Asymmetric Catalysis

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Chiral Primary Amine Catalyzed Enantioselective Protonation via an Enamine Intermediate**

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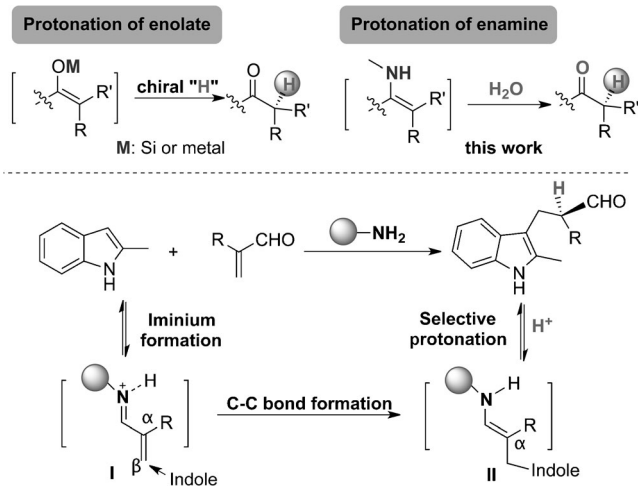
Enantioselective protonation is one of the most straightforward approaches for building α-chiral carbonyl compounds in nature and in synthetic chemistry.[1] The majority of methods rely on protonation of a prochiral enolate, which is either preformed[2] or generated in situ, in the presence of a chiral Lewis acid,[3] transitional metal,[4] or organocatalyst[5] (Scheme 1). Once regarded as complementary to the enolate



Scheme 1. Tandem Friedel–Crafts and enantioseletive protonation via an enamine intermediate.

chemistry, enamine-based processes[6] are now prominent catalytic strategies that facilitate a range of chiral transformations which are beyond the reach of typical enolate approaches.[7] Despite the prevalence of enamine-based methods in the field of asymmetric organocatalysis,[8] enantioselective protonation through enamine catalysis has remained an elusive goal. This is understandable, considering the tremendous challenges associated with this transformation. Manipulating a proton is a nontrivial task, as frequently encountered in the enolate-based processes.[1b,2] The problem may be further exacerbated with enamines, since enamine formation inherently involves multiple proton transfers.[7b] Furthermore, unlike its enolate counterpart that is normally employed as a well-defined *E*/*Z* isomer, catalytic enamine intermediates are highly dynamic, with variable *E*/*Z* geometry.[7b] Finally, the tendency of the chiral product to undergo racemization is of serious concern in enamine catalysis. Indeed, enamine formation has been successfully utilized as the key racemization step in several dynamic kinetic resolutions.[9] Considering the potential pitfalls, we were surprised to find that enantioselective protonation through enamine catalysis with a vicinal primary–tertiary diamine/toluenesulfonic acid (TfOH) catalyst is feasible, and that high enantioselectivity can be achieved under carefully tuned conditions.

In this study, we chose to explore Friedel–Crafts reactions of α-substituted acroleins with indoles through an iminium–enamine-catalyzed process (Scheme 1).[10] In previous studies of iminium-based, asymmetric Friedel–Crafts reactions with α,β-unsaturated enals or enones,[10,11] the stereoselectivity was generated in the C–C bond-forming step at the β position. In contrast, an asymmetric Friedel–Crafts reaction of an α-substituted acrolein, which involves tandem C–C bond formation and enantioselective protonation of the enamine intermediate at the α position (Scheme 1, **II**), has not been reported to date.[12] Asymmetric Friedel–Crafts reactions of α-substituted, α,β-unsaturated enals with indoles have been attempted.[13] These reactions achieve good enantioselectivity but rather poor diastereoselectivity,[13b] which clearly indicates the lack of stereocontrol in the protonation step and further attests to the difficulties in enantioselective protonation of enamines.

