Asymmetric Catalysis

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# Asymmetric Construction of Polycyclic Indoles through Olefin Cross-Metathesis/Intramolecular Friedel–Crafts Alkylation under Sequential Catalysis**

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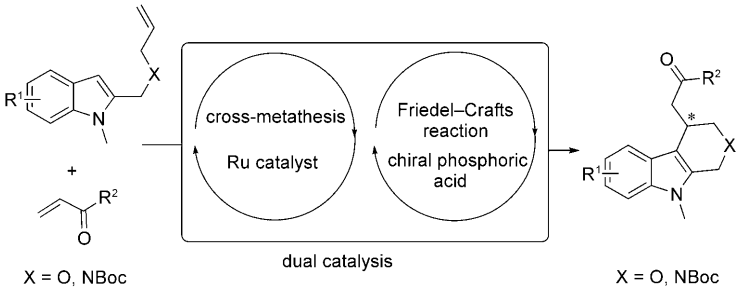
The combination of mechanistically distinct organocatalysis and transition-metal catalysis has enabled novel transformations beyond those possible with single catalytic systems.[1] Sequential catalysis involving a binary catalytic system often reduces labor and waste and enables the use of more readily available starting materials for a given transformation.[2] Chiral Brønsted acids have been shown to be efficient catalysts for asymmetric Friedel–Crafts reactions.[3,4] In particular, intramolecular Friedel–Crafts-type reactions provide a direct route to polycyclic indoles, such as tetrahydropyrano[3,4-*b*]indoles (THPIs) and tetrahydro-β-carbolines (THBCs),[5,6] which are frequently encountered in biologically active natural products and pharmaceuticals.[7] Despite considerable efforts devoted to asymmetric intramolecular Friedel–Crafts-type Michael addition reactions, there are few successful examples.[8] Most notably, the tedious procedure for the preparation of substrates for the intramolecular Friedel–Crafts reaction limits its synthetic applications.




***Scheme 1.*** Cascade reaction involving cross-metathesis and an asymmetric Friedel–Crafts alkylation. Boc = *tert*-butoxycarbonyl.

Xiao et al. recently demonstrated an elegant ruthenium-catalyzed tandem cross-metathesis (CM)/intramolecular hydroarylation sequence for the efficient synthesis of polycyclic indoles.[9] The Lewis acidic ruthenium species generated in situ catalyzes the Friedel–Crafts alkylation reaction. As part of our research program towards the development of enantioselective Friedel–Crafts reactions,[10] we envisaged that sequential olefin cross-metathesis and asymmetric intramolecular Friedel–Crafts alkylation reactions might be used to construct enantiomerically pure polycyclic indoles (Scheme 1). Chiral phosphoric acids were chosen as catalysts for the asymmetric Friedel–Crafts reaction because of their strong activation of unsaturated carbonyl compounds. We hoped that these catalysts would suppress the racemic reaction caused by Lewis acidic ruthenium species.[9] Furthermore, the Friedel–Crafts reaction should accelerate the CM reaction by converting the metathesis product into an alkylation product. Herein, we report our preliminary results on an enantioselective intramolecular Friedel–Crafts alkylation based on sequential catalysis.

When we began our study, no efficient enantioselective Friedel–Crafts alkylation of indolyl enones was known.[11] We chose the indolyl enone **1a** as the model substrate and explored the use of chiral Brønsted acid catalysts for this transformation. With chiral phosphoric acids **5** (5 mol%) in toluene at −20 °C, the desired reaction proceeded smoothly to give **2a** with 59–96% *ee* (Table 1). The chiral phosphoric acid **5h** bearing 9-phenanthryl groups afforded **2a** with greater than 95% conversion and 96% *ee* and thus proved to be the optimal catalyst (Table 1, entry 8). Further examination of the reaction conditions revealed that the reaction proceeded with optimal enantioselectivity (98% *ee*) at 0 °C in toluene (Table 1, entry 13).

