monohydrate were used as received.

Summary of the Preparation of Substrates

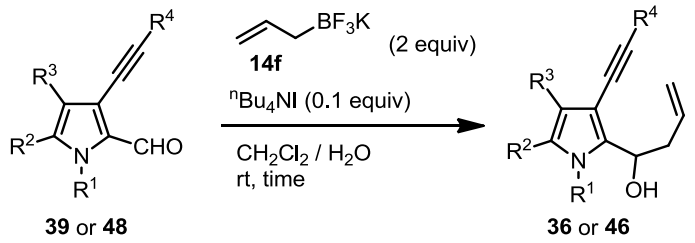



12b
38a
G. P. G
39a: R = CHO
R = Me, OH
39h: R = Me, O
MeMgBr
MnO2
14c
36i
12a
38d
14f
36j
44a
DIBAL-H
39i: R = CHO
38h
G. P. G
39j
36k
38i
39k
36l
47a
48a
46a
36a
IBX
50a
terminal acetylenes
38a
38b
38c
38d
38e
38f
38g
38h
38i
allylation reagents
14f
14c
14d
40
18
+ In
+ Cu, Al, Zn

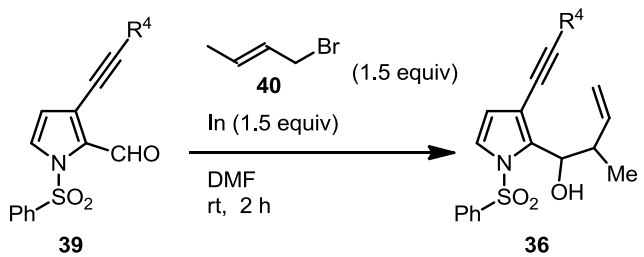
General Procedures.



General procedure G: Sonogashira coupling. To a mixture of $PdCl_2(PPh_3)_2$ (5 mol %) and **12** or **47** in THF (1/7 M for **12** or **47**) was added NEt_3 (3 equiv). After being stirred for 10 min at room temperature, terminal acetylene **38** (1.3 equiv) and CuI (5 mol %) were added to the mixture. The resulting mixture was stirred overnight (ca. 16 h). The reaction mixture was diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography to give **39** or **48**.

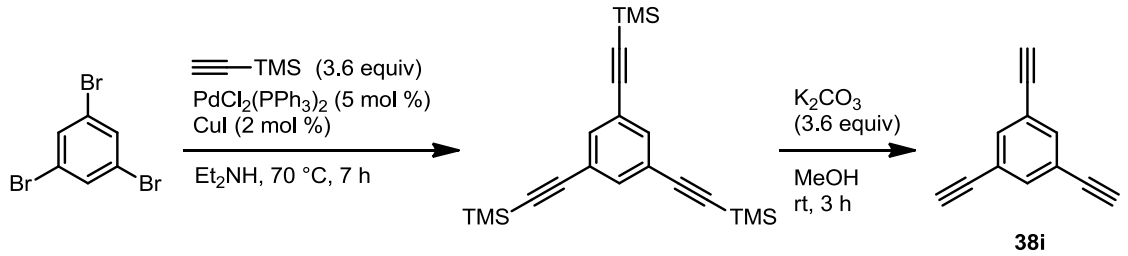


General procedure H: Allylation with allyltrifluoroborate.[49] To a solution of aldehyde **39** or **48** and $^nBu_4NI$ (0.1 equiv) in CH_2Cl_2 (1/3 M for **39** or **48**) were added **14f** (2 equiv) and water (2/3 M for **14f**). The biphasic reaction mixture was vigorously stirred at room temperature until the starting material disappeared (ca. 1 h). The reaction mixture was then diluted with CH_2Cl_2 and extracted with CH_2Cl_2 three times. The organic layers were combined and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography to give **36** or **46**.



General procedure I: Allylation with indium and 1-bromo-2-butene.[50] To a suspension of an indium powder (1.5 equiv) in DMF (1 M for indium) was added a mixture of 4-bromo-2-butene **40** (1.5 equiv) and aldehyde **39** in DMF (2 M for **39**). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by diluted hydrochloric acid and extracted with Et_2O three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography to give **36**.

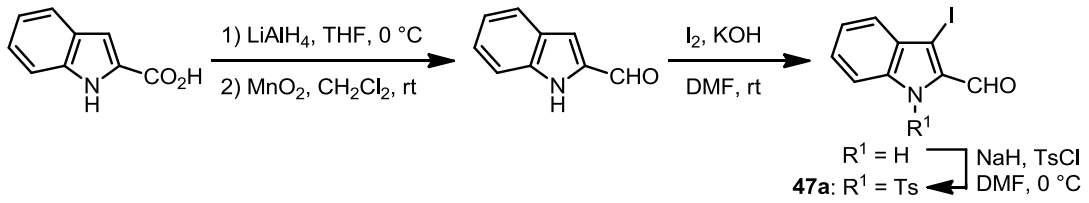
Procedures for the Preparation of 1,3,5-Triethynylbenzene (38i).



1,3,5-Triethynylbenzene (38i); The Sonogashira coupling was performed according to the reported procedure.[51]

To a solution of 1,3,5-tris((trimethylsilyl)ethynyl)benzene (2.56 g, 6.99 mmol) in degassed methanol (40 mL) and THF (40 mL) was added K_2CO_3 (3.48 g, 25.2 mmol, 3.6 equiv). After stirring 3 h at room temperature, the mixture was diluted with water at 0 °C, concentrated under reduced pressure to decrease the solvents, and extracted with Et_2O three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give **38i** (933 mg, 6.21 mmol, 89% yield). The analytical data were identical to previously reported data.[52]

Procedures for the Preparation of 3-Iodo-1-tosyl-1*H*-indole-2-carbaldehyde (47a).

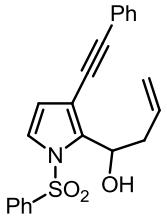


3-Iodo-1-tosyl-1*H*-indole-2-carbaldehyde (47a); The sequential reduction and oxidation of the carboxylic group were performed according to the reported procedure.[53]

The iodination step was performed according to the reported procedure;[54] The crude product was purified by silica-gel column chromatography (CH_2Cl_2).

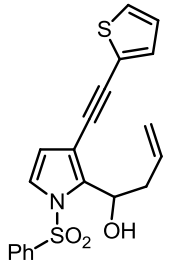
The tosylation step was performed according to the reported procedure,[55] where TsCl was employed instead of MOMCl; 3-Iodo-1*H*-indole-2-carbaldehyde (110 mg, 0.405 mmol) was used; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/4) to give **47a** (131 mg, 0.307 mmol, 76% yield). The analytical data were identical to previously reported data.[56]

Procedures for the Preparation of 1-(3-Ethynyl-1-1*H*-pyrrol-2-yl)but-3-en-1-ols 36.



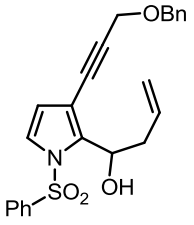
36a

1-(3-(Phenylethynyl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-3-en-1-ol (36a); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.636 mmol) and **38a** were used; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/3 ~ toluene) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39a** (213 mg, 0.634 mmol, >99% yield). The allylation step was carried out according to the general procedure H; **39a** (90.5 mg, 0.270 mmol) was used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **36a** (99.1 mg, 0.263 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73-2.90 (m, 3H), 5.01-5.12 (m, 2H), 5.25 (td, *J* = 8.2, 6.2 Hz, 1H), 5.76 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 6.39 (d, *J* = 3.4 Hz, 1H), 7.25 (d, *J* = 3.4 Hz, 1H), 7.30-7.35 (m, 3H), 7.42-7.46 (m, 2H), 7.53 (t, *J* = 8.1 Hz, 2H), 7.64 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.26, 66.82, 82.28, 94.08, 109.20, 115.04, 118.05, 122.77, 122.87, 126.77, 128.37, 128.41, 129.56, 131.20, 133.85, 134.23, 138.88, 139.21. HRMS (ESI) calcd for $C_{22}H_{19}NNaO_3S$ (M^++Na) 400.0978, found 400.0971.



36b

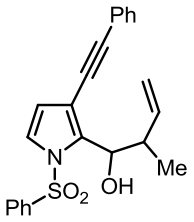
1-(1-(Phenylsulfonyl)-3-(thiophen-2-ylethynyl)-1*H*-pyrrol-2-yl)but-3-en-1-ol (36b); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.637 mmol) and **38b** were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 1/4) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39b** (208 mg, 0.608 mmol, 95% yield). The allylation step was carried out according to the general procedure H; **39b** (208 mg, 0.608 mmol) was used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give **36b** (217 mg, 0.569 mmol, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 (dddt, *J* = 14.1, 7.2, 6.0, 1.1 Hz, 1H), 2.79 (d, *J* = 8.3 Hz, 1H), 2.83 (dddt, *J* = 14.3, 8.1, 6.9, 1.1 Hz, 1H), 5.03-5.06 (m, 1H), 5.09 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (td, *J* = 8.1, 6.9 Hz, 1H), 5.74 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 6.38 (d, *J* = 3.5 Hz, 1H), 6.99 (dd, *J* = 5.2, 3.7 Hz, 1H), 7.20 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.24 (d, *J* = 3.4 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.51-7.56 (m, 2H), 7.64 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.81-7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.20, 66.72, 85.94, 87.21, 108.97, 114.92, 118.22, 122.86, 126.80, 127.11, 127.44, 129.59, 131.75, 133.75, 134.29, 138.85, 139.30. HRMS (ESI) calcd for $C_{20}H_{17}NNaO_3S_2$ (M^++Na) 406.0542, found 406.0533.