Previously, we established that chiral primary–tertiary diamines are effective catalysts for activation of ketones and aldehydes as enamines,[14] and this approach has recently been applied to the activation of α-substituted acroleins as iminium ions.[14e,f] On extending our catalytic system to the hitherto unexplored Friedel–Crafts reaction of α-substituted acroleins, we were pleased to observe significant enantioselectivity in this tandem Friedel–Crafts and protonation sequence. After extensive screening of different diamine catalysts (see the Supporting Information for the screening results), we eventually identified diamine **1**/TfOH (Table 1) as the optimum catalyst system. The reaction of indole **2a** with acrolein **3a** catalyzed by **1**/TfOH in dichloromethane at room temperature afforded a 61% yield of product **4a,** with a promising 79% *ee* (Table 1, entry 1). Optimization of the reaction parameters revealed that the reaction was more efficient

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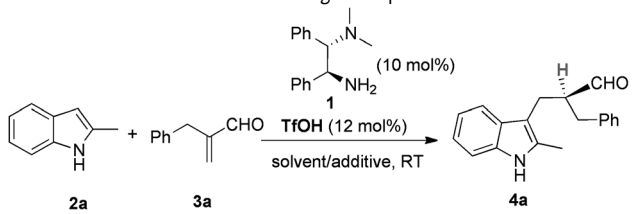
Table 1: Selected results of screening and optimization.[a]

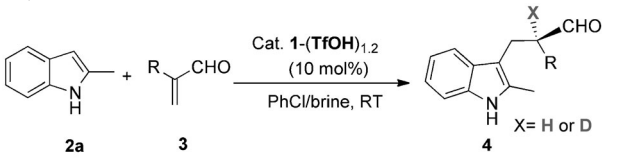


2a 3a 4a

Entry	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	none	61	79
2	DMF[d]	none	43	7
3	MTBE[e]	none	40	74
4	brine	none	34	85
5	toluene	none	76	85
6	PhCl	none	76	87
7	PhCl	(*R*)-BINOL	57	82
8	PhCl	BHT[f] (1 equiv)	61	84
9	PhCl	H_2O (5 equiv)	76	88
10	PhCl	brine (5 equiv)	72	91
11	PhCl	brine (50 equiv)	74	93

[a] General conditions: **2** (0.100 mmol), **3** (0.200 mmol), **1** (10 mol%), and TfOH (12 mol%) in solvent (0.2 mL) at room temperature, 5 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] DMF: dimethylformamide. [e] MTBE: methyl *tert*-butyl ether. [f] BHT: 2,6-di-*tert*-butyl-4-methylphenol.

Table 2: Survey of different α-substituted acroleins in the primary amine catalyzed Friedel–Crafts reaction.[a]



2a 3 4

Entry	Product	Yield [%][d]	*ee* [%][d]
1[b]	R = $PhCH_2$- (**4a**)	74 (76)	93 (94)
2[b]	R = 1-NaphthCH_2- (**4b**)	75 (78)	90 (90)
3	R = 2-MeO$PhCH_2$- (**4c**)	72	88
4	R = 2,4-$(MeO)_2PhCH_2$- (**4d**)	75	87
5[c]	R = 4-Cl$PhCH_2$- (**4e**)	72 (78)	92 (91)
6[c]	R = 2-F$PhCH_2$- (**4f**)	80	89
7[b,c,e]	R = Me (**4g**)	40	83
8	R = $Ph(CH_2)_3$- (**4h**)	64	89
9	R = *n*-C_6H_{13}- (**4i**)	70 (68)	82 (88)
10	R = *n*-C_7H_{15}- (**4j**)	56	86
11	R = cyclohexyl- (**4k**)	80	83
12	R = 1-oct-2-enyl- (**4l**)	52	75

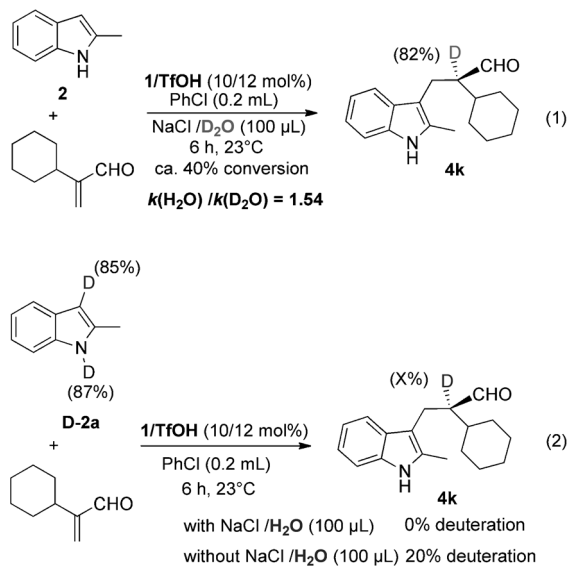
[a] General conditions: **2** (0.100 mmol), **3** (0.200 mmol), **1**/**TfOH** (10/12 mol%) in PhCl (0.2 mL), and brine or saturated NaCl/D_2O (9 μL) at room temperature for 5–14 h. [b] With brine (100 μL). [c] Isolated as alcohol after in situ reduction with $NaBH_4$. [d] Data in parenthesis refer to yields obtained in the presence of D_2O (X = D). [e] In the presence of 11 mol% TfOH. Completed conversion of starting material and decomposition of product **4g** were observed.

