Asymmetric Catalysis

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Asymmetric Binary Acid Catalysis: A Regioselectivity Switch between Enantioselective 1,2- and 1,4-Addition through Different Counteranions of In^{III}**

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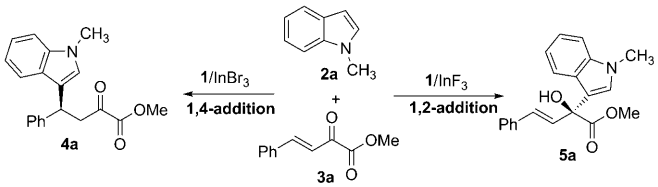
The enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes and ketones is one of the most important approaches for the synthesis of biologically active indole alkaloids.[1] Hence, a number of asymmetric catalysts[2–4] have been developed for this type of reactions. Though amenable to both 1,2- and 1,4-addition pathways, most of these reactions afford 1,4-addition products and there are surprisingly few precedents for 1,2-addition in the reactions.[5] This disparity may stem from the difficulties in re-adjusting the innate reactivity of enals and enones, and the instability and tendency of the 1,2-adducts to form bisindole compounds.[4,6] For example, a recent report indicated that the 1,2-adduct from indole and a β,γ-unsaturated α-keto esters easily reacts with another indole to form bisindole in the catalysis mediated by chiral *N*-triflylphosphoramides.[4] Given the challenges associated with the control of 1,2- and 1,4-additions in both a regio- and stereoselective manner, it is not surprising that enantioselective additions of indoles to α,β-unsaturated aldehydes and ketones with tunable regioselectivity remain unknown. Herein, we present an asymmetric binary acid catalyst that synergistically combines a chiral phosphoric acid[7] and an indium halide salt to achieve both 1,2- and 1,4-selective Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-keto esters (Scheme 1). In this catalytic system, a simple swap of counteranions of indium(III) from fluoride to bromide or chloride switches the regioselectivity from 1,2- to 1,4-addition with excellent reactivity and enantioselectivity in both cases.

In our earlier studies, it was found that a highly efficient binary acid catalyst could be generated from two individually inert species, phosphoric acid **1a** and MgF_2, for the asymmetric Friedel–Crafts reactions of phenols and indoles.[8,9] These findings validated our postulate that the complexation between the Brønsted and Lewis acids would lead to mutually enhanced acidity with concomitant generation of multiacidic centers for synergistic catalysis. Interestingly, when *N*-methyl indole (**2a**) was employed instead of free indole, the binary acid **1a**/MgF_2 catalyzed reactions with β,γ-unsaturated α-keto esters afforded predominantly 1,2-adducts (e.g. **5a**) with exceedingly high regioselectivity (>30:1) and excellent enantioselectivity (Table 1, entry 2). This unexpected finding promoted us to further explore the regioselectivity control in this type of reaction.



Scheme 1. Regioselective and enantioselective 1,2- and 1,4-addition reactions.

Different Lewis acids, chiral phosphoric acids, and combinations thereof were then examined in the model reactions of indole **2a** and keto ester **3a** (see the Supporting Information for details). Several general trends became evident from these experiments:

(1) Besides their critical role in stereocontrol, the judicious selection of chiral phosphoric acid, Lewis acid, and combinations thereof was also essential to attain high catalytic activity. This trend is highlighted by the observed low reactivity or total lack of reactivity when phosphoric acid (e.g. **1a** and **1e**; Table 1, entries 1 and 15) or Lewis acid (e.g. InX_3; Table 1, entry 9) was applied individually.