36c

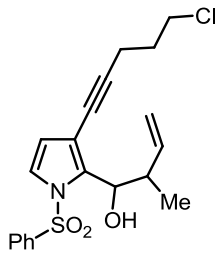
1-(3-(3-(Benzyloxy)prop-1-yn-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-3-en-1-ol (36c); The coupling reaction was carried out according to the general procedure G; **12b** (150 mg, 0.478 mmol) and **38c** were used; The crude product was purified twice by silica-gel column chromatography (first: hexane/EtOAc = 1/3, second: hexane/toluene = 10/1 ~ toluene ~ toluene/Et_2O = 15/1) to give corresponding 3-ethynylpyrrole-2-calbaldehyde **39c** (103 mg, 0.271 mmol, 57% yield). The allylation step was carried out according to the general procedure H; **39c** (103 mg, 0.271 mmol) was used; The crude product was purified by silica-gel column chromatography

(hexane/EtOAc = 2/1) to give **36c** (104 mg, 0.248 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (quint, *J* = 6.9 Hz, 1H), 2.75-2.84 (m, 2H), 4.35 (s, 2H), 4.62 (s, 2H), 5.00-5.08 (m, 2H), 5.19 (q, *J* = 6.6 Hz, 1H), 7.52 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 6.32 (d, *J* = 3.5 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 7.27-7.36 (m, 5H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.26, 57.81, 66.76, 71.62, 79.47, 90.21, 108.56, 115.21, 118.05, 122.65, 126.76, 127.89, 128.05, 128.43, 129.57, 133.79, 134.26, 137.28, 138.84, 139.65. HRMS (ESI) calcd for $C_{24}H_{23}NNaO_4S$ (M^++Na) 444.1240, found 444.1233.



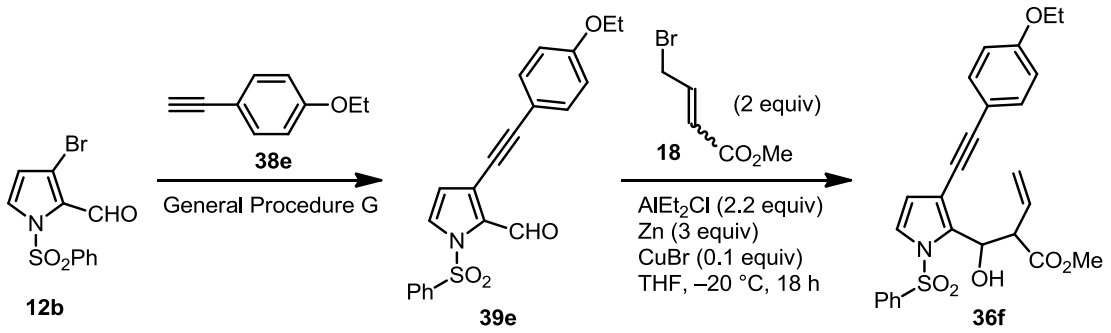
36d

2-Methyl-1-(3-(phenylethynyl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-3-en-1-ol (36d); The coupling reaction was carried out according to the general procedure G; **12b** (199 mg, 0.634 mmol) and **38a** were used; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/3 ~ toluene) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39a**. The allylation step was then carried out according to the general procedure I; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give a diastereomeric mixture of **36d** (0.58/0.42) (205 mg, 0.525 mmol, 83% yield; 2 steps). Data for the diastereomeric mixture; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.9 Hz, 3H (minor)), 1.23 (d, *J* = 6.9 Hz, 3H (major)), 2.69 (d, *J* = 8.0 Hz, 1H (minor)), 2.82 (d, *J* = 9.4 Hz, 1H (major)), 3.09 (sextet, *J* = 7.7 Hz, 1H (major)), 3.15 (sextet, *J* = 8.0 Hz, 1H (minor)), 4.80 (ddd, *J* = 10.4, 1.7, 0.9 Hz, 1H (major)), 4.90 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 1H (major)), 4.98 (t, *J* = 8.8 Hz, 1H (major) and 1H (minor)), 5.17-5.23 (m, 2H (minor)), 5.51 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H (major)), 5.92 (ddd, *J* = 17.2, 10.4, 8.1 Hz, 1H (minor)), 6.37 (d, *J* = 6.8 Hz, 1H (major)), 6.40 (d, *J* = 3.5 Hz, 1H (minor)), 7.20 (d, *J* = 3.4 Hz, 1H (major)), 7.25 (d, *J* = 3.4 Hz, 1H (minor)), 7.30-7.35 (m, 3H (major) and 3H (minor)), 7.41-7.46 (m, 2H (major) and 2H (minor)), 7.50-7.55 (m, 2H (major) and 2H (minor)), 7.59-7.65 (m, 1H (major) and 1H (minor)), 7.82-7.87 (m, 2H (major) and 2H (minor)). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.66, 16.69, 44.46, 44.58, 70.75, 71.52, 82.43, 82.48, 93.97, 94.08, 109.54, 109.82, 115.02, 115.06, 116.73, 122.77, 122.87, 122.95, 123.05, 126.77, 126.82, 128.39, 128.42, 129.49, 129.53, 131.18, 131.22, 134.15, 134.19, 138.90, 138.98, 139.58, 140.53. HRMS (ESI) calcd for $C_{23}H_{21}NNaO_3S$ (M^++Na) 414.1134, found 414.1134.



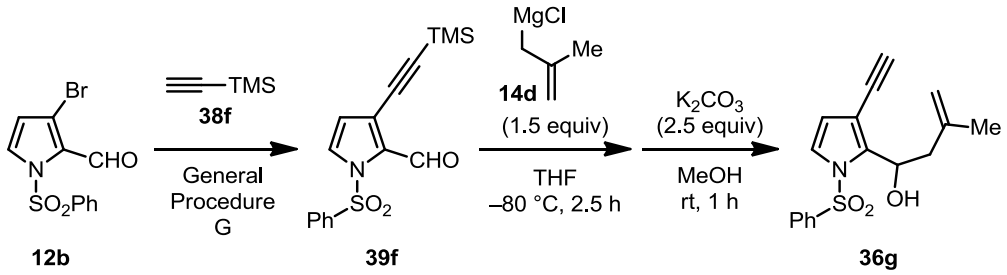
36e

1-(3-(5-Chloropent-1-yn-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)-2-methylbut-3-en-1-ol (36e); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.636 mmol) and **38d** were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39d** (200 mg, 0.596 mmol, 94% yield). The allylation step was then carried out according to the general procedure I; **39d** (200 mg, 0.596 mmol) in DMF (0.41 mL) was used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give a diastereomeric mixture of **36e** (0.56/0.44) (219 mg, 0.560 mmol, 92% yield). Data for the diastereomeric mixture; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3H (minor)), 1.19 (d, *J* = 6.9 Hz, 3H (major)), 2.00 (quintet, *J* = 6.6 Hz, 2H (minor)), 2.01 (quintet, *J* = 6.6 Hz, 2H (major)), 2.58 (t, *J* = 6.6 Hz, 2H (minor)), 2.58 (t, *J* = 6.8 Hz, 2H (major)), 2.65 (d, *J* = 8.0 Hz, 1H (minor)), 2.80 (d, *J* = 9.5 Hz, 1H (major)), 2.99 (sextet, *J* = 7.4 Hz, 1H (major)), 3.05 (sextet, *J* = 7.8 Hz, 1H (minor)), 3.67 (t, *J* = 6.3 Hz, 2H (minor)), 3.67 (t, *J* = 6.3 Hz, 2H (major)), 4.78 (ddd, *J* = 10.3, 1.7, 0.5 Hz, 1H (major)), 4.86 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 1H (major)), 4.89 (t, *J* = 8.9 Hz, 1H (major) and 1H (minor)), 5.15-5.21 (m, 2H (minor)), 5.46 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H (major)), 5.88 (ddd, *J* = 17.2, 10.4, 7.7 Hz, 1H (minor)), 6.24 (d, *J* = 3.4 Hz, 1H (major)) 6.27 (d, *J* = 3.4 Hz,.1H (minor)), 7.14 (d, *J* = 3.5 Hz, 1H (major)), 7.19 (d, *J* = 3.4 Hz, 1H (minor)), 7.49-7.54 (m, 2H (major) and 2H (minor)), 7.59-7.64 (m, 1H (major) and 1H (minor)), 7.78-7.84 (m, 2H (major) and 2H (minor)). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.51, 16.57, 16.94, 31.14, 43.57, 44.30, 44.42, 70.72, 71.46, 74.53, 74.63, 92.92, 93.11, 109.75, 110.08, 114.89, 115.19, 115.22, 116.53, 122.55, 122.83, 126.70, 126.76, 129.45, 129.50, 134.09, 134.13, 138.47, 138.99, 139.02, 139.20, 139.60, 140.56. HRMS (ESI) calcd for $C_{20}H_{22}ClNNaO_3S$ (M^++Na) 414.0901, found 414.0899.