with chlorobenzene as the solvent (Table 1, entry 6 versus entries 1–5). Furthermore, external proton donors, such as alcohols or phenols, that are typically employed to protonate enolates were not preferred in this reaction (Table 1, entries 7 and 8). Instead, the addition of water, and particularly brine, was found to increase the enantioselectivity. An *ee* value of 93% was obtained under heterogeneous conditions, in the presence of 50 equivalents of brine (entry 11).

With the new process and optimized conditions in hand, the scope of the catalytic system was examined. An array of α-substituted acroleins were tested in the reaction, resulting in good yields of products **4a–l** and high enantioselectivity (Table 2).[15,16] 2-Benzyl-substituted acroleins were identified as one class of preferred substrates, and benzyl groups bearing either electron-rich (Table 2, entries 2–4) or electron-deficient (Table 2, entries 5 and 6) substituents were also good substrates. Additionally, acroleins bearing other α-alkyl groups, including linear primary alkanes (Table 2, entries 7–10), secondary alkanes, such as cyclohexyl (Table 2, entry 11), and allyl-type groups (Table 2, entry 12) were all suitable substrates, and afforded the corresponding products in high yields and with high enantioselectivity. Acroleins with α-heteroatom substituents, such as benzyloxyl and *tert*-butyl carbamate, were not compatible with the enamine catalysis and no product formation was observed (data not shown).

The scope of the reaction with respect to indole substitution was also investigated (Table 3). A series of indoles with different substituents at the C5- (Table 3, entries 1, 2 and 9), C2- (Table 3, entries 3 and 4), and N-positions (Table 3, entries 7 and 8) were tested in the reaction with catalyst **1**/TfOH. The desired products **5a–i** were obtained in high yields and with high enantioselectivity. The use of 2-unsubstituted indoles led to some loss of enantioselectivity, but the reactions still proceeded smoothly to furnish high yields of the desired products **5c** and **5d** (Table 3, entries 5 and 6). An example of a 3-substituted indole, 3-methylindole, was also examined in the reaction with catalyst **1**/TfOH. In this case, the reaction was much slower and we were unable to isolate the desired product from the compex reaction mixture. Additionally, we determined that α-deuterated products (> 80% deuteration) could be readily obtained with similar enantioselectivity as the α-protonated products, when the reactions were conducted in the presence of saturated NaCl/D_2O (Table 2, entries 1, 2, 5, and 9; Table 3, entries 2, 3, 5, 7, and 8).

Mechanistic studies were conducted on the sequence of iminium–enamine formation to elucidate this intriguing protonation process. No deracemization was observed when racemic **4a** was treated with **1**/TfOH. This result suggests that the enantioselectivity is generated directly from the tandem iminium–enamine sequence and is not the consequence of dynamic kinetic resolution.[9] In addition, racemization of the reaction products through enamine formation was found to be negligible when the isolated, optically pure products were subjected to the optimized reaction conditions (see the Supporting Information for details). A series of labeling experiments [Eqs. (1) and (2) and see also the examples in Tables 2 and 3] were also carried out. In the presence of saturated NaCl/D_2O, deuterated products (> 80% deuteration) were generally obtained. On the other hand, the use of deuterated indole D-**2** led to only 20% α-deuteration in anhydrous chlorobenzene, or nearly no deuteration in the presence of H_2O [Eq. (2)]. Taken together, these results suggest that water, either generated in situ on formation of the iminium ion or added to the reaction, might serve as the



proton donor, and that water-mediated proton transfer is likely preferred in the current reaction.[17] The large primary kinetic isotope effect of k_{H_2O}/k_{D_2O} =1.54 for added water is clearly consistent with this hypothesis [Eq. (1)].

From the absolute configuration of product **5i** (determined by X-ray crystallography; see the Supporting Information for details), we propose the transition states shown in Figure 1 to account for the stereoinduction. Accordingly, stereospecific, H_2O-bridged protonation of the dominant *E*-enamine **a1**, which is generated from the preferred *s-trans*-iminium **III** in situ, leads to the enantioselectivity observed.

