

Asymmetric Friedel–Crafts Alkylation of Indoles: The Control of Enantio- and Regioselectivity

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Received 14 December 2009

Abstract: The asymmetric Friedel–Crafts reaction of indoles is a synthetic methodology that enables direct access to the enantiopure indole derivatives. In this review, work mainly carried out by You and his co-workers on the regio- and enantioselective synthesis of indole derivatives will be discussed. Chiral Brønsted acids or iridium complexes promote highly enantioselective Friedel–Crafts reactions of indoles and 4,7-dihydroindoles starting with various electrophilic reagents, such as imines, *N*-tosyl-substituted amines, β,γ -unsaturated α -keto esters, nitro-substituted olefins, aldehydes, and allyl carbonates. These methodologies can be used to readily prepare diverse enantioenriched indoles, such as indol-3-ylmethanamines, indol-2-ylmethanamines, unsymmetrical arylbis(indol-3-yl)methanes, 9-indol-3-ylfluorenes, tetrahydropyrano[3,4-*b*]indoles, tetrahydro- γ -carbolines, and tetrahydro- β -carbolines.

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Key words: chiral Brønsted acids, enantioselectivity, Friedel–Crafts reactions, indoles, organocatalysis

1 Introduction

Indoles are among the most widely distributed heterocyclic compounds in nature and they serve as the structural core of numerous biologically active natural products and

pharmaceuticals.¹ In addition to tryptophan, an essential amino acid, there are many enantiopure natural and synthetic indole derivatives that display interesting biological activities. Representative examples are yohimbine, tadalafil (Cialis), and reserpine which all have interesting biological properties (Figure 1). Therefore, the synthesis of enantiomerically pure indole derivatives represents an extremely important goal for synthetic organic chemists.

The development of synthetic methods to prepare enantiopure indoles which rely on asymmetric catalysis has been one of my main research goals since starting my academic career in April 2006. Among the existing methods for this purpose, asymmetric Friedel–Crafts reactions of indoles with different alkylating reagents are the most important (Scheme 1).^{2,3} However, the success of Friedel–Crafts alkylations is limited by the fact that the alkylation products normally display higher reactivity than the starting compounds. This phenomenon causes the production of multi-alkylated side products. Yet, indoles are good substrates in Friedel–Crafts reactions because they display dramatically different reactivities at different sites of the indole ring.

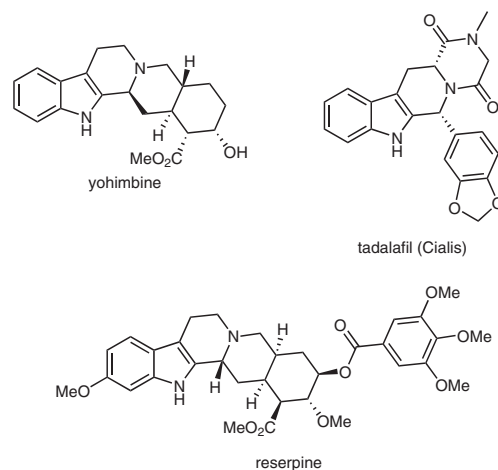
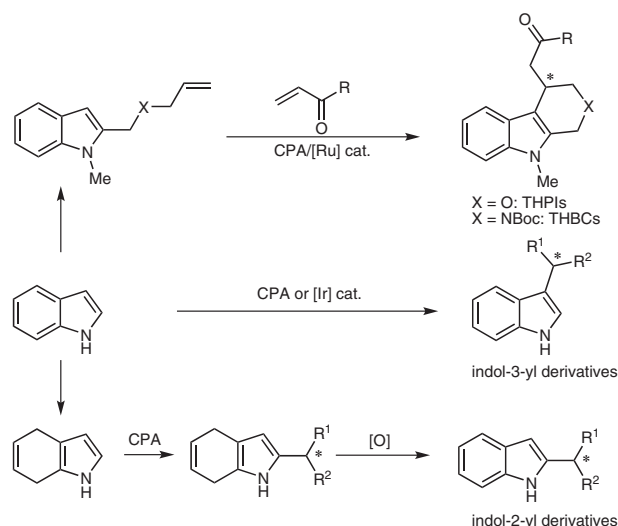


Figure 1 Selected chiral indole derivatives

The development of asymmetric Friedel–Crafts alkylation reactions of indoles has rapidly progressed in recent years, but several important limitations to these processes still exist. Firstly, the electrophilic partners that are suitable for highly enantioselective Friedel–Crafts alkylation reactions are limited. For instance, until 2006, routes for the



Scheme 1 Asymmetric Friedel–Crafts reactions of indoles

asymmetric Friedel–Crafts reactions of imines were restricted to a diastereoselective approach starting with enantiopure imines.⁴ Only one report by Johannsen existed describing an asymmetric catalytic version of this reaction utilizing a chiral Tol-BINAP–copper complex.⁵ The chiral ligand–copper salt complex acts as a Lewis acid to activate the electrophilic partners in these processes. The slow progress made in this area was mainly a consequence of the lack of new catalysts and activation modes. However, more recently, the iminium catalysis strategy developed by MacMillan has greatly expanded the repertoire of substrates that can be used in asymmetric Friedel–Crafts reactions, as exemplified by the highly enantioselective processes that take place with α,β -unsaturated aldehydes.⁶

1,1'-Bi-2-naphthol-derived chiral phosphoric acids (CPAs) have been used for a long period as chiral resolution agents and ligands for transition metals. However, these substances have gained greater attention in asymmetric catalysis following the simultaneous reports by Terada and Akiyama and their co-workers describing the applications of such compounds as chiral Brønsted acids in organocatalytic reactions.⁷ Subsequently, Nakashima and Yamamoto introduced *N*-triflyl-containing phosphoramides (CPAmides), a family of stronger acids that broaden the substrate scope for Friedel–Crafts reactions.⁸ Inspired by the high efficiency, broad activation scope, and great functional group compatibility of CPAs and guided by the goal of expanding the scope of electrophilic partners, we have used these substances as Brønsted acid catalysts for asymmetric Friedel–Crafts reactions.

Secondly, most of the processes uncovered for carrying out enantioselective Friedel–Crafts reactions of indoles lead to the formation of 3-substituted indole derivatives. This outcome is a result of the high nucleophilic reactivity at the 3-position of this heterocycle. Although this feature contributes to the high regioselectivity of indole alkylations, it stands as a limitation preventing access to 2-substituted indole derivatives⁹ that are also widely distributed in nature and have interesting biological activities. Although some indirect methods exist to synthesize these compounds, highly enantioselective routes for the preparation of 2-substituted indoles, especially those that do not possess substituents at the 1- and 3-positions, have not been uncovered. Çavdar and Saraçoğlu found that reactions of 4,7-dihydroindole with α,β -unsaturated carbonyl compounds followed by oxidation lead to the generation of 2-substituted indole derivatives.¹⁰ Pioneering studies

Biographical Sketches



Mi Zeng was born in 1983 in Longchang, Sichuan province, P. R. of China. She received her B.Sc. in chemistry from Sichuan

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Shu-Li You was born in 1975 in Luohe, Henan province, P. R. of China, and received his B.Sc. in chemistry from Nankai University in 1996. He obtained his Ph.D. from the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Professor Li-Xin Dai before doing post-

doctoral studies with Professor Jeffery W. Kelly at The Scripps Research Institute. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a principal investigator before returning to SIOC in 2006. His current research interests include asymmetric

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by Evans et al. and Pedro et al. have also demonstrated that this protocol along with the use of chiral Lewis acid complexes is suitable for the synthesis of enantioenriched 2-substituted indole derivatives.¹¹ Intrigued by this unique protocol, we have carried out investigations, which show that this approach to 2-alkylindole synthesis is also compatible with chiral Brønsted acid catalysis. Chiral phosphoric acids and *N*-triflyl-containing phosphoramides were used in this methodology to promote the asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles with a variety of electrophilic partners, including imines, α,β -unsaturated carbonyl compounds, and nitro-substituted olefins. The corresponding 2-substituted indole products were produced efficiently upon simple *p*-benzoquinone oxidation of the initially formed alkylation products.