(2) The use of different Lewis acids have a dramatic impact on the regioselectivity (Table 1, entries 2–8). Most interestingly, in the cases with indium(III) Lewis acids, the simple swap of counteranions of indium(III) was found to switch the regioselectivity between 1,2- and 1,4-addition. For example, InF_3 in combination with phosphoric acid **1a** is as effective as MgF_2/**1a** in promoting 1,2-addition with excellent regioselectivity and enantioselectivity (87% yield, 93% *ee*; Table 1, entry 3). Meanwhile, the use of either $InBr_3$, $InCl_3$, or $In(OTf)_3$ gave exclusively 1,4-adduct (1,4-adduct/1,2-adduct >30:1) with varied enantioselectivity (Table 1, entries 4–6). The fact that the 1,4-additions are generally much faster than 1,2-additions (Table 1, entries 1–3 vs. 4–8) also pinpoints the difficulties in tuning the innate activity toward 1,2-

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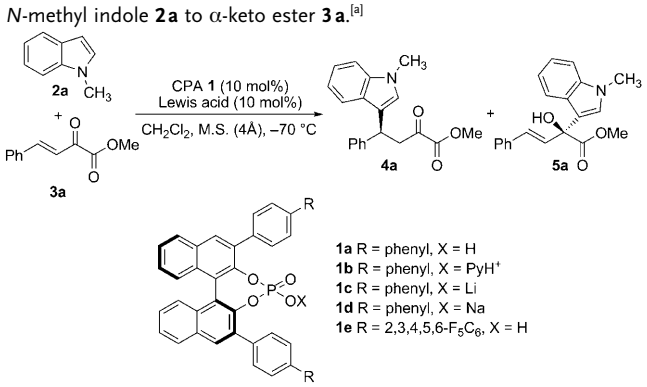
Table 1: Screen of different Lewis acid in the 1,4- or 1,2-addition of *N*-methyl indole **2a** to α-keto ester **3a**.[a]



Entry	**1**/Lewis acid	Yield [%][b]	**4a**/**5a**[c]	*ee* of **4a** [%][d]	*ee* of **5a** [%][d]
1	**1a**/none	75	1:30	–	90
2	**1a**/MgF_2	85	1:30	–	90
3	**1a**/InF_3	**87**	**1:30**	–	**93**
4	**1a**/$InCl_3$	78	31:1	61	–
5	**1a**/$InBr_3$	93	31:1	69	–
6	**1a**/$In(OTf)_3$	70	42:1	−15	–
7	**1a**/$Sc(OTf)_3$	70	45:1	0	–
8	**1a**/$FeCl_3$	95	6:1	68	–
9	InF_3 or $InBr_3$	trace	–	–	–
10	**1b**/$InBr_3$	trace	–	–	–
11	**1c**/$InBr_3$	**90**	**>30:1**	**95**	–
12	**1d**/$InBr_3$	99	>30:1	88	–
13	**1e**/$InBr_3$	**98**	**>30:1**	**97**	–
14	**1e**/InF_3	50	1:30	–	91
15	**1e**	28	1:30	–	88

[a] General conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), **1a** (10 mol%), Lewis acid (10 mol%), and molecular sieves (M.S., 4 Å, 20 mg) at −70°C, for entries 1–8, 14, and 15, 24 h; for entries 9–13, 12 h. [b] Combined yield of isolated products. [c] Determined by NMR analysis. [d] Determined by HPLC on a chiral stationary phase. CPA = chiral phosphoric acid, Py = pyridyl, Tf = trifluoromethanesulfonyl.

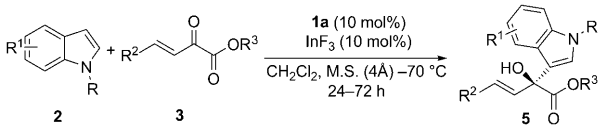
addition. Furthermore, the regioselectivity switch seems to be independent of the chiral phosphoric acid employed, and a similar counteranion effect can be observed with other phosphoric acids such as **1e** (Table 1, entries 13 and 14). To the best of our knowledge, this represents a rare example on switchable regioselectivity by tuning of the counteranion in enantioselective Friedel–Crafts reactions.