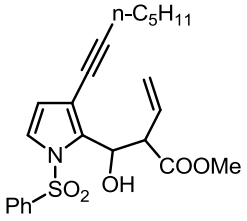
Methyl 2-((3-((4-ethoxyphenyl)ethynyl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)(hydroxy)methyl)but-3-enoate (36f); The coupling reaction was carried out according to the general procedure G; **12b** (264 mg, 0.840 mmol) and **38e** were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 3/1; Substantial amount of CH_2Cl_2 was used for loading the crude product on silica gel) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39e** (321 mg, 0.845 mmol, >99% yield). The allylation step was then carried out as follows; Diethylaluminum chloride (0.95 M solution in hexane, 1.96 mL, 1.86 mmol, 2.2 equiv) was added to a slurry of zinc dust (165.9 mg, 2.54 mmol, 3.0 equiv) and copper bromide (12.20 mg, 0.0850 mmol, 0.10 equiv) in THF (34 mL) with stirring at 0 °C. The resulting mixture was cooled to –20 °C. A solution of methyl 4-bromocrotonate **18** (3.03 mg, 1.69 mmol, 2.0 equiv) and aldehyde **39e** (321 mg, 0.845 mmol) in THF (8.5 mL) was added slowly to the mixture over 30 min at –20 °C. After stirring for 18 h at the same temperature, the reaction mixture was quenched by addition of pyridine (0.4 mL), well stirred, and poured into 1N hydrochloric acid. The mixture was warmed up to room temperature and filtered to remove remaining zinc dust. After extraction three times with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (CH_2Cl_2 ~ CH_2Cl_2/EtOAc = 100/1 ~ 50/1 ~ 30/1 ~ 15/1) to give a diastereomeric mixture of **36f** (0.64/0.36) with trace of inseparable by-products such as isomerized product or α-adduct, which are tentatively assigned by ^{1}H NMR (379 mg, 0.790 mmol, 93% yield; ca. 95% purity estimated by ^{1}H NMR analysis). Further purification was performed by recycling gel permeation chromatography before use for the next step. Data for the diastereomeric mixture; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (t, *J* = 6.9 Hz, 3H (major) and 3H (minor)), 3.19 (d, *J* = 8.3 Hz, 1H (major)), 3.20 (d, *J* = 8.3 Hz, 1H (minor)), 3.57 (s, 3H (major)), 3.76 (s, 3H (minor)), 4.03 (q, *J* = 7.1 Hz, 2H (major)), 4.03 (q, *J* = 6.9 Hz, 2H (minor)), 4.08 (t, *J* = 8.6 Hz, 1H (major)), 4.22 (t, *J* = 9.4 Hz, 1H (minor)), 4.91 (dd, *J* = 10.3, 1.1 Hz, 1H (minor)), 5.03 (dt, *J* = 16.8, 1.2 Hz, 1H (minor)), 5.24 (dt, *J* = 17.1, 0.9 Hz, 1H (major)), 5.32 (dd, *J* = 10.0, 1.2 Hz, 1H (major)), 5.46-5.62 (m, 1H (major) and 2H (minor)), 6.09 (ddd, *J* = 17.2, 10.1, 9.2 Hz, 1H (major)), 6.34 (d, *J* = 3.4 Hz, 1H (major)), 6.35 (d, *J* = 3.4 Hz, 1H (minor)), 6.82-6.87 (m, 2H (major) and 2H (minor)), 7.22 (d, *J* = 3.4 Hz, 1H (major)), 7.24 (d, *J* = 3.4 Hz, 1H

(minor)), 7.37-7.44 (m, 2H (major) and 2H (minor)), 7.52 (t, J = 8.3 Hz, 2H (major) and 2H (minor)), 7.60-7.64 (m, 1H (major) and 1H (minor)), 7.84-7.89 (m, 2H (major) and 2H (minor)). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.68, 51.96, 52.20, 55.85, 56.34, 63.48, 67.59, 67.84, 80.53, 94.22, 94.72, 110.86, 114.32, 114.51, 114.54, 114.60, 114.70, 114.85, 115.15, 119.48, 120.62, 123.06, 123.40, 126.84, 126.97, 129.49, 131.21, 132.38, 132.70, 132.73, 134.19, 134.22, 135.92, 136.40, 138.73, 138.80, 159.13, 159.17, 171.31, 172.73. HRMS (ESI) calcd for $C_{26}H_{25}NNaO_6S$ (M^++Na) 502.1295, found 502.1296.



1-(3-Ethynyl-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)-3-methylbut-3-en-1-ol (36g); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.637 mmol) and **38f** were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4.5/1) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39f** (205 mg, 0.617 mmol, 97% yield). To a stirred solution of the aldehyde **39f** (99.4 mg, 0.0300 mmol) in THF (6.0 mL, 0.05 M) was added allyl Grignard reagent **14d** (0.67 M solution in THF, 0.671 mL, 0.450 mmol, 1.5 equiv) at –80 °C and the reaction mixture was stirred for 2.5 h. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution at the same temperature, warmed to room temperature, and extracted with EtOAc three times. The organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give corresponding alcohol (113 mg, 0.290 mmol, 97% yield). To a solution of the alcohol (113 mg, 0.290 mmol) in degassed methanol (5.8 mL, 0.05 M) was added K_2CO_3 (100 mg, 0.726 mmol, 2.5 equiv). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C, diluted with water, warmed to room temperature, and extracted with CH_2Cl_2 three times. The organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) followed by further purification performed by recycling gel permeation chromatography to give **36g** (61.6 mg, 0.195 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 3H), 2.56 (dd, J = 13.9, 4.8 Hz, 1H), 2.68 (d, J = 7.9 Hz, 1H), 2.78 (ddd, J = 14.1, 9.2, 0.7 Hz, 1H), 3.24 (s, 1H), 4.76 (d, J = 0.9 Hz, 1H), 4.84 (t, J = 1.3 Hz, 1H), 5.31 (ddd, J = 9.3, 7.9, 4.9 Hz, 1H), 6.34 (d, J = 3.4 Hz, 1H), 7.20 (d, J = 3.4 Hz, 1H), 7.53 (t, J = 8.2 Hz, 2H), 7.64 (tt, J = 7.5, 1.2 Hz, 1H), 7.81-7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.08, 45.14, 65.10, 76.84, 82.41,

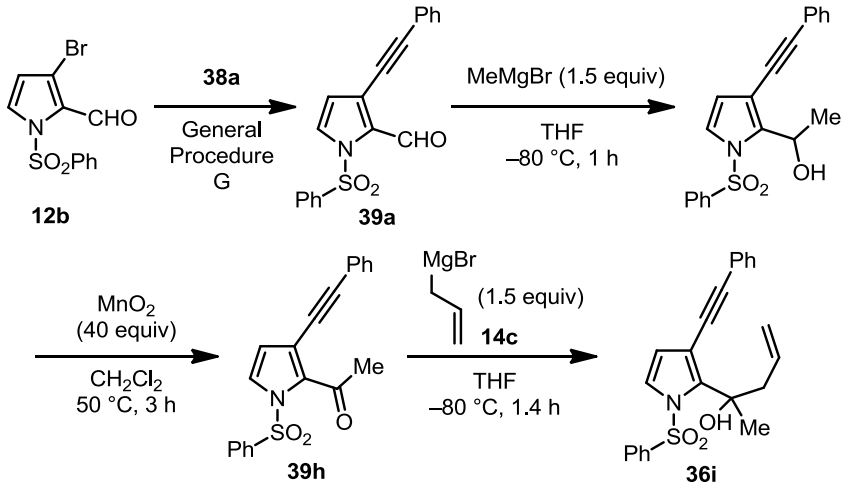
107.85, 113.89, 115.23, 122.47, 126.80, 129.59, 134.29, 138.80, 140.98, 141.69. HRMS (ESI) calcd for $C_{17}H_{17}NNaO_3S$ (M^++Na) 338.0821, found 338.0817.