Finally, intramolecular asymmetric Friedel–Crafts reactions have been employed in efficient syntheses of polycyclic indoles, such as tetrahydropyrano[3,4-*b*]indoles (THPIs) and tetrahydro- β -carbolines (THBCs). However, owing to the fact that tedious procedures are required for the preparation of the substrates, the examples of the use of this strategy are limited to the asymmetric Pictet–Spengler reaction. Inspired by recent developments made in studies of processes that simultaneously rely on both organocatalysis and mechanistically distinct transition-metal catalysis,¹² we recently developed a strategy for the efficient synthesis of THPIs and THBCs that employs sequential olefin cross-metathesis and CPA-catalyzed asymmetric intramolecular Friedel–Crafts alkylation reactions.

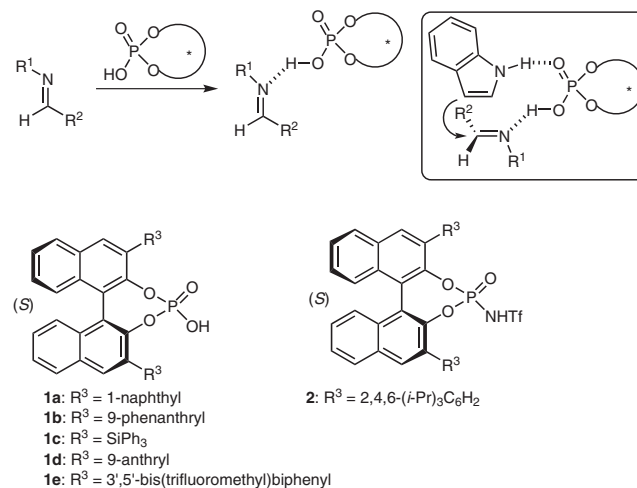
Over the past three years, efforts in our laboratory have focused on the regio- and enantioselective synthesis of enantiomerically pure indole derivatives, concentrating on the use of chiral Brønsted acids or iridium complexes to promote asymmetric Friedel–Crafts reactions of indoles with imines, *N*-tosyl-substituted amines, alcohols, and allyl carbonates. In addition, Friedel–Crafts reactions of 4,7-dihydroindoles with imines, β,γ -unsaturated α -keto esters, and nitro-substituted olefins have been developed to produce 2-substituted indole derivatives. Moreover, sequential catalysis to promote olefin cross-metathesis and CPA-catalyzed asymmetric intramolecular Friedel–Crafts alkylation reactions has been successfully investigated. Below, we summarize the results of these studies that have contributed to the area of asymmetric indole synthesis.

2 Asymmetric Friedel–Crafts Alkylation of Indoles at the 3-Position

2.1 Chiral Phosphoric Acids and Their Activation Mode

Chiral phosphoric acids have been used for several decades as chiral resolving agents and chiral ligands. In 2004, Terada and Akiyama and their co-workers independently demonstrated that these substances can be employed as effective organocatalysts.⁷ Soon after these

reports, catalysis by *N*-triflyl-substituted phosphoramides was described by Nakashima and Yamamoto.⁸ In addition, the rigid framework of the 1,1'-bi-2-naphthol (BINOL) scaffold creates an ideal chiral environment on to which phosphoric acids and *N*-triflyl-containing phosphoramides can be appended. Similar to the mode of operation of Lewis acids, chiral Brønsted acids activate various functional groups (C–X double bond) by lowering the energies of their lowest unoccupied molecular orbitals through hydrogen bonding interactions (Scheme 2). In most cases, CPAs and CPAmides act as bifunctional catalysts with their phosphoryl oxygen moieties simultaneously functioning as Lewis bases.



Scheme 2 Chiral phosphoric acids and *N*-triflyl-substituted phosphoramides and their mode of activation of imines and indoles

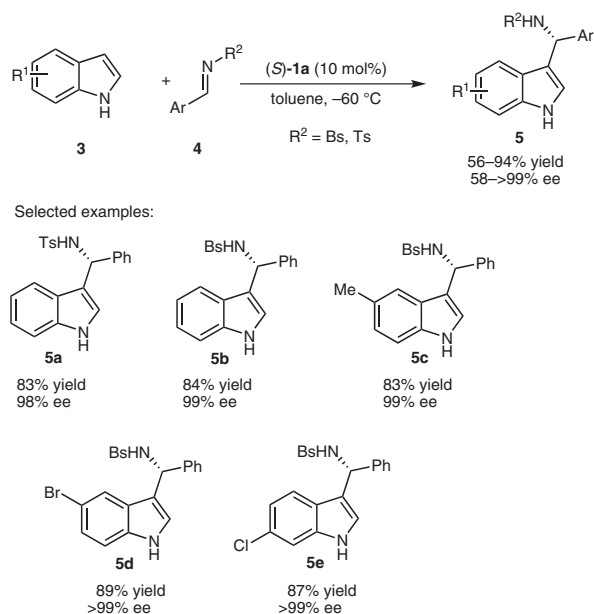
2.2 Asymmetric Friedel–Crafts Alkylation of Indoles with Imines

The asymmetric Friedel–Crafts alkylation of indoles with imines is an important reaction that provides easy access to enantiopure indol-3-ylmethanamines, which serve as the structural core of many biologically interesting natural and nonnatural products.¹ Following the first report by Johannsen of enantioselective catalytic entry to members of this family,⁵ Zhou and co-workers described an asymmetric Friedel–Crafts reaction of indoles with *N*-tosyl-substituted imines promoted by a chiral copper–bis-oxazoline complex in 2006.¹³ This was followed soon by the work of Deng and co-workers, who used cinchona alkaloid derived thioureas as the catalysts.¹⁴ In both cases, the indol-3-ylmethanamines were obtained with high enantiomeric purities.

Inspired by the report of Terada and co-workers summarizing their work on the CPA-catalyzed asymmetric Friedel–Crafts reaction of 2-methoxyfuran with an *N*-tert-butoxycarbonyl (Boc) aldimine,^{7c} we began an exploratory study probing CPAs as potential catalysts for the asymmetric Friedel–Crafts alkylation of indoles with imines.¹⁵ We observed that when phosphoric acid is used as the catalyst, reaction of an *N*-Boc aldimine with indole leads to the formation of a dialkylated product owing to the high

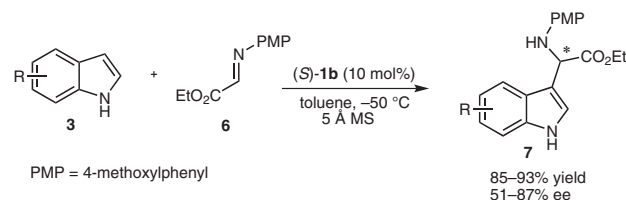
reactivity of the initially formed alkylation product. Fortunately, when the starting materials are changed to *N*-tosyl aldimines, almost all CPAs catalyze asymmetric Friedel–Crafts mono-alkylations of indoles. Variations of the substituents at the 3- and 3'-positions of the binaphthyl scaffold in the catalysts were found to have a dramatic influence on enantioselectivity. After screening several reactions, the following optimal conditions were determined: 10 mol% of CPA **1a** in toluene at -60°C . Reactions in which excess indole was used proceeded more rapidly and resulted in reduced yields of the bis-indole byproduct. Rewardingly, a wide range of substituted indoles **3** and *N*-sulfonyl-containing imines **4** can be used in this process to afford indol-3-ylmethanamine derivatives **5** in moderate to excellent yields (56–94%) and in up to >99% enantiomeric excess (ee) (Scheme 3). However, the reactions of aliphatic imines were sluggish and took place with low enantioselectivities.