Various substituted indolyl enones were subjected to the intramolecular Friedel–Crafts alkylation under these optimized reaction conditions to examine the generality of the reaction (Table 2). The phosphoric acid catalyzed intramolecular Friedel–Crafts alkylation was found to be effective with a wide range of substrates. Indolyl phenyl enones **1b–f**, which contain either an electron-donating group or an electron-withdrawing group at the 5- or 6-position of the indole, were good substrates; the desired products were formed in 97–99% yield with 90–97% *ee* (Table 2, entries 2–6). When the protecting group on the N atom of the indole ring was changed from methyl to benzyl, the reaction proceeded relatively slowly, but the yield and enantioselectivity were satisfactory (97% yield, 95% *ee*; Table 2, entry 7). In general, electron-rich indolyl enones (Table 2, entries 2

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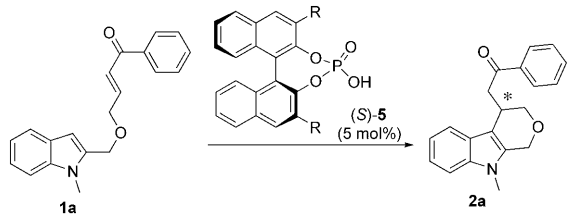
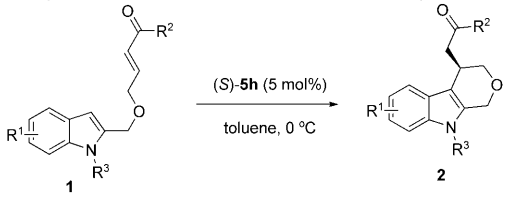
***Table 1:*** Optimization of the reaction conditions for the enantioselective Friedel–Crafts reaction.[a]




| Entry | **5**, R | Solvent | *T* [°C] | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **5a**, phenyl | toluene | −20 | >95 | 59 |
| 2 | **5b**, 9-anthryl | toluene | −20 | >95 | 81 |
| 3 | **5c**, 2-naphthyl | toluene | −20 | >95 | 89 |
| 4 | **5d**, 4-biphenyl | toluene | −20 | >95 | 84 |
| 5 | **5e**, 4-$NO_2$-$C_6H_4$ | toluene | −20 | >95 | 61 |
| 6 | **5f**, 1-naphthyl | toluene | −20 | >95 | 87 |
| 7 | **5g**, 3,5-$(CF_3)C_6H_3$ | toluene | −20 | >95 | 63 |
| 8 | **5h**, 9-phenanthryl | toluene | −20 | >95 | 96 |
| 9 | **5h**, 9-phenanthryl | $CH_2Cl_2$ | −20 | >95 | 96 |
| 10 | **5h**, 9-phenanthryl | $CH_2ClCH_2Cl$ | −20 | >95 | 96 |
| 11 | **5h**, 9-phenanthryl | toluene | −40 | >95 | 96 |
| 12 | **5h**, 9-phenanthryl | toluene | RT | >95 | 97 |
| 13 | **5h**, 9-phenanthryl | toluene | 0 | >95 | 98 |
| 14 | **5h**, 9-phenanthryl | toluene | 40 | >95 | 96 |

[a] Reaction conditions: (*S*)-**5** (5 mol%), **1a** (15 mg), solvent (0.5 mL). [b] The conversion was determined by $^1$H NMR spectroscopy. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase (Daicel Chiralpak AD-H).

***Table 2:*** Scope of the intramolecular Friedel–Crafts alkylation.[a]



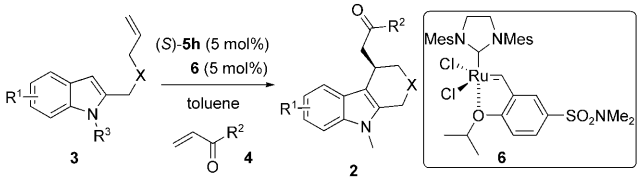

| Entry | **1**, $R^1$, $R^2$, $R^3$ | *t* [min] | **2**, yield [%] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | **1a**, H, $C_6H_5$, Me | 3 | **2a**, 99 | 98 |
| 2 | **1b**, 6-MeO, $C_6H_5$, Me | 6 | **2b**, 99 | 97 |
| 3 | **1c**, 5-Me, $C_6H_5$, Me | 3 | **2c**, 98 | 96 |
| 4 | **1d**, 6-Br, $C_6H_5$, Me | 15 | **2d**, 99 | 97 (*R*)[c] |
| 5 | **1e**, 5-F, $C_6H_5$, Me | 13 | **2e**, 99 | 96 |
| 6 | **1f**, 5-Br, $C_6H_5$, Me | 15 | **2f**, 98 | 90 |
| 7 | **1g**, H, $C_6H_5$, Bn | 180 | **2g**, 97 | 95 |
| 8 | **1h**, H, 3-$MeOC_6H_4$, Me | 10 | **2h**, 97 | 97 |
| 9 | **1i**, H, 4-$ClC_6H_4$, Me | 5 | **2i**, 98 | 97 |
| 10 | **1j**, H, 4-$BrC_6H_4$, Me | 5 | **2j**, 97 | 96 |
| 11 | **1k**, H, 4-$MeC_6H_4$, Me | 10 | **2k**, 99 | 98 |