36h

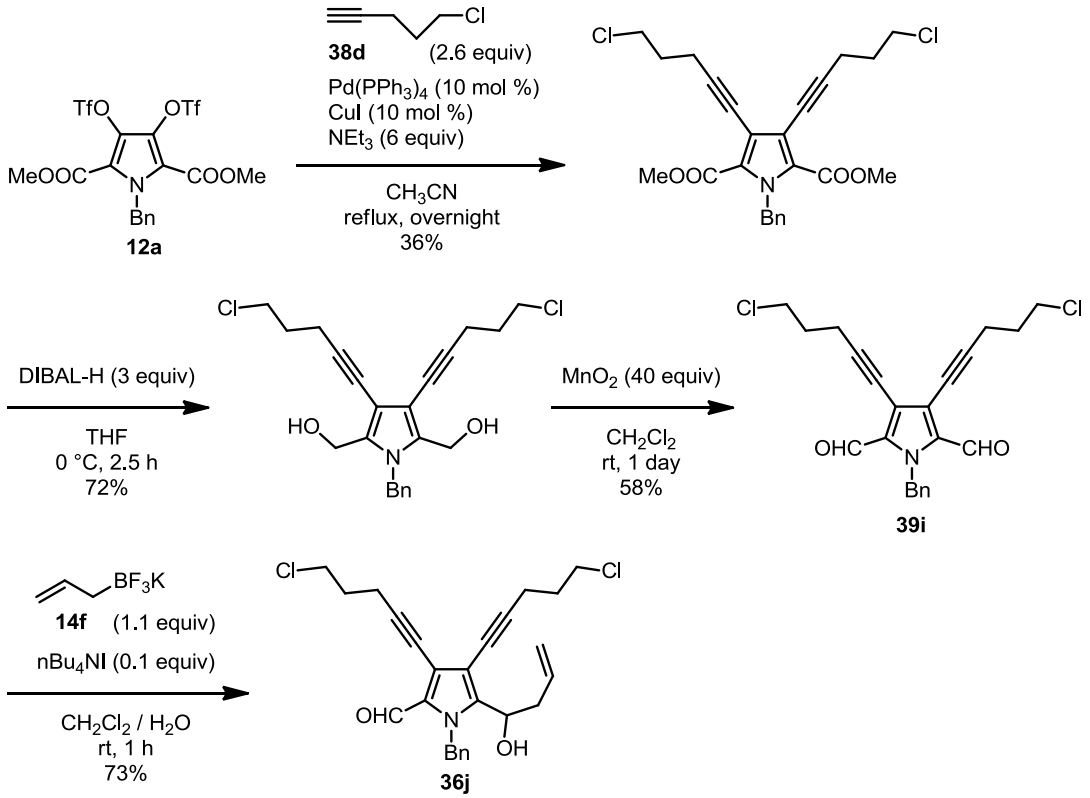
Methyl 2-((3-(hept-1-yn-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)(hydroxy)methyl)but-3-enoate (36h); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.636 mmol) and **38g** were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39g**. The allylation step was then carried out as follows; Diethylaluminum chloride (0.95 M solution in hexane, 1.48 mL, 1.40 mmol, 2.2 equiv) was added to a slurry of zinc dust (125.3 mg, 1.92 mmol, 3.0 equiv) and copper bromide (9.17 mg, 0.0639 mmol, 0.10 equiv) in THF (26 mL) with stirring at 0 °C. The resulting mixture was cooled to –20 °C. A solution of methyl 4-bromocrotonate **18** (228.4 mg, 1.28 mmol, 2.0 equiv) and aldehyde **39g** in THF (6.4 mL) was added slowly to the mixture over 55 min at –20 °C. After stirring for 14 h at the same temperature, the reaction mixture was quenched by addition of pyridine (0.3 mL), well stirred, and poured into 1N hydrochloric acid. The mixture was warmed up to room temperature and filtered to remove remaining zinc dust. After extraction three times with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified twice by silica-gel column chromatography (first: hexane/EtOAc = 2/1, second: hexane/EtOAc = 3/1) to give a diastereomeric mixture of **36h** (0.81/0.19) with trace of inseparable by-products (145 mg, 0.337 mmol, 53% yield). Further purification was performed by recycling gel permeation chromatography before use for the next step. Data for the diastereomeric mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.3 Hz, 3H (major) and 3H (minor)), 1.25-1.45 (m, 4H (major) and 4H (minor)), 1.53-1.64 (m, 2H (major) and 2H (minor)), 2.36 (t, *J* = 7.1 Hz, 2H (minor)), 2.39 (t, *J* = 6.4 Hz, 2H (major)), 3.12 (d, *J* = 8.5 Hz, 1H (major)), 3.20 (d, *J* = 8.7 Hz, 1H (minor)), 3.60 (s, 3H (minor)), 3.75 (s, 3H (major)), 4.00 (t, *J* = 8.7 Hz, 1H (minor)), 4.14 (t, *J* = 9.6 Hz, 1H (major)), 4.89 (dd, *J* = 10.3, 1.4 Hz, 1H (major)), 4.98 (dt, *J* = 17.4, 1.2 Hz, 1H (major)), 5.19 (d, *J* = 17.4 Hz, 1H (minor)), 5.30 (dd, *J* = 10.3, 1.4 Hz, 1H (minor)), 5.41-5.56 (m, 2H (major) and 1H (minor)), 6.06 (ddd, *J* = 17.4, 10.3, 9.4 Hz, 1H (minor)), 6.23 (d, *J* = 3.4 Hz, 1H (minor)), 6.25 (d, *J* = 3.4 Hz, 1H (major)), 7.16 (d, *J* = 3.4 Hz, 1H (minor)), 7.18 (d, *J* = 3.4 Hz, 1H (major)), 7.49-7.55 (m, 2H (major) and 2H (minor)), 7.62 (tt, *J* = 7.8, 1.2 Hz, 1H (major) and 1H (minor)), 7.82-7.87 (m, 2H (major) and 2H (minor)). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 13.89, 19.50, 22.15, 28.19, 31.10, 51.95, 52.13, 55.89, 56.40, 67.72, 67.80, 73.02, 95.84, 96.18, 111.20, 115.14, 115.45, 119.31, 120.48, 122.79, 123.10, 126.83, 126.95, 129.47, 131.26, 132.28, 134.15, 135.79, 138.89, 171.31, 172.73. HRMS (ESI) calcd for $C_{23}H_{27}NNaO_5S$ (M^++Na) 452.1502, found 452.1493.



2-(3-(Phenylethynyl)-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)pent-4-en-2-ol (36i); The coupling reaction was carried out in the same manner in the synthesis of **36a**. To a stirred solution of **39a** (107 mg, 0.318 mmol) in THF (9.62 mL, 0.033 M) was added methylmagnesium bromide (3.0 M solution in Et_2O, 0.156 mL, 0.476 mmol, 1.5 equiv) at –80°C and the reaction mixture was stirred for 3 h. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution at the same temperature, warmed to room temperature, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3/1) to give corresponding alcohol (96.2 mg, 0.274 mmol, 86% yield). MnO_2 (230 mg, 2.65 mmol, 40 equiv) was added to a solution of the alcohol (23.2 mg, 0.0660 mmol) in dichloromethane (1.3 mL, 0.05 M) at room temperature under air. The reaction mixture was stirred at 50 °C with a cold finger condenser for 3 h. The mixture was cooled to room temperature and then was filtered through Celite. The residual solid was washed thoroughly with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give corresponding ketone **39h** (20.5 mg, 0.0587 mmol, 89% yield). To a stirred solution of the ketone **39h** (24.2 mg, 0.0691 mmol) in THF (0.033 M) was added allyl Grignard reagent **14c** (0.52 M solution in Et_2O, 0.199 mL, 0.104 mmol, 1.5 equiv) at –80 °C and the reaction mixture was stirred for 1.4 h. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution at the same temperature, warmed to room temperature, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na_2SO_4. After

filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give **36i** (22.6 mg, 0.0654 mmol, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 3H), 2.53 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.21 (dd, *J* = 13.8, 6.5 Hz, 1H), 3.56 (s, 1H), 5.00-5.09 (m, 2H), 5.55 (dddd, *J* = 17.2, 10.1, 8.1, 6.6 Hz, 1H), 6.41 (d, *J* = 3.7 Hz, 1H), 7.29-7.35 (m, 3H), 7.41-7.46 (m, 3H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.59 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.72 (dd, *J* = 8.3, 0.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.83, 47.17, 73.09, 83.86, 94.09, 108.16, 114.40, 119.30, 123.23, 124.34, 126.43, 128.27, 128.38, 128.96, 131.00, 133.14, 133.46, 140.49, 143.36. HRMS (ESI) calcd for $C_{23}H_{21}NNaO_3S$ (M^++Na) 414.1134, found 414.1131.

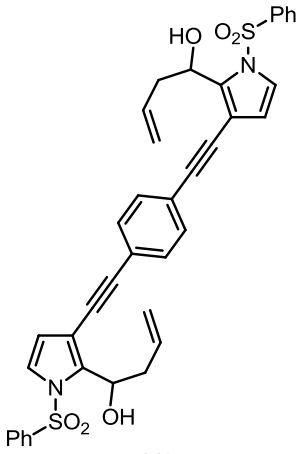


1-Benzyl-3,4-bis(5-chloropent-1-yn-1-yl)-5-(1-hydroxybut-3-en-1-yl)-1*H*-pyrrole-2-carbal dehyde (36j); To a mixture of $Pd(PPh_3)_4$ (73.1 mg, 0.0633 mmol, 10 mol %) and **12a** (360.2 mg, 0.633 mmol) in CH_3CN (6.3 mL, 0.1 M for **12a**) was added NEt_3 (529 μL, 3.80 mmol, 6.0 equiv). After being stirred for 10 min at room temperature, terminal acetylene **38** (169 mg, 1.64 mmol, 2.6 equiv) and CuI (12.1 mg, 0.0634 mmol, 10 mol %) were added to the mixture. The resulting mixture was refluxed for 13 h. The reaction mixture was diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc three times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give corresponding diyne (108 mg, 0.227 mmol, 36% yield).

To a solution of the diyne (108 mg, 0.227 mmol) in THF (4.5 mL, 0.05 M) at 0ºC, $LiAlH_4$ (25.8 mg, 0.680 mmol) in THF (0.68 mL, 1 M) was added dropwise. The mixture was stirred at the same temperature for 2.5 h. Then MeOH and a mixture of saturated aqueous solution of potassium sodium tartrate (Rochelle salt)-EtOAc 1:1 were added to the reaction mixture. After extraction with EtOAc three times, the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 1/1) to give corresponding alcohol (68.5 mg, 0.164 mmol, 72% yield).