Application of this chemistry to a large-scale synthesis of indol-3-ylmethanamine **5b** (over 3 g) was successfully carried out using 2 equivalents of the indole and 5 mol% of the catalyst. Furthermore, ready recycling of the catalyst proved to be feasible.



Scheme 3 Chiral phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation of indoles with imines (Bs = benzenesulfonyl)

We envisaged that the Friedel–Crafts reaction of indoles with imino derivatives of glyoxylates would afford the corresponding indol-3-ylglycine derivatives,¹⁶ an important class of nonproteinogenic amino acids that are useful synthetic intermediates and building blocks for natural products, such as druggable molecules.¹⁷ To test this proposal, asymmetric Friedel–Crafts reactions of indoles with imino derivatives of glyoxylates were explored.¹⁸ Chiral phosphoric acid **1b** was found to be the best catalyst for this process which affords indol-3-ylglycine derivatives in excellent yields (85–93%) and with high enantioselectivity (51–87% ee). Notably, slow addition (over 1.5 h) of ethyl glyoxylate derivative to the reaction mixture by employing a syringe pump led to slightly increased ee. In addition, we found that use of molecular sieves also benefits the enantioselectivity of this reaction (Scheme 4). Finally, the reactions are suitable for a three-component process starting with indole, ethyl glyoxylate, and *p*-anisidine.



Scheme 4 Chiral phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation of indoles with an imino derivative of a glyoxylate

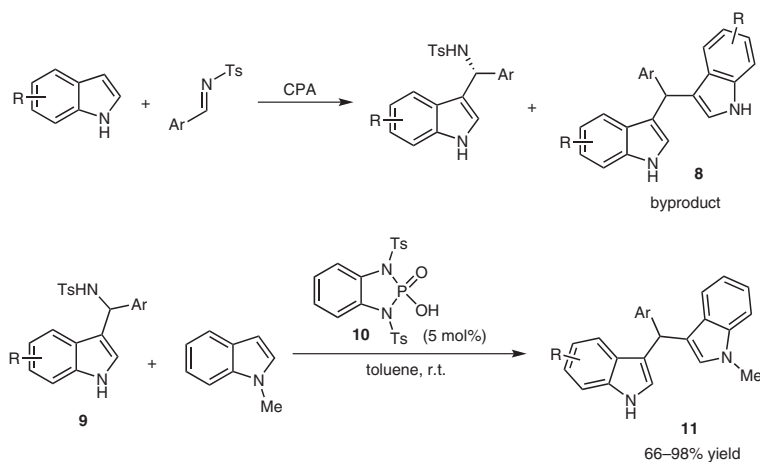
2.3 Asymmetric Friedel–Crafts Alkylation of Indoles with *N*-Tosyl-Substituted Amines

The synthesis of triarylmethanes has attracted great attention as a result of their use as biologically active compounds, protecting groups in organic synthesis, and important dyes.¹⁹ Although progress has been made,²⁰ the synthesis of unsymmetrically substituted triarylmethanes remains a challenging task.²¹ During the study of the CPA-catalyzed Friedel–Crafts reactions of indoles, a side reaction was noted to occur that affords arylbis(indolyl)methane **8** as a byproduct (Scheme 5).¹⁵ This observation was used advantageously in the design of a method for the facile synthesis of unsymmetrical arylbis(indolyl)methanes.²² Specifically, using acid **10** as a catalyst, Friedel–Crafts alkylation of indol-3-ylmethanamines **9** with 1-methyl-1*H*-indole takes place smoothly to afford unsymmetrical arylbis(indol-3-yl)methanes **11** in good to excellent yields (66–98%) (Scheme 5).

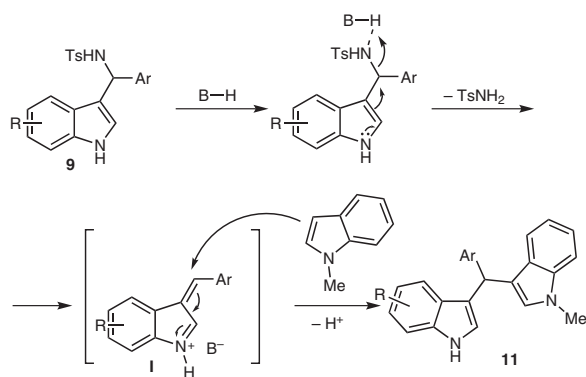
The proposed mechanism for this reaction, depicted in Scheme 6, involves Brønsted acid (B–H) promoted elimination of tosylamine from α -indol-3-yl-substituted benzylamine **9** to afford indolium intermediate **I**. The reaction of intermediate **I** with 1-methyl-1*H*-indole in a Friedel–Crafts-type process gives alkylation product **11**. In support of this mechanistic proposal is the observation that no reaction takes place when a simple *N*-(diarylmethyl)tosylamine is used in place of indol-3-ylmethanamine **9**. In addition, *N*-methyl protection of the indole moiety in indol-3-ylmethanamine **9** leads to a less-reactive substrate.

In a subsequent effort, the asymmetric version of this reaction using a CPA was developed.²³ In the presence of 5 mol% of CPA (*S*)-**1e**, asymmetric Friedel–Crafts alkylation of indol-3-ylmethanamines with 1-methyl-1*H*-indole or 1,3,5-trimethoxybenzene occurs to produce unsymmetrical triarylmethanes in up to 98% yield and 91% ee (Scheme 7).