[a] Reaction conditions: **1** (0.1 mol $L^{-1}$), (*S*)-**5h** (5 mol%), toluene (2 mL). [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [c] The absolute configuration of **2d** was determined by single-crystal X-ray diffraction. Bn = benzyl.

and 3) were more reactive than electron-deficient substrates (Table 2, entries 4–6). Excellent yields and enantioselectivities were observed for aryl indolyl enones with a variety of aryl groups (97–99% yield, 96–98% *ee*; Table 2, entries 8–11). Single-crystal X-ray analysis of enantiomerically pure **2d** revealed the absolute configuration to be *R*.[12,13]

Following the success of the asymmetric intramolecular Friedel–Crafts alkylation, we investigated the sequential catalysis of olefin cross-metathesis and asymmetric Friedel–Crafts alkylation. Optimization of the reaction conditions led to efficient sequential catalysis:[13] When the indolyl allyl ether **3a** and the phenyl enone **4a** (1.5 equiv) were combined and heated in toluene at 40°C with **5h** (5 mol%) and the Ru catalyst **6** (5 mol%), the desired product **2a** was obtained in 85% yield with 94% *ee* (Table 3, entry 1). Notably, the

***Table 3:*** Scope of the cross-metathesis/Friedel–Crafts cascade reaction.[a]




| Entry | **3**, $R^1$, $R^3$, X | **4**, $R^2$ | *T* [°C] | **2**, yield [%] | *ee*[b] [%] |
|---|---|---|---|---|---|
| 1 | **3a**, H, Me, O | **4a**, $C_6H_5$ | 40 | **2a**, 85 | 94 |
| 2 | **3a**, H, Me, O | **4a**, $C_6H_5$ | 60 | **2a**, 94 | 92 |
| 3 | **3b**, 6-OMe, Me, O | **4a**, $C_6H_5$ | 40 | **2b**, 43 | 90 |
| 4 | **3c**, 5-Me, Me, O | **4a**, $C_6H_5$ | 60 | **2c**, 89 | 90 |
| 5 | **3d**, 6-Br, Me, O | **4a**, $C_6H_5$ | 40 | **2d**, 78 | 92 |
| 6 | **3d**, 6-Br, Me, O | **4a**, $C_6H_5$ | 60 | **2d**, 90 | 88 |
| 7 | **3e**, 5-F, Me, O | **4a**, $C_6H_5$ | 40 | **2e**, 75 | 92 |
| 8 | **3e**, 5-F, Me, O | **4a**, $C_6H_5$ | 60 | **2e**, 84 | 91 |
| 9 | **3f**, 5-Br, Me, O | **4a**, $C_6H_5$ | 60 | **2f**, 96 | 91 |
| 10 | **3g**, H, Bn, O | **4a**, $C_6H_5$ | 60 | **2g**, 97 | 93 |
| 11 | **3a**, H, Me, O | **4b**, 4-Cl-$C_6H_5$ | 60 | **2i**, 91 | 92 |
| 12 | **3a**, H, Me, O | **4c**, 4-$BrC_6H_5$ | 60 | **2j**, 90 | 89 |
| 13 | **3a**, H, Me, O | **4d**, 4-$MeC_6H_5$ | 60 | **2k**, 93 | 92 |
| 14 | **3a**, H, Me, O | **4e**, 4-$MeOC_6H_5$ | 60 | **2l**, 96 | 90 |
| 15 | **3a**, H, Me, O | **4f**, 4-$NO_2C_6H_5$ | 60 | **2m**, 91 | 87 |
| 16 | **3a**, H, Me, O | **4g**, 2-naphthyl | 60 | **2n**, 88 | 91 |
| 17 | **3a**, H, Me, O | **4f**, 2-furyl | 60 | **2o**, 64 | 80 |
| 18 | **3h**, H, Me, NBoc | **4a**, $C_6H_5$ | 60 | **2p**, 90 | 83 |

[a] Reaction conditions: **3** (0.1 mol $L^{-1}$), **4** (1.5 equiv), (*S*)-**5h** (5 mol%), **6** (5 mol%), toluene (2 mL). [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase. Mes = 2,4,6-trimethylphenyl.