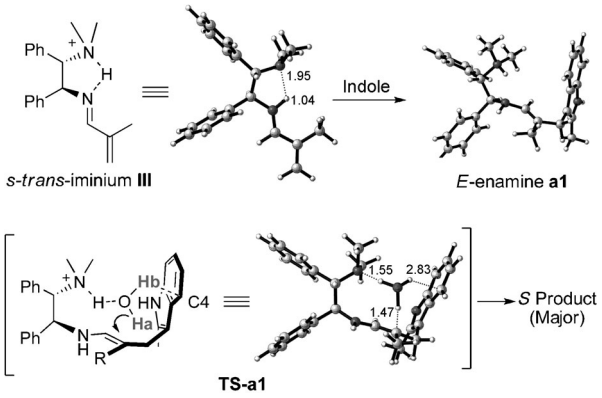
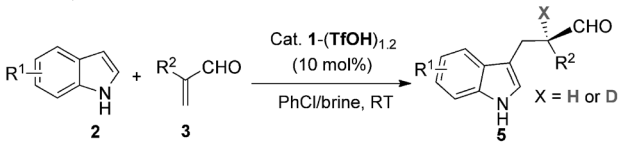
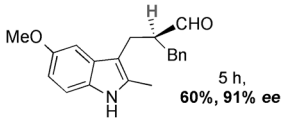
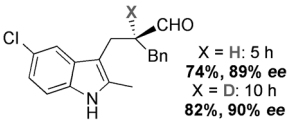
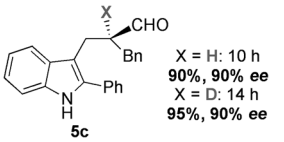
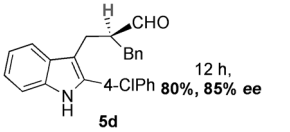
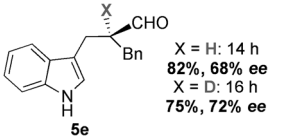
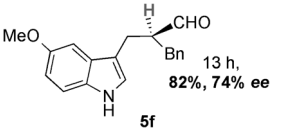
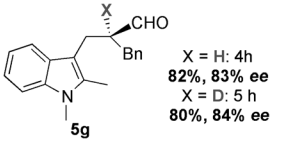
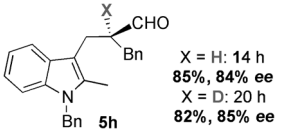
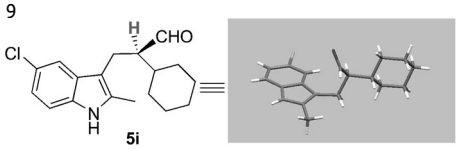


Figure 1. Calculated intermediates and transition structures for water-bridged proton transfer (only enamine **a1** and **TS-a1** shown).

Table 3: Survey of different indoles.[a]



Entry	Product	Entry	Product
1[b]	 5 h, **60%, 91% *ee*** **5a**	2	 X = H: 5 h **74%, 89% *ee*** X = D: 10 h **82%, 90% *ee*** **5b**
3	 X = H: 10 h **90%, 90% *ee*** X = D: 14 h **95%, 90% *ee*** **5c**	4[b]	 12 h, **80%, 85% *ee*** **5d**
5	 X = H: 14 h **82%, 68% *ee*** X = D: 16 h **75%, 72% *ee*** **5e**	6	 13 h, **82%, 74% *ee*** **5f**
7	 X = H: 4h **82%, 83% *ee*** X = D: 5 h **80%, 84% *ee*** **5g**	8	 X = H: **14** h **85%, 84% *ee*** X = D: 20 h **82%, 85% *ee*** **5h**
9	 **7** h, **82%, 80% *ee*** **5i**		

[a] General conditions: **2a** (0.100 mmol), **3** (0.200 mmol), **1/TfOH** (10/12 mol%) in PhCl (0.2 mL), and brine or saturated NaCl/D_2O (100 μL), at room temperature for 4–20 h. [b] With brine (9 μL). Bn = benzyl