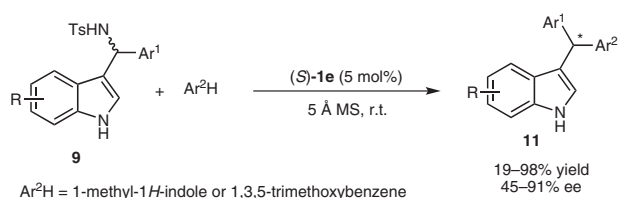
Interestingly, kinetic resolution of substrate **5a** was observed to occur in this process (Scheme 8). Specifically, the reaction carried out with a 1:0.6 ratio of tosylamine



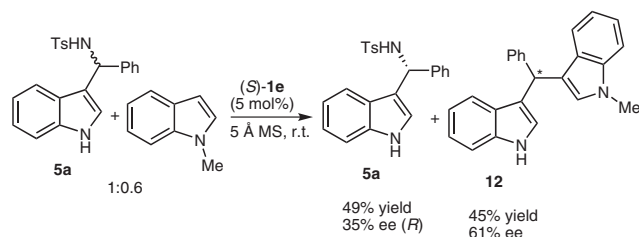
Scheme 5 Brønsted acid catalyzed Friedel–Crafts alkylation of indol-3-ylmethanamines with 1-methyl-1*H*-indole



Scheme 6 The mechanism of the Brønsted acid catalyzed Friedel–Crafts alkylation of indol-3-ylmethanamines with 1-methyl-1*H*-indole



Scheme 7 Chiral phosphoric acid catalyzed Friedel–Crafts alkylation of indol-3-ylmethanamines with 1-methyl-1*H*-indole or 1,3,5-trimethoxybenzene



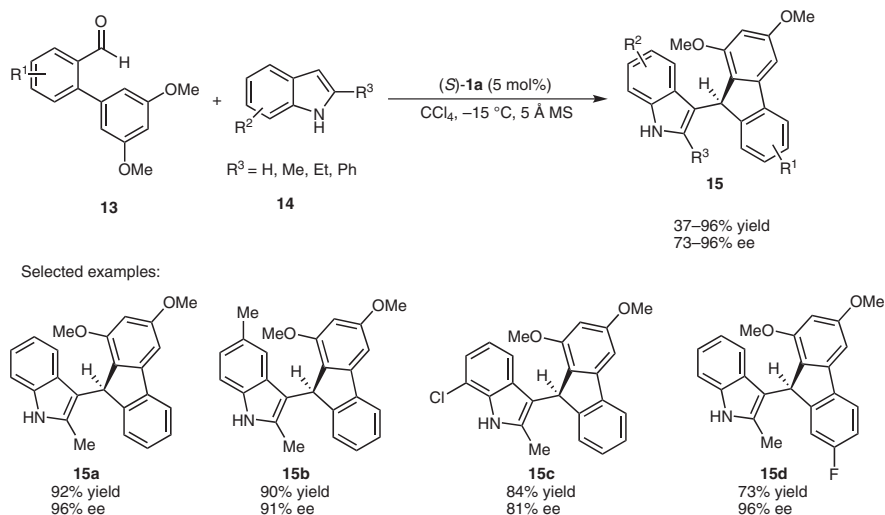
Scheme 8 The kinetic resolution of indol-3-ylmethanamines in the chiral phosphoric acid catalyzed Friedel–Crafts alkylation of indol-3-ylmethanamines with 1-methyl-1*H*-indole

5a/1-methyl-1*H*-indole led to recovered substrate **5a** in 49% yield and 35% ee with the *R*-enantiomer predominating. The observation that the configuration of recovered compound **5a** is the same as those of products formed in the CPA-catalyzed Friedel–Crafts reactions of indole with *N*-tosyl-substituted imines suggests that the formation of an arylbis(indol-3-yl)methane byproduct leads to an increase in the ee of the desired product.

2.4 Tandem Friedel–Crafts Alkylation of Indoles with Aldehydes and Alcohols

As described above, *N*-tosyl-substituted amines can be used as electrophilic partners in Friedel–Crafts alkylation reactions with indoles. The potential suitability of alcohols in asymmetric Friedel–Crafts reactions was also probed.²⁴ Alcohols are among the most-abundant chemicals and synthetic intermediates; however, their utility as electrophilic partners in CPA-catalyzed Friedel–Crafts reactions has not been fully explored.²⁵ To test their use in this context, a tandem reaction was designed in which an initial Friedel–Crafts reaction of an indole with a 2-formylbiphenyl was followed by the intramolecular asymmetric Friedel–Crafts reaction of the generated alcohol.²⁶ It was envisaged that this process would lead to 9-indol-3-ylfluorene derivatives.²⁷ Despite the wide application of these products in organic synthesis, to our knowledge, no report existed describing the asymmetric synthesis of such fluorene derivatives prior to our study.²⁸

By employing CPA (*S*)-**1a** as the catalyst, the tandem Friedel–Crafts reaction of indoles with 2-formylbiphenyl derivatives proceeds smoothly to afford 9-indol-3-ylfluorene derivatives **15** with high enantioselectivity (Scheme 9). A variety of substituted 2-methylindoles and 2-formylbiphenyls participate in this reaction and generate the fluorene products in good to excellent yields (37–96%) and with good to excellent stereoselectivity (73–96% ee). Under the specified conditions, indole, 2-ethylindole, and 2-phenylindole also undergo the reaction in a highly enantioselective fashion (73–89% ee).



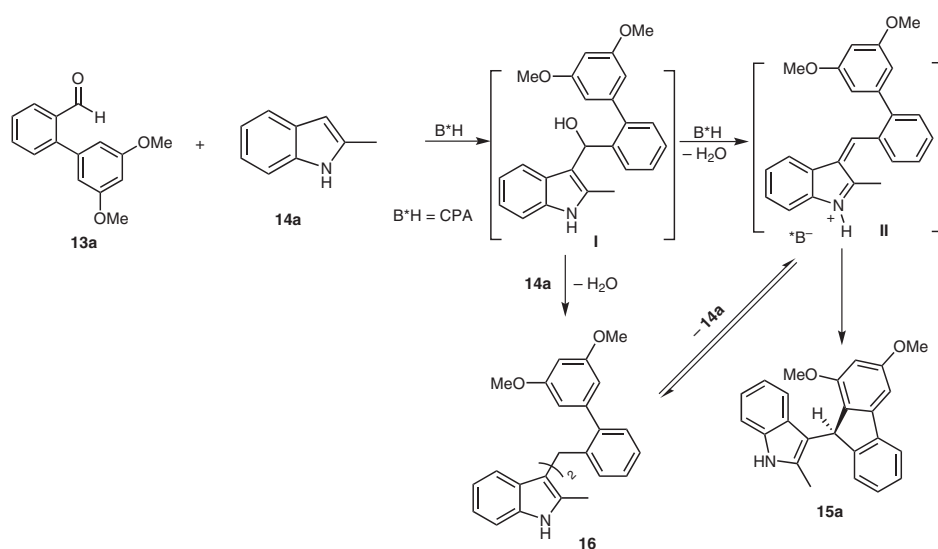
Scheme 9 Chiral phosphoric acid catalyzed Friedel–Crafts reaction of indoles with 2-formylbiphenyl derivatives

The mechanism proposed for this process is shown in Scheme 10 using the reaction to give product **15a** as an example. The first step involving the Friedel–Crafts reaction between 2-formylbiphenyl **13a** and indole **14a** is catalyzed by phosphoric acid and affords secondary alcohol **I**. The exposure of intermediate **I** to the CPA produces conjugated iminium salt **II**,²⁹ which is paired with the chiral phosphate anion that creates a chiral environment to control facial selectivity in the second Friedel–Crafts reaction. The existence of intermediate **II** in this pathway is consistent with the fact that a dramatic decrease of both the ee (down to 35% ee) and the reaction rate is observed when 1,2-dimethyl-1*H*-indole (**17**) is used as the starting material instead of 2-methyl-1*H*-indole (Scheme 11). In addition, bis-indole **16** is observed during the reaction and can be isolated as a stable product. When compound **16** is subjected to the standard reaction conditions, product **15a** is generated in 50% yield and 83% ee (Scheme 11). This finding suggests that an alternative pathway involving the

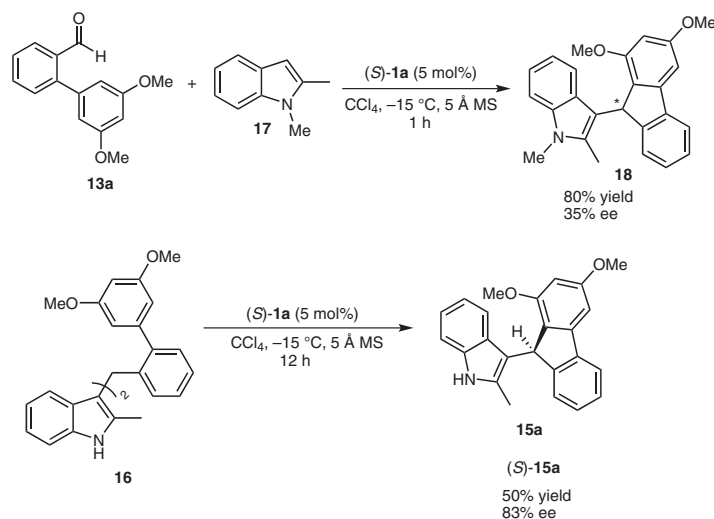
transformation of bis-indole **16** into intermediate **II** should be included in the mechanistic route for this process (Scheme 10).