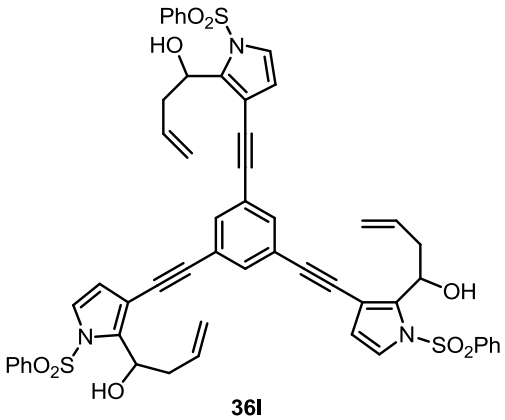
MnO_2 (582 mg, 6.69 mmol, 41 equiv) was added in one portion to a solution of the alcohol (68.5 mg, 0.164 mmol) in CH_2Cl_2 (3.3 mL, 0.05 M) at room temperature under air. The mixture was stirred at the same temperature for 24 h and then was filtered through Celite. The residual solid was washed thoroughly with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give corresponding aldehyde **39i** (39.7 mg, 0.0958 mmol, 58% yield).

To a solution of aldehyde **39i** (39.7 mg, 0.0958 mmol) and $^nBu_4NI$ (3.57 mg, 0.00967 mmol, 0.1 equiv) in CH_2Cl_2 (0.96 mL, 0.1 M for **39i**) were added **14f** (15.6 mg, 0.105 mmol, 1.1 equiv) and water (0.1 M for **39i**). The biphasic reaction mixture was vigorously stirred at room temperature for 1 h. The reaction mixture was then diluted with CH_2Cl_2 and extracted with CH_2Cl_2 three times. The organic layers were combined and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3.5/1 ~ 2.5/1 ~ EtOAc) to give **36j** (31.8 mg, 0.0698 mmol, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (quint, *J* = 6.6 Hz, 2H), 2.08 (quint, *J* = 6.6 Hz, 2H), 2.36-2.43 (m, 2H), 2.52-2.60 (m, 1H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.6 Hz, 2H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.76 (t, *J* = 6.3 Hz, 2H), 4.85 (dt, *J* = 8.3, 6.1 Hz, 1H), 5.01 (ddt, 17.2, 1.8, 1.4 Hz, 1H), 5.05-5.08 (m, 1H), 5.64 (ddt, *J* = 17.2, 10.3, 7.2 Hz, 1H), 5.70 (d, *J* = 16.3 Hz, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 2H), 7.21-7.30 (m, 3H), 9.74 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.03, 17.14, 31.17, 40.82, 43.49, 43.53, 49.01, 66.50, 77.12, 72.94, 94.32, 96.20, 108.19, 119.01, 122.69, 125.90, 127.53, 128.74, 130.75, 132.99, 137.08, 144.66, 178.91. HRMS (ESI) calcd for $C_{26}H_{28}Cl_2NO_2$ (M^++H) 456.1492, found 456.1488.



36k

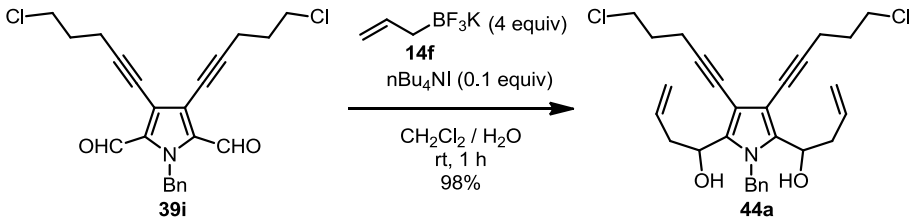
1,1'-(3,3'-(1,4-Phenylenebis(ethyne-2,1-diyl))bis(1-(phenylsulfonyl)-1*H*-pyrrole-3,2-diyl)) bis(but-3-en-1-ol) (36k); The coupling reaction was carried out according to the general procedure G; **12b** (200 mg, 0.637 mmol) and **38h** (0.7 equiv) were used; The crude product was purified by silica-gel column chromatography (CH_2Cl_2/EtOAc = 99/1 ~ 50/1) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39j** (117 mg, 0.197 mmol, 62% yield). The allylation step was carried out according to the general procedure H; **39j** (48.0 mg, 0.0811 mmol) and **14f** (3.5 equiv) were used; The crude product was purified by silica-gel column chromatography (CH_2Cl_2/EtOAc = 80/1 ~ 35/1 ~ 10/1) to give a diastereomeric mixture of **36k** (47.5 mg, 0.0702 mmol, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73-2.88 (m, 6H), 5.02-5.05 (m, 2H), 5.07 (dd, *J* = 17.2, 1.7 Hz, 2H), 5.24 (t, *J* = 6.9 Hz, 2H), 5.73 (ddt, *J* = 17.2, 10.1, 6.9 Hz, 2H), 6.39 (d, *J* = 3.4 Hz, 2H), 7.25 (d, *J* = 3.4 Hz, 2H), 7.38 (s, 4H), 7.54 (t, *J* = 8.3 Hz, 4H), 7.64 (tt, *J* = 7.5, 1.1 Hz, 2H), 7.84 (dd, *J* = 8.3, 1.1 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.19, 66.75, 84.34, 93.60, 108.98, 114.98, 118.18, 122.84, 126.78, 129.58, 131.12, 133.74, 134.31, 138.76, 139.30. HRMS (ESI) calcd for $C_{38}H_{32}N_2NaO_6S_2$ (M^++Na) 699.1594, found 699.1585.



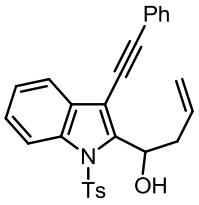
36l

1,1',1''-(3,3',3''-(Benzene-1,3,5-triyltris(ethyne-2,1-diyl))tris(1-(phenylsulfonyl)-1*H*-pyrro

le-3,2-diyl))tris(but-3-en-1-ol) (36l); The coupling reaction was carried out according to the general procedure G; **12b** (400 mg, 1.27 mmol, 2.9 equiv) and **38i** were used and the reaction was performed for 23 h; A mixture of EtOAc, Et_2O, and CH_2Cl_2 was used for the extraction; The crude product was purified three times by silica-gel column chromatography (first: $CHCl_3$ ~ $CHCl_3$/EtOAc = 100/1, second: $CHCl_3$, third: CH_2Cl_2 ~ CH_2Cl_2/EtOAc = 100/1) to give corresponding 3-ethynylpyrrole-2-carbaldehyde **39k** (164 mg, 0.193 mmol, 44% yield). The allylation step was carried out according to the general procedure H; **39k** (164 mg, 0.193 mmol), **14f** (5.5 equiv), and $^{n}Bu_4NI$ (0.3 equiv) were used; The crude product was purified by silica-gel column chromatography (CH_2Cl_2/EtOAc = 20/1) to give a diastereomeric mixture of **36l** (130 mg, 0.133 mmol, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72-2.86 (m, 9H), 5.00-5.04 (m, 3H), 5.06 (dq, *J* = 17.2, 1.7 Hz, 3H), 5.23 (q, *J* = 6.6 Hz, 3H), 5.71 (ddt, *J* = 17.2, 10.3, 7.2 Hz, 3H), 6.38 (d, *J* = 3.4 Hz, 3H), 7.25 (d, *J* = 3.5 Hz, 3H), 7.42 (s, 3H), 7.53 (tt, *J* = 7.4, 1.7 Hz, 6H), 7.64 (tt, *J* =7.4, 1.1 Hz, 3H), 7.81-7.85 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.16, 66.71, 83.87, 92.11, 108.71, 115.02, 118.22, 122.91, 123.87, 126.80, 129.59, 133.22, 133.64, 134.32, 138.81, 139.57. HRMS (ESI) calcd for $C_{54}H_{45}N_3NaO_9S_3$ (M^++Na) 998.2210, found 998.2228.