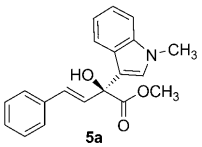
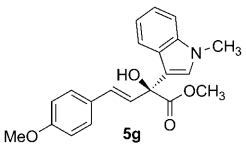
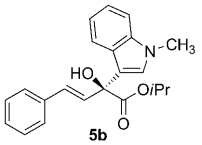
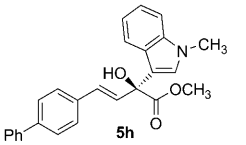
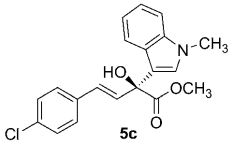
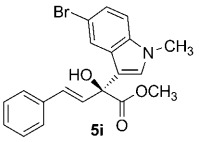
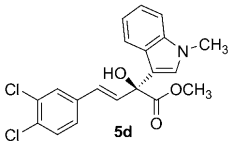
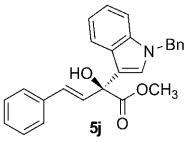
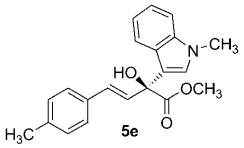
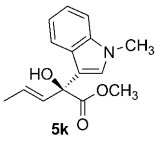
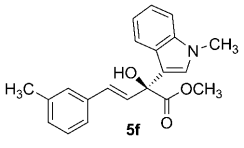
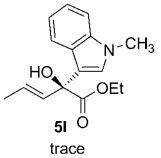
(3) In addition, the binary acid system allows for combinatorial flexibility in identifying an optimal catalytic system. Accordingly, significantly improved enantioselectivity for the 1,4-addition reaction can be achieved by varying the phosphoric acid component. In this regard, two phosphoric acids **1c** and **1e**, generated by straightforward cation metathesis of **1a** with Li^+ or remote substitute tuning respectively, appeared as the optimal partners with $InBr_3$ and gave >95% *ee* in the 1,4-addition reaction (Table 1, entries 11 and 13).

Eventually, InF_3 and $InBr_3$, coupled with chiral phosphoric acid **1a** and its simple derivatives (**1c** and **1e**), were identified as the optimal catalysts for the respective 1,2- and 1,4-addition reactions. These combinations gave excellent regio- and stereoselective control.

Next, the scope of these catalytic systems was explored. In the presence of **1a**/InF_3 (10 mol%), a variety of β,γ-unsaturated α-keto esters were subjected to the reaction with *N*-methyl indole **1a** and gave the desired 1,2-addition products **5a**–**h** in good yields and with up to 99% *ee* (Table 2, entries 1–8). The reactions accommodated *N*-alkyl-substituted indoles including those bearing a methyl or a benzyl substituent,

Table 2: Enantioselective 1,2-addition of N-protected indoles **2** with various α-keto esters **3**.[a]



Entry	Product	Entry	Product
1	 **5a** 82% yield, 93% *ee*	7	 **5g** 63% yield, 99% *ee*
2	 **5b** trace	8	 **5h** 56% yield, 93% *ee*
3	 **5c** 85% yield, 96% *ee* (40% yield, 89% *ee*)[b]	9	 **5i** 75% yield, 82% *ee*
4	 **5d** 77% yield, 95% *ee*	10	 **5j** 61% yield, 93% *ee*
5	 **5e** 70% yield, 89%*ee* (60% yield, 85% *ee*)[b]	11	 **5k** 35% yield, 94% *ee*
6	 **5f** 73% yield, 92% *ee*	12	 **5l** trace

[a] General conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), **1a** (10 mol%), InF_3 (10 mol%), and M.S. (4 Å, 20 mg) at −70°C, for entry 1: 24 h; for entries 3–6: 48 h; entries 2 and 7–12: 72 h. [b] In the absence of InF_3. Bn = benzyl.

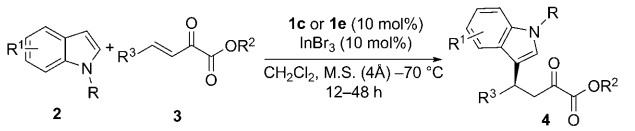
however, no activity was observed with *N*-Boc-protected indoles (data not shown). α-Keto ester **3b** bearing an isopropyl ester substituent was also an inert substrate, and is probably due to the steric hindrance of the bulky ester moiety (Table 2, entry 2). Aliphatic β,γ-unsaturated α-keto esters were also examined in the current catalysis and gave excellent enantioselectivity but low reactivity (Table 2, entry 11).[10] The use of an ethyl ester substituent led to only trace amounts of product (Table 2, entry 12) and this outcome is consistent with the result shown in Table 2, entry 2. In addition, the reaction did not work with γ-heteroatom-substituted keto esters such as (*E*)-methyl-4-ethoxy-2-oxobut-3-enoate, and is probably due to the electron-donating ethoxyl substituent (data not shown).