2.5 Iridium-Catalyzed Asymmetric Friedel–Crafts Allylic Alkylation of Indoles

Transition-metal- π -allyl complexes also serve as electrophilic partners in Friedel–Crafts reactions. In 1999, Kočovský and co-workers described the first allylic alkylation of indole with allyl acetates in the presence of a molybdenum(II) catalyst.³⁰ Subsequent elegant work by Bandini and co-workers led to the development of palladium-catalyzed allylic alkylations of indole using allylic carbonates and related enantioselective intramolecular allylic alkylation reactions.³¹ In addition, Chan and co-workers observed that intermolecular reactions between indoles and 1,3-diphenylprop-2-enyl acetate can be promoted by a chiral palladium complex.³² Despite the fact

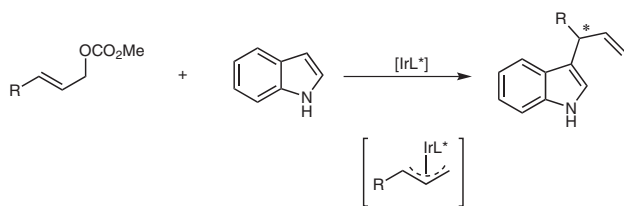


Scheme 10 Proposed mechanism for the chiral phosphoric acid catalyzed tandem Friedel–Crafts reaction of indoles with 2-formylbiphenyl derivatives



Scheme 11 Mechanistic study of the chiral phosphoric acid catalyzed Friedel–Crafts reaction of indoles with 2-formylbiphenyl derivatives

that transition-metal-catalyzed asymmetric allylic alkylations of indoles represent potentially excellent routes for the synthesis of optically pure indole derivatives, studies of this process have remained sparse.³³ As an outgrowth of an interest in iridium-catalyzed allylic alkylation reactions with 1,3-unsymmetric allyl carbonates,³⁴ we recently developed a regio- and enantioselective iridium-catalyzed Friedel–Crafts allylic alkylation reaction of indole (Scheme 12).³⁵



Scheme 12 The preferred branched product in the iridium-catalyzed allylic alkylation reaction

Our efforts showed that by using the iridium catalyst derived from chloro(cycloocta-1,5-diene)iridium dimer $\{[\text{Ir}(\text{cod})\text{Cl}]_2\}$ and Feringa ligand $(S,S,S_a)\text{-L1}$ (Figure 2), the alkylation of indoles with allylic carbonates proceeds smoothly to yield optically active indoles bearing a terminal alkene moiety. In the presence of 2 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$, 4 mol% of $(S,S,S_a)\text{-L1}$, and 1 equivalent of cesium carbonate in refluxing dioxane, the reactions take place with excellent regioselectivity (ratio of **20/21** up to >93:7) to afford the branched alkylation products **20** in up to 92% ee. This process readily takes place with different indoles and variously substituted allyl substrates, except for allyl carbonates containing *ortho*-substituted aryl groups. For example, when 2-methoxyphenyl-, 2-chlorophenyl-, 2-bromophenyl- and 1-naphthyl-substituted allyl carbonates are used as starting materials, the enantioselectivities are dramatically lowered (Scheme 13).

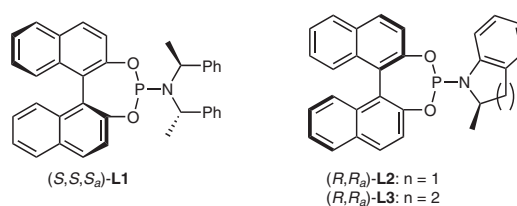


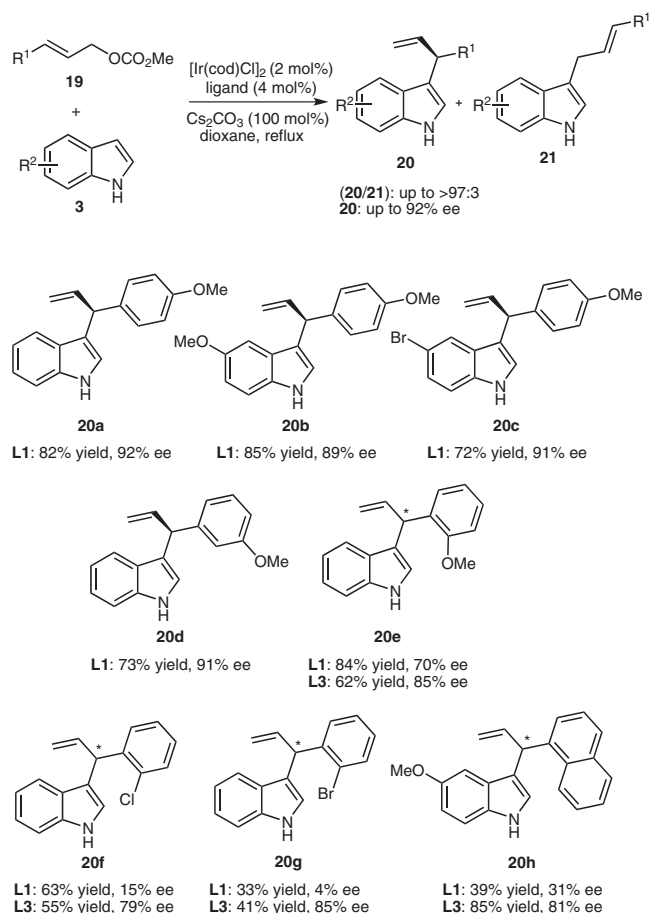
Figure 2 Ligands used in the iridium-catalyzed allylic alkylation reaction

To overcome this unfavorable *ortho*-substituent effect that is also observed using nucleophiles other than indoles,³⁶ we recently developed a new series of phosphoramidite ligands from enantiopure BINOL and 2-methylindoline or 2-methyl-1,2,3,4-tetrahydroquinoline (Figure 2).³⁷ These ligands were found to participate in iridium-catalyzed Friedel–Crafts reactions of indoles with allylic carbonates that afford branched products with high regio- and enantioselectivities. More importantly, these ligands also promote reactions of allyl carbonates containing *ortho*-substituted phenyl groups, and a significant improvement was observed in the enantioselectivities of these reactions compared with those performed using the Feringa ligand. This is exemplified by the results of the reactions of 2-methoxyphenyl- (85 vs 70% ee), 2-chlorophenyl- (79 vs 15% ee), 2-bromophenyl- (85 vs 4% ee), and 1-naphthyl-substituted allyl carbonates (81 vs 31% ee) (Scheme 13).