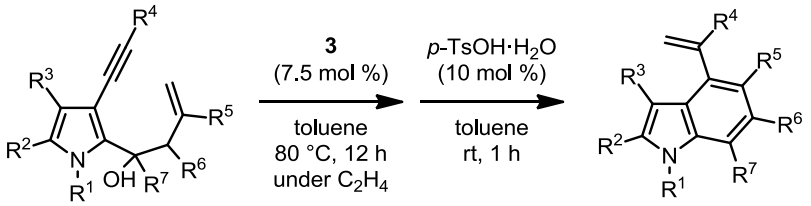
1,1'-(1-Benzyl-3,4-bis(5-chloropent-1-yn-1-yl)-1*H*-pyrrole-2,5-diyl)bis(but-3-en-1-ol) (44a); The allylation step was carried out according to the general procedure H; **39j** (28.9 mg, 0.0698 mmol), CH_2Cl_2 (0.70 mL, 0.1 M for **39i**), H_2O (0.70 mL, 0.1 M for **39i**), and **14f** (41.1 mg, 0.278 mmol, 4.0 equiv) were used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 1.5/1) to give a diastereomeric mixture of **44a** (0.50/0.50) (34.1 mg, 0.0684 mmol, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (quint, *J* = 6.3 Hz, 4H (dl) and 4H (meso)), 2.20-2.23 (br m, 2H (dl) and 2H (meso)), 2.45-2.53 (m, 2H (dl) and 2H (meso)), 2.60-2.66 (m, 2H (dl) and 2H (meso)), 2.66 (t, *J* = 6.9 Hz, 4H (dl) and 4H (meso)), 3.77 (t, *J* = 6.3 Hz, 4H (dl) and 4H (meso)), 4.69-4.76 (m, 2H (dl) amd 2H (meso)), 4.99-5.06 (m, 4H (dl) and 4H (meso)), 5.29 (d, *J* = 17.2 Hz, 1H (dl)), 5.35 (s, 2H (meso)), 5.42 (d, *J* = 17.5 Hz, 1H (dl)), 5.64-5.73 (m, 2H (dl) and 2H (meso)), 6.89-6.93 (m, 2H (dl) and 2H (meso)), 7.22-7.32 (m, 3H (dl) and 3H (meso)). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.13, 31.45, 40.95, 41.12, 43.68, 47.95, 48.00, 66.87, 66.89, 74.36, 74.38, 92.74, 105.84, 105.90, 118.17, 118.22, 125.42, 125.44, 127.52, 128.84, 134.06, 136.47, 137.68. HRMS (ESI) calcd for $C_{29}H_{32}Cl_2NO_2$ (M^-–H) 496.1816, found 496.1830.



46a

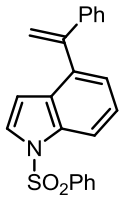
1-(3-(Phenylethynyl)-1-tosyl-1*H*-indol-2-yl)but-3-en-1-ol (46a); The coupling reaction was carried out according to the general procedure G; **47a** (131 mg, 0.307 mmol) and **38a** were used; The crude product was purified by silica-gel column chromatography (hexane/toluene = 1/4 ~ 1/6) to give corresponding 3-ethynylindole-2-carbaldehyde **48a** (111 mg, 0.277 mmol, 90% yield). The allylation step was carried out according to the general procedure H; **48a** (111 mg, 0.277 mmol) was used; The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 4/1) to give **46a** (110 mg, 0.249 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.93-3.06 (m, 2H), 3.63 (d, *J* = 10.3 Hz, 1H), 5.08-5.12 (m, 1H), 5.19 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.64 (ddd, *J* = 10.3, 7.4, 6.3 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.0, 6.8 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.28-7.40 (m, 5H), 7.52-7.57 (m, 2H), 7.64-7.68 (m, 1H), 7.74 (dt, *J* = 8.6, 1.8 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.55, 41.85, 68.35, 80.26, 97.82, 106.42, 114.98, 118.27, 120.20, 122.77, 124.26, 125.86, 126.59, 128.45, 128.65, 129.69, 129.94, 131.43, 133.77, 135.01, 136.06, 144.85, 145.34. HRMS (ESI) calcd for $C_{27}H_{23}NNaO_3S$ (M^++Na) 464.1291, found 464.1284.

Procedures for the Preparation of 4-Vinylindoles 37.



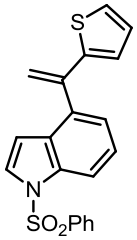
36 **37**

General procedure J: RCEM/dehydration. To a solution of **36** in toluene (0.01 M) was added catalyst **3** (7.5 mol %) in one portion under nitrogen and then the system was evacuated carefully and filled with ethylene gas in three cycles. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the reaction mixture was treated with *p*-toluenesulfonic acid (10 mol %) and stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and purified by PTLC on silica gel to give 4-vinylindoles **37**.



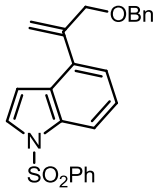
37a

1-(Phenylsulfonyl)-4-(1-phenylvinyl)-1*H*-indole (37a); The reaction was carried out according to the general procedure J; **36a** (40.5 mg, 0.107 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 3.5/1) to give **37a** (38.1 mg, 0.106 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (d, *J* = 1.1 Hz, 1H), 5.68 (d, *J* = 1.4 Hz, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 7.19 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.22-7.32 (m, 6H), 7.40-7.46 (m, 3H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.86-7.91 (m, 2H), 7.97 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.85, 112.83, 116.09, 123.97, 124.51, 125.85, 126.80, 127.49, 127.82, 128.26, 129.24, 129.62, 133.79, 134.89, 135.19, 138.24, 141.03, 147.95. HRMS (ESI) calcd for $C_{22}H_{17}NNaO_2S$ (M^++Na) 382.0872, found 382.0870.



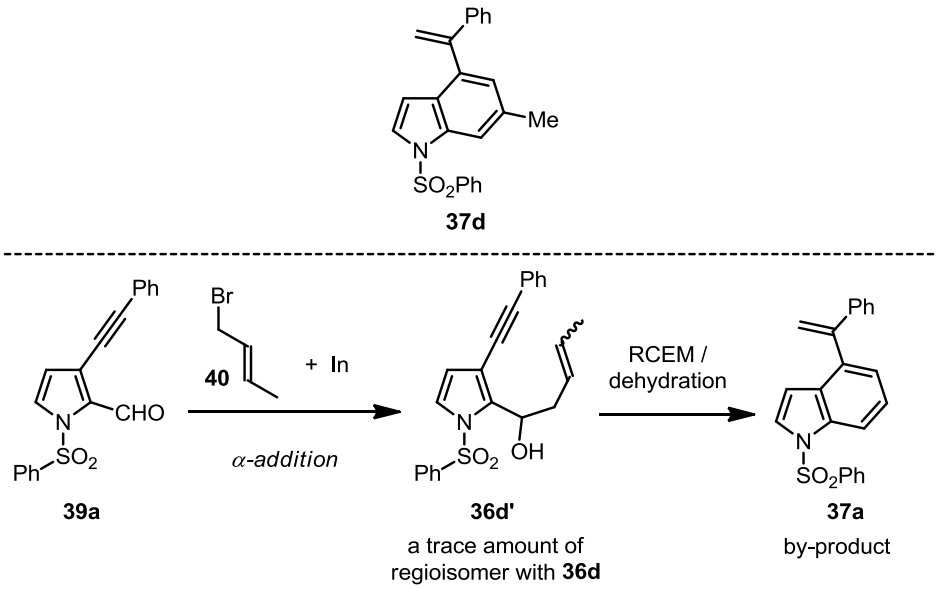
37b

1-(Phenylsulfonyl)-4-(1-(thiophen-2-yl)vinyl)-1*H*-indole (37b); The reaction was carried out according to the general procedure J; **36b** (38.4 mg, 0.100 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 4/1) to give **37b** (36.1 mg, 0.987 mmol, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.75 (d, *J* = 0.5 Hz, 1H), 6.49 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.69 (dd, *J* = 3.7, 1.1 Hz, 1H), 6.89 (dd, *J* = 5.2, 3.7 Hz, 1H), 7.20 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.43-7.48 (m, 2H), 7.51 (d, *J* = 3.7 Hz, 1H), 7.55 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.88-7.92 (m, 2H), 7.99 (dt, *J* = 8.3, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.71, 113.09, 114.77, 123.66, 124.45, 125.09, 126.01, 126.49, 126.82, 127.34, 129.29, 129.62, 133.84, 134.43, 134.88, 138.25, 141.09, 144.53. HRMS (ESI) calcd for $C_{20}H_{15}NNaO_2S_2$ (M^++Na) 388.0436, found 388.0430.