Overall, the 1,2-addition reactions proceeded cleanly with only trace amounts of 1,4-adducts being detected in all cases. In addition, no bisindole products were observed in our studies and most of the indole starting material was easily recovered. The use of only **1a** in the absence of InF_3 generally gave lower activity and enantisoelectivity (Table 2, entries 3 and 5), thus highlighting again the synergistic combination of **1a** and InF_3. The absolute configuration of **5c** was assigned as *S* by X-ray diffraction analysis and other 1,2-adduct can therefore be assigned by analogy (see the Supporting Information).[11]

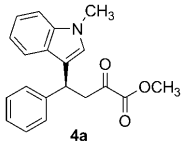
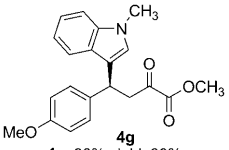
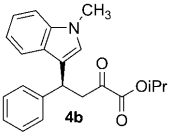
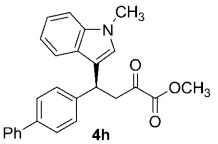
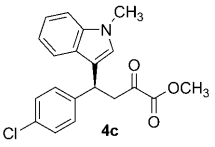
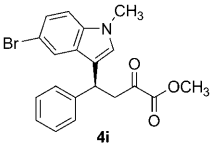
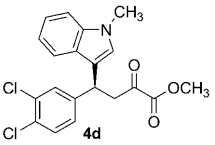
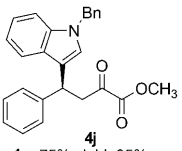
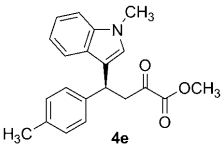
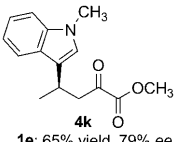
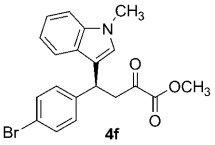
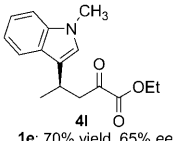
The scope of the 1,4-addition reactions was then examined with **1c**/$InBr_3$ or **1e**/$InBr_3$ binary systems (Table 3). The reaction worked well with a variety of β,γ-unsaturated α-keto esters bearing either γ-aromatic or aliphatic substitutents and *N*-protected indoles **2**. These reactions gave the desired 1,4-addition products **4a–l** in good yields and with excellent regioselectivity and enantioselectivity (Table 3, entries 1–12). The reaction did not work with γ-heteroatom-substituted keto esters such as (*E*)-methyl 4-ethoxy-2-oxobut-3-enoate (data not shown). In the cases examined, **1c**/$InBr_3$ and **1e**/$InBr_3$ performed equally well with the latter showing slightly better enantioselectivity in several cases (Table 3, entries 1, 3, 4, 6, and 8). Interestingly, the use of **1c**/$InBr_3$ enabled a successful reaction (87% yield and 93% *ee*; (Table 3, entry 2) even when **1e**/$InBr_3$ failed. The **1c**/$InBr_3$ system also showed improved enantioselectivity over **1e**/$InBr_3$ with aliphatic β,γ-unsaturated α-keto esters (Table 3, entries 11 and 12). Though the definite role of the lithium cation remains unclear, these results further highlight the combinatorial power of the binary acid catalysis. The absolute configuration of **4i** was assigned as *S* by X-ray diffraction analysis and other 1,4-adduct can therefore be assigned by analogy (see the Supporting Information).[11]