3 Asymmetric Friedel–Crafts Alkylation of Indoles at the 2-Position

3.1 Asymmetric Friedel–Crafts Alkylation of 4,7-Dihydroindoles with Imines

As a consequence of the much lower nucleophilic reactivity of the 2-position of indole compared with the 3-posi-

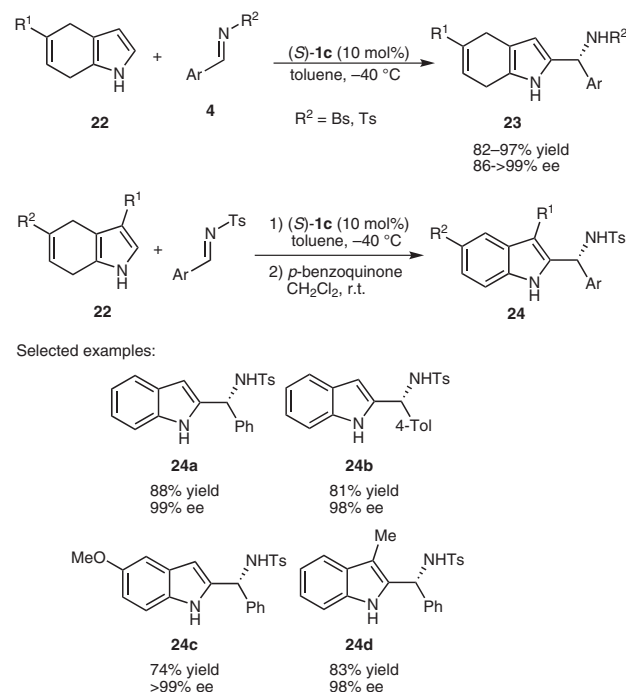


Scheme 13 Iridium-catalyzed allylic alkylation reaction of indoles

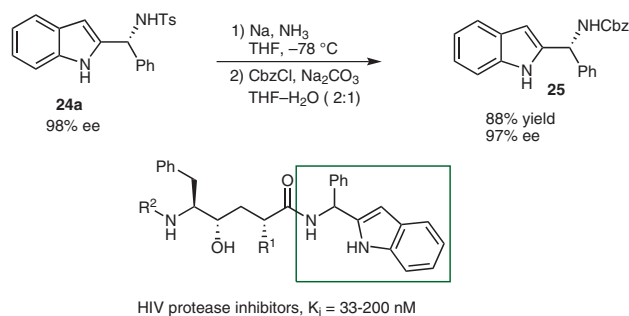
tion, it is difficult to obtain 2-substituted indole derivatives using direct Friedel–Crafts reactions, especially in the cases of indoles that do not possess substituents at N-1 and C-3. A useful strategy to circumvent this problem was introduced by Çavdar and Saraçoğlu.¹⁰ The approach relies on the use of 4,7-dihydroindoles, which are prepared through the Birch reduction of indoles and in which the 2-position is more reactive than the 3-position.

In continuation of our efforts probing the CPA-catalyzed Friedel–Crafts reaction of indoles with imines, we demonstrated that 4,7-dihydroindoles also are reactive when the same catalytic system is employed.³⁸ Chiral phosphoric acid **1c** was found to be superior in promoting the formation of the 2-substituted products in up to 97% yield and in 86–>99% ee (Scheme 14). A one-pot procedure that incorporates the Friedel–Crafts reaction of 4,7-dihydroindoles with imines and subsequent oxidation of the alkylation products with *p*-benzoquinone was developed. This process can be used to generate indol-2-ylmethanamine derivatives in good yields with excellent enantioselectivity (74–88% yield, 98–>99% ee). Moreover, the tosyl group in the products of these reactions can be readily removed and the resulting amine can be converted into its benzyloxycarbonyl-protected derivative in excellent yield and without the loss of enantiomeric purity, e.g. formation of product **25** (Scheme 15). Notably, the removal

of the tosyl group from indol-2-ylmethanamine derivative **24a** produces a key intermediate in the synthesis of HIV protease inhibitors.³⁹



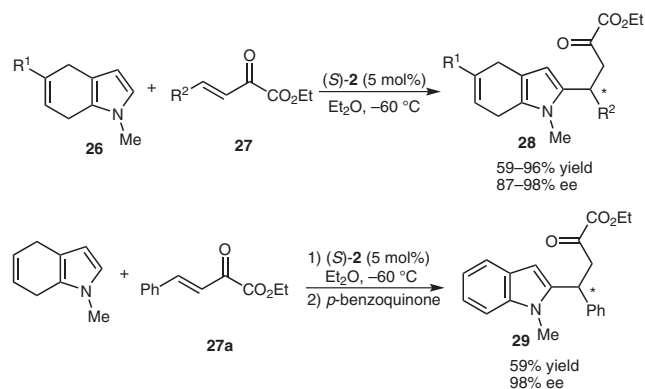
Scheme 14 Chiral phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation of 4,7-dihydroindoles with imines (Bs = benzenesulfonyl)



Scheme 15 Removal of the tosyl group in product **24a**

3.2 Asymmetric Friedel–Crafts Alkylation of 4,7-Dihydroindoles with Keto Esters

Yamamoto and co-workers have shown that a chiral *N*-triflyl-substituted phosphoramidate is a strong acid that enables activation of carbonyl groups.⁸ For example, β,γ -unsaturated α -keto esters are electrophiles that can be activated using such an acid.²⁵ In 2008, we observed that the CPA **(S)-2** serves as an efficient catalyst for Friedel–Crafts reactions of 4,7-dihydroindoles with β,γ -unsaturated α -keto esters.⁴⁰ Using 5 mol% of catalyst **(S)-2**, a wide range of 2-substituted 4,7-dihydroindoles were generated in up to 98% ee. For example, 2-substituted indole **29** was formed in 59% yield and 98% ee through the use of the



Scheme 16 Chiral *N*-triflyl-substituted phosphoramidate catalyzed, asymmetric Friedel–Crafts alkylation of 4,7-dihydroindoles with unsaturated keto esters

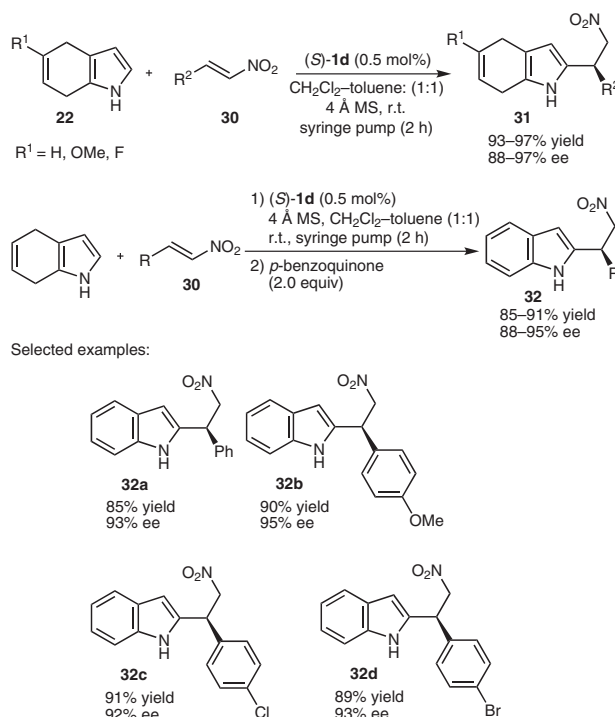
one-pot Friedel–Crafts alkylation/*p*-benzoquinone oxidation procedure (Scheme 16).