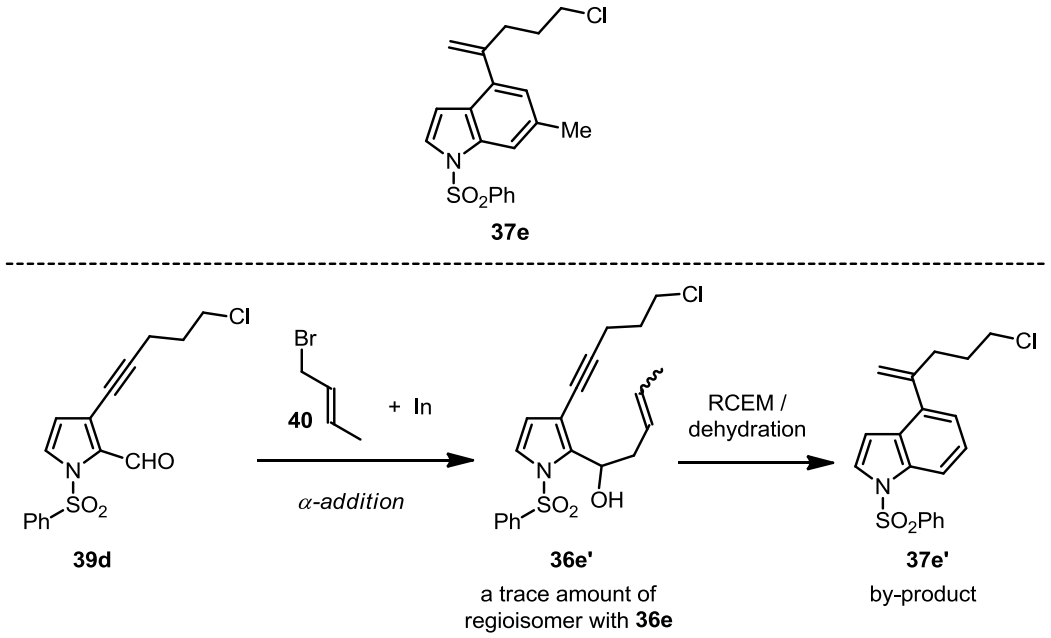


37c

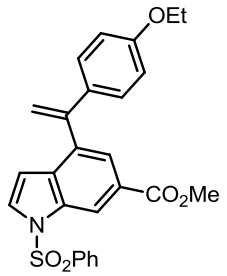
4-(3-(Benzyloxy)prop-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-indole (37c); The reaction was carried out according to the general procedure J; **36c** (36.8 mg, 0.873 mmol) was used and the crude product was purified twice by PTLC (first: hexane/EtOAc = 3/1, second: toluene) to give **37c** (26.1 mg, 0.0647 mmol, 74% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (t, *J* = 1.2 Hz, 2H), 4.55 (s, 2H), 5.40-5.42 (m, 1H), 5.60 (q, *J* = 1.4 Hz, 1H), 6.81 (dd, *J* = 3.8, 0.9 Hz, 1H), 7.17 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.24-7.32 (m, 6H), 7.44 (tt, *J* = 8.0, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.58 (d, *J* = 3.8 Hz, 1H), 7.88-7.91 (m, 2H), 7.93 (dt, *J* = 8.3, 0.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.28, 72.59, 108.62, 112.78, 116.93, 122.00, 124.56, 126.28, 126.94, 127.75, 127.83, 128.47, 129.09, 129.41, 133.58, 133.97, 135.17, 138.12, 138.33, 143.70. HRMS (ESI) calcd for $C_{24}H_{20}NO_3S$ (M^-–H) 402.1169, found 402.1180.



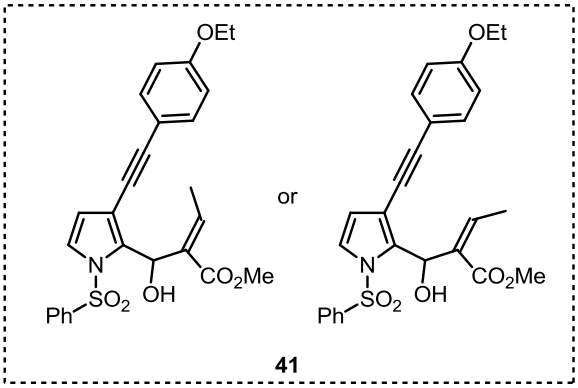
6-Methyl-1-(phenylsulfonyl)-4-(1-phenylvinyl)-1*H*-indole (37d); The reaction was carried out according to the general procedure J; **36d** (38.6 mg, 0.0985 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 4/1) to give a mixture of **37d** (31.4 mg, 0.0840 mmol, 85% yield) and **37a** (0.81 mg, 0.00226 mmol, 2% yield). The by-product **37a** which was assigned by ^{1}H NMR might be derived from trace of impurity **36d'** with **36d**. The impurity **36d'** might be obtained by α-addition of allylic indium reagent to aldehyde **39a** during the preparation of **36d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 5.37 (d, *J* = 1.4 Hz, 1H), 5.66 (d, *J* = 1.4 Hz, 1H), 6.21 (d, *J* = 3.9 Hz, 1H), 7.03 (s, 1H), 7.23-7.30 (m, 5H), 7.37 (d, *J* = 3.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.54 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.79 (s, 1H), 7.85-7.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.87, 108.80, 112.99, 115.90, 125.25, 125.48, 126.76, 127.43, 127.52, 127.79, 128.25, 129.24, 133.72, 134.65, 134.74, 135.34, 138.42, 141.11, 148.05. HRMS (ESI) calcd for $C_{23}H_{19}NNaO_2S$ (M^++Na) 396.1029, found 396.1028.



4-(5-Chloropent-1-en-2-yl)-6-methyl-1-(phenylsulfonyl)-1*H*-indole (37e); The reaction was carried out according to the general procedure J; **36e** (38.1 mg, 0.0971 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 3/1) to give a mixture of **37e** (29.9 mg, 0.0800 mmol, 82% yield) and 4-(5-chloropent-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-indole **37e'** (0.98 mg, 0.00273 mmol, 3% yield). The by-product **37e'** which was assigned by ^{1}H NMR and analogy of the case of **37d** might be derived from trace of impurity **36e'** with **36e**. The impurity **36e'** might be obtained by α-addition of allylic indium reagent to aldehyde **39d** during the preparation of **36e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (quint, J = 7.1 Hz, 2H), 2.46 (s, 3H), 2.66 (t, J = 7.1 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 5.17 (d, J = 1.7 Hz, 1H), 5.29 (d, J = 1.7 Hz, 1H), 6.71 (dd, J = 3.7, 0.6 Hz, 1H), 6.94 (s, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.50 (d, J = 3.7 Hz, 1H), 7.54 (tt, J = 7.8, 1.1 Hz, 1H), 7.73 (s, 1H), 7.89 (dd, J = 8.3, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.93, 30.70, 33.86, 44.38, 108.31, 112.53, 115.76, 123.11, 125.47, 126.60, 126.76, 129.27, 133.76, 134.58, 134.95, 135.42, 138.31, 145.88. HRMS (ESI) calcd for $C_{20}H_{20}ClNNaO_2S$ (M^++Na) 396.0795, found 396.0793.

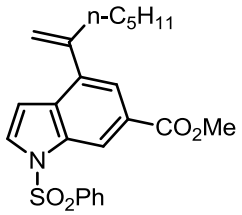


37f



41

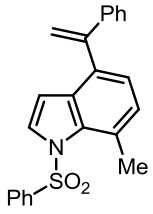
Methyl 4-(1-(4-ethoxyphenyl)vinyl)-1-(phenylsulfonyl)-1*H*-indole-6-carboxylate (37f); The reaction was carried out according to the general procedure J; The reaction was performed with a mixture of **36f** and its regio isomer **41** (1/0.014) (**36f**: 71.4 mg, 0.149 mmol, dr = 0.65/0.35); The crude product was purified by PTLC (CH_2Cl_2) to give **37f** (45.9 mg, 0.0994 mmol, 67% yield). mp 141-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, *J* = 6.9 Hz, 3H), 3.95 (s, 3H), 4.02 (q, *J* = 6.9 Hz, 2H), 5.31 (d, *J* = 1.2 Hz, 1H), 5.64 (d, *J* = 1.2 Hz, 1H), 6.29 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.79 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.15 (dt, *J* = 8.9, 2.3 Hz, 2H), 7.47 (t, *J* = 8.3 Hz, 2H), 7.54-7.59 (m, 2H), 7.91-7.94 (m, 3H), 8.67 (t, *J* = 1.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.78, 52.26, 63.41, 108.89, 114.23, 114.37, 114.98, 124.81, 126.57, 126.90, 128.57, 128.59, 129.42, 132.93, 133.33, 134.08, 134.42, 135.47, 138.02, 146.73, 158.89, 167.16. HRMS (ESI) calcd for $C_{26}H_{23}NNaO_5S$ (M^++Na) 484.1189, found 484.1188.



37h

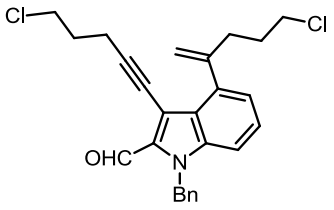
Methyl 4-(hept-1-en-2-yl)-1-(phenylsulfonyl)-1*H*-indole-6-carboxylate (37h); The reaction was carried out according to the general procedure J; **36j** (31.2 mg, 0.0726 mmol) was used. The dehydration step was followed by additional stirring for 1 h at 80 °C. The crude product was purified by PTLC (hexane/EtOAc = 2.5/1) to give **37h** with trace of inseparable by-products (15.7 mg, ca. 0.07 mmol, ca. 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78-0.84 (m, 3H), 1.20-1.39 (m, 6H), 2.50 (t, *J* = 7.3 Hz, 2H), 3.96 (s, 3H), 5.12 (d, *J* = 1.6 Hz, 1H), 5.28 (d, *J* = 1.6 Hz, 1H), 6.81, (dd, *J* = 3.7, 0.7 Hz, 1H), 7.45-7.50 (m, 2H), 7.57 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.70 (d, *J* = 3.7 Hz, 1H), 7.81 (d, *J* = 1.4 1H), 7.91-7.96 (m, 2H), 8.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.97, 22.36, 27.67, 31.35, 36.77, 52.27, 108.61, 113.71, 115.30, 122.61, 126.37, 126.90, 128.71, 129.42, 132.66, 134.07,

134.54, 136.39, 138.06, 147.17, 167.26. HRMS (ESI) calcd for $C_{23}H_{25}NNaO_4S$ (M^++Na) 434.1397, found 434.1393.