DFT calculations were undertaken to study the proposed mode of stereocontrol. The reaction between 2-methylindole and methacraldehyde was chosen for our study. The theoretical calculations were carried out with B3LYP/6-311++G(2df,2p)//B3LYP6-31+G(d) in Gaussian 03 programs. Indeed, *S*-trans-iminium **III** was found to be the most stable iminium conformer by 3.0 kcal mol^{-1} (Figure 1). The iminium **III** is stabilized by a strong hydrogen bond between the vicinal amino groups. A similar proton-fixed iminium conformer has also been proposed for other primary amine catalysts.[12a] Subsequent addition of an indole to iminium **III** would lead preferentially to *E*-enamine intermediates with varied conformations. Accordingly, we have located four *E*-enamine conformers **a1**–**a4** and successfully reached the corresponding transition states for H_2O-bridged proton-transfer processes (Table 4, **TS-a1**–**a4**; structures are shown in Scheme S3 in the Supporting Information). The activation barrier was calculated to be 13.7 kcal mol^{-1}, which indicates that the water-bridged process is quite facile. The calculated enantioselectivity based on the four transition states was 76% *ee* in favor of the *S* product (Table 4), which is in good agreement with the experimental result (83% *ee*). In addition, the most favored transition state **TS-a1** was stabilized by an O–H/π interaction between the water molecule and the indole ring.[18] This interaction was absent in the other three transition states (see Scheme S3 in the Supporting Information).

Table 4: DFT-predicted enantiomeric excess for the reaction of 2-methylindole and methacrylaldehyde in chlorobenzene.

Transition state[a]	E_{rel} [kcal mol^{-1}][b]	Ratio at 25 °C [%]	Product	Calcd *ee* [%]
TS-a1	0	82.2	*S*	
TS-a2	1.59	5.6	*S*	76
TS-a3	1.53	6.2	*R*	(exptl 83)[c]
TS-a4	1.54	6.0	*R*	

[a] Calculated at the B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G(d) level; the structures of *E*-enamine **a2-a4** and **TS-a2-a4** are listed in Scheme S3 in the Supporting Information. [b] Enthalpy in chlorobenzene solution. [c] With brine (100 μL).

Although unprecedented in asymmetric catalysis, such an O–H/π interaction is prevalent in biological systems involving tryptophan residues, and account for the favorable conformation and catalysis.[19] With its propensity for participating in O–H/π interactions, the indole moiety in the current system seems to be critical for stereocontrol, since similar reactions with pyrrole, 3-methoxybenezenethiol, or benzotriazole give low chiral induction.[20]

In conclusion, we have successfully developed the first enantioselective protonation via a catalytic enamine intermediate. This process is made possible through chiral primary amine catalyzed Friedel–Crafts reactions of α-substituted acroleins. Critical to the success of the reaction was the identification of a vicinal primary–tertiary diamine/Brønsted acid catalyst and the finding that water, particularly brine, is the inherently preferred proton donor. Theoretical studies indicated that the water-bridged proton transfer is indeed a favorable pathway and an unprecedented O–H/π interaction was found to contribute significantly to the stereocontrol of the reaction. The current enantioselective protonation protocol, which accommodates a range of acroleins and indoles, represents the first such catalytic protonation processes that produces chiral aldehydes, and also has significant potential for generating chiral indole derivatives.

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[15] Minor side products were observed by TLC and NMR spectroscopic analysis of the crude reaction mixtures. However, we were unable to characterize these products because of their instability during isolation and purification.

[16] A larger scale (3 mmol) reaction has been conducted to afford **4a** (0.59 g) in 71 % yield and 90 % *ee* in 4 h.

[17] A possible intramolecular proton transfer cannot be excluded, since the deuterated indole D-**2** was found to undergo rapid H/D exchange under the optimized reaction conditions with a rate comparable to or even faster than that of the Friedel–Crafts reaction. Further theoretical studies are necessary to examine this issue. We thank the referee for bringing our attention to this point.

[18] In **TS-a1**, the shortest $O{-}H^{b}{-}C^{4}$ distance is 2.33 Å. Atoms in Molecules (AIM) analysis at the bond critical point suggested a weak interaction between H^{b} and C^{4} where the electron denstity (ρ_{b}) is 0.0137 au and the Laplacian values ($\Delta^{2}\rho_{b}$) is 0.0431 au. These values indicate that an O–H/π interaction is present.

[19] Tryptophan is known to be one of the most potent and prevalent π acceptors in O–H (H_2O)/π interactions, see T. Steiner, G. Koellner, *J. Mol. Biol.* **2001**, *305*, 535 – 557.

[20] *N*-Methylpyrrole: −10 °C, 16 h, 87 % yield, 40 % *ee*; 3-methoxylbenzenethiol (thio-addition product), −10 °C, 16 h, 90 % yield, 3 % *ee*; benzotriazole, 12 h, 65 %, 7 % *ee*. Ethyl malonate has also been examined, but showed no product formation was observed.