3.3 Asymmetric Friedel–Crafts Alkylation of 4,7-Dihydroindoles with Nitro-Substituted Olefins

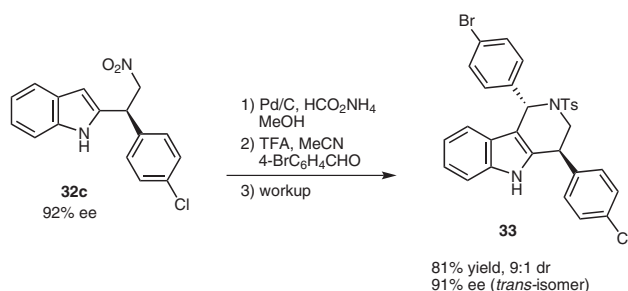
Nitro-substituted olefins participate as electrophilic partners in asymmetric Friedel–Crafts reactions. This is a very attractive process because the nitro group of the products can be manipulated in a number of ways to introduce interesting functionality.⁴¹ As a result, many types of asymmetric catalytic systems have been developed for this reaction.⁴² However, most of the systems require relatively high catalyst loadings (5–20 mol%) and long reaction times (days). In studies resulting from our interest in the synthesis of 2-substituted indoles, we recently found that CPAs promote efficient asymmetric Friedel–Crafts reactions of nitro-substituted olefins with 4,7-dihydroindoles.⁴³ All of the reactions proceed to completion in 2 hours at room temperature with only 0.5 mol% of the catalyst. The reactions explored thus far were carried out using slow syringe pump addition of the nitro-substituted olefins. These processes provide the corresponding dihydroindole products in 93–97% yield and 88–97% ee. The final 2-substituted indoles are produced in high yields (85–91%) with excellent enantioselectivity (88–95% ee) following oxidation (Scheme 17). Room temperature reaction conditions and low catalyst loading are notable features of this new approach to 2-substituted indole synthesis.

The new asymmetric Friedel–Crafts reaction also plays a role in a practical route for the synthesis of highly enantio-merically enriched tetrahydro- γ -carboline derivatives.⁴⁴ This is exemplified by the transformation of compound **32c**, a product of the formal addition of a nitro-substituted olefin to 1*H*-indole, into tetrahydro- γ -carboline **33** via reduction and Pictet–Spengler cyclization (Scheme 18).

Very recently, Wang and co-workers took advantage of the sequential 4,7-dihydroindole Friedel–Crafts alkyla-



Scheme 17 Chiral phosphoric acid catalyzed asymmetric Friedel–Crafts alkylation of 4,7-dihydroindoles with nitro-substituted olefins



Scheme 18 Transformation of nitro compound **32c** into tetrahydro- γ -carboline **33**

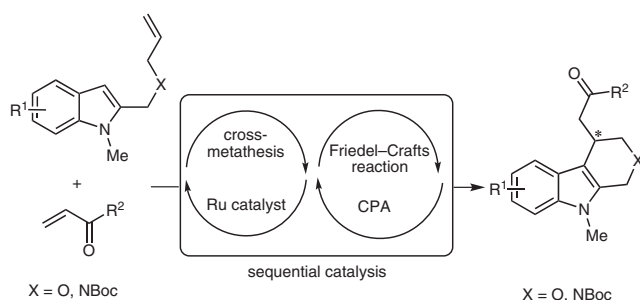
tion/oxidation strategy to conduct a highly enantioselective synthesis of 2-substituted indoles using iminium catalysis.⁴⁵

Pyrrole derivatives represent another class of important heterocyclic compounds. Interestingly, enantioselective Friedel–Crafts alkylations of pyrroles have not been fully explored.⁴⁶ Only a few catalytic systems involving chiral zinc or copper complexes have been used to date for this purpose.⁴⁷ We recently observed that CPAs serve as efficient catalysts for asymmetric Friedel–Crafts alkylation reactions between nitro-substituted olefins and pyrroles, giving the corresponding products in 87–94% yield and 86–94% ee.⁴⁸ In these reactions, the CPA acts as a bifunctional catalyst in which the acidic proton and phosphoryl oxygen form hydrogen bonds with the nitro oxygen of the olefin and the pyrrole N–H, respectively.

4 Sequential Catalysis for the Enantioselective Synthesis of Polycyclic Indoles

Intramolecular Friedel–Crafts reactions of indoles serve as a direct route for the preparation of polycyclic indole derivatives, such as tetrahydropyrano[3,4-*b*]indoles and tetrahydro- β -carboline. Despite the considerable effort that has been given to the development of asymmetric intramolecular Friedel–Crafts-type Michael addition reactions, only a few successful examples have been described thus far.⁴⁹

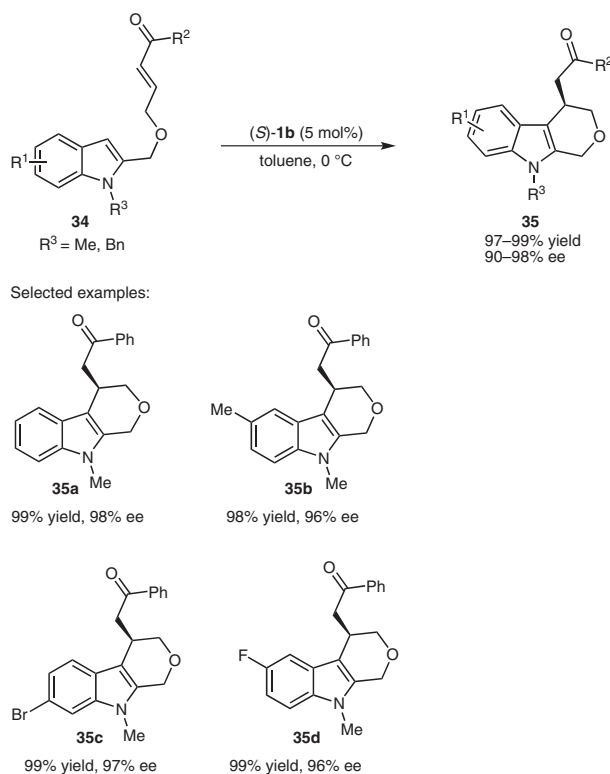
Inspired by the report from Xiao and co-workers that a ruthenium-catalyzed, tandem cross-metathesis/intramolecular hydroarylation sequence takes place efficiently,⁵⁰ we designed a sequential olefin cross-metathesis/asymmetric intramolecular Friedel–Crafts alkylation reaction sequence for the synthesis of enantiomerically pure polycyclic indoles (Scheme 19).⁵¹ Chiral phosphoric acids were chosen as catalysts for these processes as a result of their strong activation of unsaturated carbonyl compounds, avoiding the racemization that is seen with in situ generated Lewis acidic ruthenium species. This combination of mechanistically distinct organocatalysis and transition-metal catalysis reduces labor and waste, and enables the use of more readily available starting materials.