Preliminary experiments were conducted to elucidate the mechanism of the current binary acid catalysis and its dramatic counteranion effect. An ESI-MS experiment (anionic mode) of a solution containing 1:1 **1e** and $InBr_3$ gave three prominent new peaks *m*/*z* 1186, 1663, 1936, corresponding to **1e**·$InBr_3$, $(\mathbf{1e})_2$, and $(\mathbf{1e})_2$·$InBr_2$. No other peaks with a higher *m*/*z* ratio were observed, thus suggesting that phosphoric acid would predominantly form a complex with indium bromide in 1:1 and 2:1 ratio in the solution phase (see the Supporting Information). The ESI-MS studies of **1a** and $InBr_3$ gave similar results.[12] A Job plot by fluorescence titration indicates a 1:1 complexation between **1e** and $InBr_3$ under dilute conditions (see the Supporting Information). These results, together with the observation of a linear correlation between the catalyst *ee* value and product *ee* value, provide strong evidences for a catalytic active complex involving a 1:1 ratio of phosphoric acid and indium(III). In addition, the dramatic counteranion effect on

Table 3: Enantioselective 1,4-addition of N-protected indoles **2** with various α-keto esters **3**.[a]



2 3 4

Entry	Product	Entry	Product
1	 **4a** **1e**: 98% yield, 97% *ee* **1c**: 90% yield, 95% *ee*	7	 **4g** **1e**: 90% yield, 90% *ee*
2	 **4b** **1e**: trace **1c**: 87% yield, 93% *ee*	8	 **4h** **1e**: 87% yield, 93% *ee* **1c**: 75% yield, 70% *ee*
3	 **4c** **1e**: 97% yield, 99% *ee* **1c**: 95% yield, 90% *ee*	9	 **4i** **1e**: 98% yield, 97% *ee*
4	 **4d** **1e**: 95% yield, 98% *ee* **1c**: 92% yield, 97% *ee*	10	 **4j** **1e**: 75% yield, 95% *ee*
5	 **4e** **1e**: 85% yield, 88% *ee* **1c**: 90% yield, 88% *ee*	11	 **4k** **1e**: 65% yield, 79% *ee* **1c**: 70% yield, 93% *ee*
6	 **4f** **1e**: 91% yield, 98% *ee* **1c**: 93% yield, 97% *ee*	12	 **4l** **1e**: 70% yield, 65% *ee* **1c**: 65% yield, 79% *ee*

[a] General conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), **1e** or **1c** (10 mol%), $InBr_3$ (10 mol%), and M.S. (4 Å, 20 mg) at −70°C, for entries 1–2: 12 h; for entries 3–6, 11 and 12: 24 h; for entries 7–10: 48 h.

regio- and stereoselectivity as well as the observation that $In(OTf)_3$ is almost nonselective compared with indium halide (Table 1, entry 6) strongly suggest a unique catalytically active complex should be invoked in the transition state in which the halides remain as an integrate component rather than simply as balancing anions. This is a scenario frequently encountered but largely overlooked in the typical asymmetric Lewis acid catalysis.[13]

Accordingly, the halides may serve as ligands that fine tune the indium(III) metal center in our catalytic systems to afford specific electronic and steric properties.[14–16] The high level of control of both regio- and stereoselectivity could be presumably understood as a result of a combination of innate electronic tuning[15] and steric effects[14,16] upon bidendate activation of the α-keto ester substrate with the indium complex. In both aspects, halide anions would be the delicate, but critical adjustor of the reaction outcome. Unfortunately, the structures of the active catalytic complex remain undetermined so far, and thus limits clear-cut assignments of the functioning modes of halides in this complicated catalytic system (see the Supporting Information for tentative transition states and discussions). Further mechanistic and structural studies are therefore highly warranted.

In summary, a regioselectivity switch and highly enantioselective Friedel–Crafts reaction of N-protected indoles with β,γ-unsaturated α-keto esters has been realized with the aid of an asymmetric binary acid catalyst that synergistically combines chiral phosphoric acid and indium halide. The essential roles of the indium halides (InF_3 and $InBr_3$) lies in their capacity to significantly enhance both the reactivity and stereoselectivity in 1,2- and 1,4-addition as well as the unexpected finding that a simple swap of the counteranions of indium from fluoride to bromide or chloride leads to a regioselective shift between 1,2- and 1,4-additions with excellent regioselectivity and enantioselectivity in both cases. These results underline the potential importance of counteranions in tuning both chemoselectivity and stereoselectivity. Detailed mechanistic studies are ongoing and will be reported in due course.

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