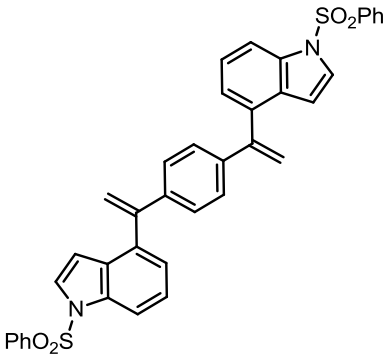
37i

7-Methyl-1-(phenylsulfonyl)-4-(1-phenylvinyl)-1*H*-indole (37i); The reaction was carried out according to the general procedure J; **36i** (27.5 mg, 0.0702 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 4/1) to give **37i** (25.3 mg, 0.0678 mmol, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (s, 3H), 5.37 (d, *J* = 1.4 Hz, 1H), 5.72 (d, *J* = 1.1 Hz, 1H), 6.34 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.23-7.30 (m, 5H), 7.42-7.47 (m, 2H), 7.56 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.64 (d, *J* = 3.7 Hz, 1H), 7.67 (dd, *J* = 8.6, 1.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.66, 108.75, 115.82, 124.36, 124.61, 126.39, 127.35, 127.78, 128.13, 128.27, 129.22, 129.42, 131.78, 133.00, 133.47, 134.92, 139.84, 141.13, 147.82. HRMS (ESI) calcd for $C_{23}H_{20}NO_2S$ (M^++H) 374.1209, found 374.1208.



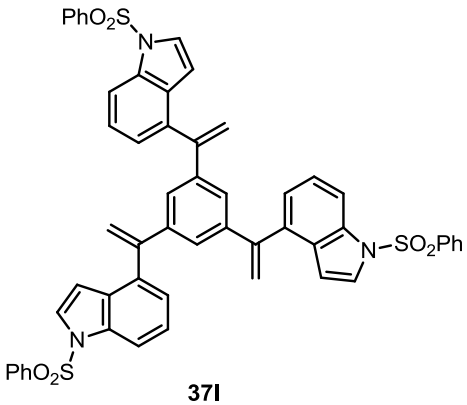
37j

1-Benzyl-4-(5-chloropent-1-en-2-yl)-3-(5-chloropent-1-yn-1-yl)-1*H*-indole-2-carbaldehyde (37j); The reaction was carried out according to the general procedure J; **36j** (31.8 mg, 0.0697 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 4/1) to give **37j** (4.0 mg, 0.00912 mmol, 13% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84-1.91 (m, 2H), 2.10 (quint, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.73 (t, *J* = 6.3 Hz, 2H), 5.15 (d, *J* = 1.7 Hz, 1H), 5.36 (q, *J* = 1.5 Hz, 1H), 5.82 (s, 2H), 6.95 (dd, *J* = 6.6, 1.5 Hz, 1H), 7.09-7.13 (m, 2H), 7.20-7.34 (m, 5H), 10.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.32, 30.76, 31.27, 35.64, 43.74, 44.57, 47.95, 73.43, 97.28, 110.16, 112.54, 115.99, 121.81, 124.24, 126.66, 127.39, 127.48, 128.65, 135.83, 137.14, 138.84, 139.57, 146.01, 182.62. HRMS (ESI) calcd for $C_{26}H_{26}Cl_2NO$ (M^++H) 438.1386, found 438.1384.



37k

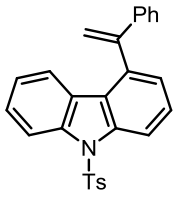
1,4-Bis(1-(1-(phenylsulfonyl)-1*H*-indol-4-yl)vinyl)benzene (37k); The reaction was carried out according to the general procedure J; **36k** (24.9 mg, 0.0368 mmol) and **3** (15 mol %) were used and the crude product was purified twice by PTLC (first: hexane/EtOAc = 2/1, second: CH_2Cl_2/EtOAc = 100/1) to give **37k** (22.1 mg, 0.0346 mmol, 94% yield). mp 219-222 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (d, *J* = 1.1 Hz, 2H), 5.72 (d, *J* = 1.1 Hz, 2H), 6.31 (dd, *J* = 3.7, 0.6 Hz, 2H), 7.18 (s, 4H), 7.19 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.31 (t, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 4H), 7.47 (d, *J* = 3.7 Hz, 2H), 7.55 (tt, *J* = 7.4, 1.2 Hz, 2H), 7.88-7.92 (m, 4H), 7.97 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.80, 112.85, 116.15, 123.95, 124.53, 125.85, 126.83, 127.40, 129.29, 129.58, 133.86, 134.84, 134.99, 138.18, 140.41, 147.38. HRMS (ESI) calcd for $C_{38}H_{28}N_2NaO_4S_2$ (M^++Na) 663.1383, found 663.1378.



37l

1,3,5-Tris(1-(1-(phenylsulfonyl)-1*H*-indol-4-yl)vinyl)benzene (37l); The reaction was carried out according to the general procedure J; **36l** (39.9 mg, 0.409 mmol) and **3** (15 mol %) were used and the crude product was purified by PTLC (hexane/EtOAc = 1.5/1) to give **37l** (29.5 mg, 0.0319 mmol, 78% yield). mp 101-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (d, *J* = 0.9 Hz, 3H), 5.39 (d, *J* = 0.9 Hz, 3H), 6.23 (dd, *J* = 3.6, 0.7 Hz, 3H), 7.05 (s, 3H), 7.10 (dd, *J* = 7.5, 0.7 Hz, 3H), 7.21 (t, *J* = 8.2 Hz, 3H), 7.40 (t, *J* = 8.2 Hz, 6H), 7.47 (d, *J* = 3.8 Hz, 3H), 7.51 (tt, *J* = 7.3, 1.2 Hz, 3H), 7.84-7.88 (m, 6H), 7.92 (d, *J* = 8.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.96, 113.04,

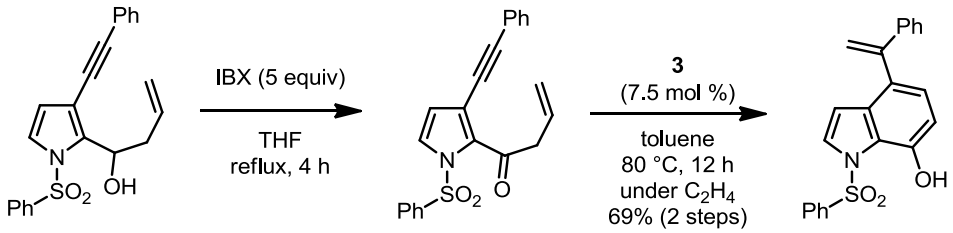
116.53, 123.90, 124.53, 125.82, 126.55, 126.73, 129.27, 129.34, 133.83, 134.64, 134.95, 138.17, 141.39, 147.58. HRMS (APCI) calcd for $C_{54}H_{40}N_3O_6S_3$ (M^++H) 922.2074, found 922.2083.



45a

4-(1-Phenylvinyl)-9-tosyl-9*H*-carbazole (45a); The reaction was carried out according to the general procedure J; **46a** (37.0 mg, 0.0837 mmol) was used and the crude product was purified by PTLC (hexane/EtOAc = 4/1) to give **45a** (35.3 mg, 0.0833 mmol, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 5.37 (d, *J* = 0.8 Hz, 1H), 6.02 (d, *J* = 0.8 Hz, 1H), 7.06-7.11 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.19-7.23 (m, 4H), 7.26-7.30 (m, 2H), 7.36 (ddd, *J* = 8.6, 7.2, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.69-7.74 (m, 3H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.38 (dd, *J* = 8.3, 0.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.51, 114.14, 114.65, 115.37, 122.89, 123.52, 124.05, 125.76, 125.94, 126.31, 126.54, 126.91, 127.99, 128.49, 129.64, 135.02, 136.70, 138.47, 138.55, 138.97, 144.84, 147.35. HRMS (ESI) calcd for $C_{27}H_{22}NO_2S$ (M^++H) 424.1366, found 424.1360.

Procedure for the Preparation of 1-(Phenylsulfonyl)-4-(1-phenylvinyl)-1*H*-indol-7-ol (49a).



36a **50a** **49a**

1-(Phenylsulfonyl)-4-(1-phenylvinyl)-1*H*-indol-7-ol (49a); IBX (155 mg, 0.554 mmol, 5.0 equiv) was added to a solution of **36a** (41.8 mg, 0.111 mmol) in THF (2.2 mL, 0.05 M). The resulting suspension was refluxed for 4 h. The mixture was cooled to room temperature and then was filtered through Celite. The residual solid was washed thoroughly with EtOAc and the filtrate was concentrated under reduced pressure to give **50a**. The product was used for the next step without further purification. To a solution of **50a** in toluene (0.01 M) was added catalyst **3** (7.5 mol %) in one portion under nitrogen and then the system was evacuated carefully and filled with ethylene gas in three cycles. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by PTLC on silica gel

(hexane/toluene = 1/3) to give **49a** (28.9 mg, 0.0769 mmol, 69% yield; 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (d, *J* = 1.5 Hz, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 6.29 (d, *J* = 3.7 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.18-7.29 (m, 5H), 7.32 (d, *J* = 3.7 Hz, 1H), 7.46 (tt, *J* = 7.4, 1.7 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.78-7.82 (m, 2H), 8.75 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.75, 113.55, 115.34, 122.81, 126.70, 126.89, 127.17, 127.43, 127.49, 127.77, 128.24, 129.47, 133.17, 134.12, 136.97, 141.36, 144.15, 147.56. HRMS (ESI) calcd for $C_{22}H_{16}NO_3S$ (M^-–H) 374.0856, found 374.0865.

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