Scheme 19 Cross-metathesis/asymmetric Friedel–Crafts alkylation cascade reaction

In an initial investigation, we determined if CPAs could catalyze the intramolecular Friedel–Crafts alkylation of indolyl-substituted enones (Scheme 20). The results show that reactions with 5 mol% of CPA (*S*)-**1b** in toluene at 0 °C produce the desired products **35** in almost quantitative yields and with excellent enantioselectivities (90–98% ee).

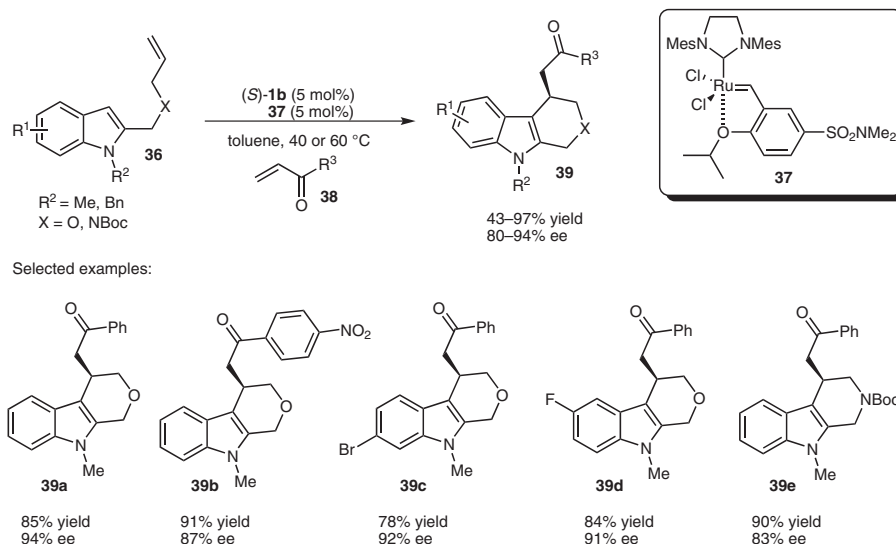
A wide range of variously substituted indolylalkenones **34** participated in the CPA-catalyzed intramolecular Friedel–Crafts reaction. Following this success, we next explored the sequential process that combines olefin cross-metathesis and asymmetric Friedel–Crafts alkylation. After screening different catalysts, CPA **1b** and ruthenium catalyst (Zhan-1B) **37** were found to be optimal for this purpose. The reaction using 1 equivalent of allyl indolyl-methyl ether or amine **36**, 1.5 equivalents of aryl vinyl ke-



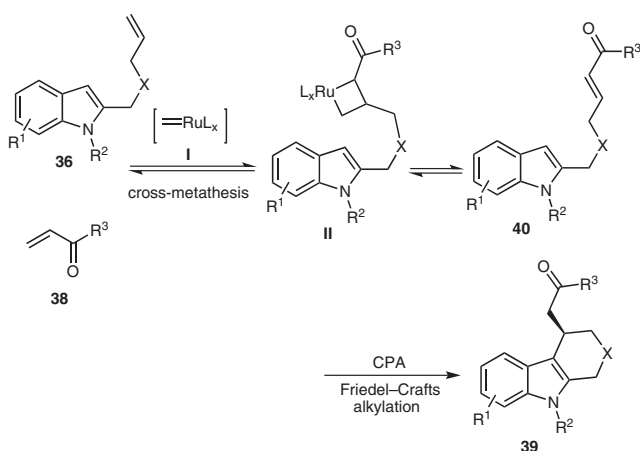
Scheme 20 Chiral phosphoric acid catalyzed intramolecular Friedel–Crafts alkylation of indolyl-substituted enones

tone **38**, 5 mol% of CPA **1b**, and 5 mol% of ruthenium catalyst **37** in toluene (at 40 or 60 °C) proceeds smoothly to generate tetrahydropyrano[3,4-*b*]indoles and tetrahydro- β -carboline in moderate to excellent yields (43–97%) and with good enantioselectivity (80–94% ee) (Scheme 21). The reactions at 60 °C led to higher yields, but occurred with slightly decreased enantioselectivity compared with those carried out at 40 °C. It is noteworthy that the enantioselectivity of the process was not eroded when it was performed using the tandem protocol, the small variation being mainly because of temperature differences.

The proposed catalytic cycle for the sequential catalysis route (Scheme 22) involves two distinct catalytic steps beginning with olefin cross-metathesis between substrates **36** and **38** catalyzed by a ruthenium complex. This is followed by an intramolecular Friedel–Crafts alkylation catalyzed by the CPA. In the presence of the ruthenium catalyst, cross-metathesis between compounds **36** and **38** occurs to afford indolyl-substituted enone **40** and Lewis acidic ruthenium complex **I**, which could competitively activate enone **40** and lead to racemization. The second step, involving the CPA-promoted Friedel–Crafts reaction, facilitates the overall process by converting the initially formed cross-metathesis product into the ultimate product. This conjecture is supported by the observation that the cross-metathesis reaction between **36** and **38** in the absence of a phosphoric acid catalyst forms **39** in only moderate yield.



Scheme 21 Sequential ruthenium-catalyzed olefin cross-metathesis and CPA-catalyzed asymmetric Friedel–Crafts alkylation



Scheme 22 The proposed catalytic cycle for the sequential catalysis of olefin cross-metathesis and asymmetric Friedel–Crafts alkylation

5 Conclusion and Outlook

The studies reviewed above demonstrate that several enantioenriched indole frameworks can be constructed using asymmetric Friedel–Crafts reactions of indoles with a variety of electrophilic reagents. *N*-Tosyl-substituted imines, an imino derivative of a glyoxylate, *N*-tosyl-substituted amines, aldehydes, and alcohols are all suitable electrophilic reagents that can be activated by chiral phosphoric acids or *N*-triflyl-containing phosphoramides. 1,3-Unsymmetrically substituted allylic carbonates are also good substrates for asymmetric Friedel–Crafts reactions promoted by chiral iridium complexes. In all of these reactions, alkylation occurs at the 3-position of the indole ring. The asymmetric Friedel–Crafts reactions of 4,7-dihydroindoles with various electrophilic reagents, such as imines, β,γ -unsaturated α -keto esters, and nitro-substituted olefins, followed by oxidation can be used to produce 2-substituted indole derivatives. In addition, a sequential ruthenium-catalyzed cross-metathesis/CPA-catalyzed

asymmetric Friedel–Crafts reaction protocol has been developed to prepare polycyclic indoles efficiently. This sequential catalytic process enables the use of more readily available starting materials and makes the synthesis of enantiopure polycyclic indoles more economical.

Although several efficient approaches have been developed for the synthesis of diverse enantiopure indole derivatives, some drawbacks of the methods do exist. For instance, the electrophilic partners that participate in these processes need to be further broadened, and novel catalysts and activation modes need to be devised. In addition, the catalyst loadings needed to promote the reactions are generally high (5–10 mol%); only in the case of the Friedel–Crafts reaction of 4,7-dihydroindoles with nitro-substituted olefins can the loading be as low as 0.5 mol%. Finally, most of the substrates explored to date are aryl-substituted and, consequently, a wider scope of substrates would be highly desirable. Our continuing studies of the synthesis of enantiopure indole derivatives focus on the design of new catalysts, the development of novel reaction modes, and the discovery of practical and useful transformations.

Acknowledgment

We thank all group members who contributed to the studies described in this review. Financial support was provided by the National Natural Science Foundation of China (20732006, 20821002, 20972177), the National Basic Research Program of China (973 Program 2009CB825300, and the Chinese Academy of Sciences.

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