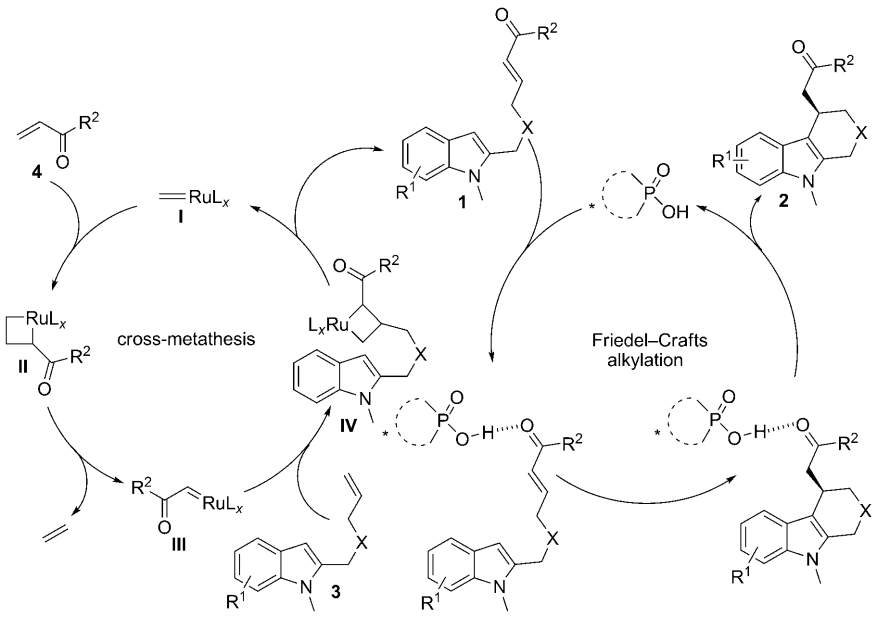
reaction of **1a** with **5h** (5 mol%) at 40°C in toluene led to **2a** with 96% *ee* (Table 1, entry 14); thus, there was almost no erosion in enantioselectivity during sequential catalysis.

To ascertain the generality of the cascade reaction, we examined various substituted indolyl allyl ethers and enones (Table 3). In most cases, the reactions proceeded smoothly to afford the desired products in good yields and with good enantioselectivity (43–97% yield, 80–94% *ee*; Table 3, entries 1–17). In general, the products were formed in higher yield but with slightly lower enantioselectivity at 60°C than at 40°C. Not only substituted phenyl enones, but also 2-naphthyl and 2-furyl enones were suitable substrates for the cascade reaction (entries 16 and 17, Table 3). This methodology could also be used to construct the THBC ring

system: the reaction between **3h** (X = NBoc) and **4a** led to the cyclized product in 90% yield with 83% *ee* (Table 3, entry 18). Sequential catalysis overcomes the low-yielding and time-consuming synthesis of substrates **1**. Moreover, some substrates **1** are very reactive, and the cyclized products were formed during their purification. Thus, sequential catalysis avoids problematic separation processes.

The proposed method based on sequential catalysis involves two distinct catalytic processes: olefin cross-metathesis of **3** and **4** catalyzed by a Ru complex, followed by an intramolecular Friedel–Crafts alkylation catalyzed by a chiral phosphoric acid. In the presence of the Ru catalyst, cross-metathesis of **3** and **4** occurs to afford the indolyl enone **1** and a Lewis acidic Ru complex **I** (Scheme 2).[9] The activation of enone **1** by the Ru complex **I** would lead to a racemic product;




***Scheme 2.*** Proposed mechanism of the cascade reaction involving olefin cross-metathesis and Friedel–Crafts alkylation.

the slightly decreased enantioselectivity observed during sequential catalysis can be explained by this side reaction. The asymmetric Friedel–Crafts reaction converts enone **1**, the metathesis product, into the alkylation product. This process facilitates the cross-metathesis reaction, as supported by the observation that the cross-metathesis reaction between **3** and **4** in the absence of a phosphoric acid led to **1** in only moderate yield.

In summary, we have developed an efficient procedure for the sequential catalysis of olefin cross-metathesis and a Friedel–Crafts alkylation to construct the THPI and THBC ring systems in excellent yields and with excellent enantioselectivity. This sequential catalysis enables the use of more readily available starting materials and makes the synthesis of the THPI and THBC systems more practical and economical.

## *Experimental Section*

General procedure: The indolyl allyl ether **3** (0.2 mmol) and enone **4** (0.3 mmol) were dissolved in toluene (2 mL) under argon in a dry Schlenk tube. The resulting solution was heated to 40 or 60 °C, and then the chiral phosphoric acid (0.01 mmol) and Ru catalyst (0.01 mmol) were added together in one portion. When the reaction (monitored by TLC or $^1$H NMR spectroscopy) was complete, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:13–1:6) to afford the product.

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[12] CCDC 736514 ((*R*)-**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] See the Supporting Information for details.

  