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Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis

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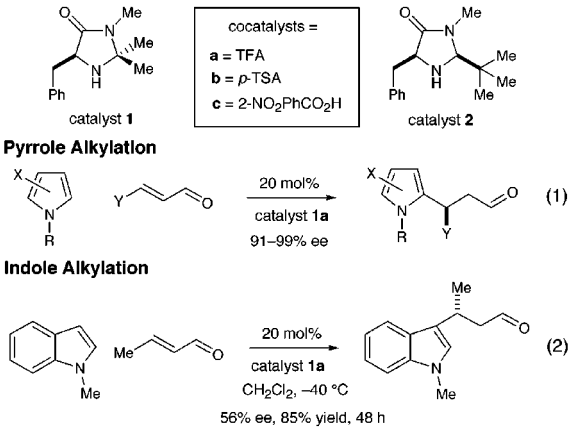
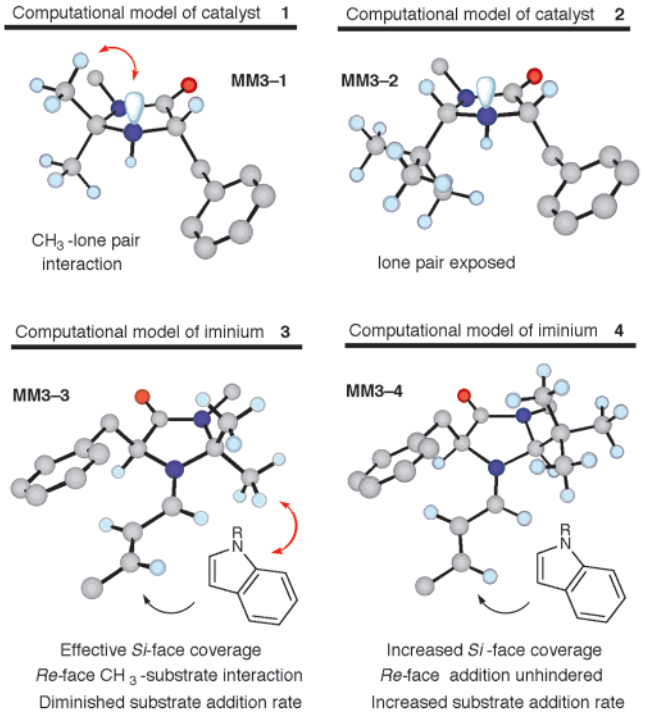
With the rapid growth of asymmetric catalysis[1] has come an increasing demand for chiral technologies that provide structural motifs of established value in medicinal chemistry or complex target synthesis. In this regard, the indole framework has become widely identified as a "privileged" structure or pharmacaphore, with representation in over 3000 natural isolates[2] and 40 medicinal agents of diverse therapeutic action.[3] Surprisingly, however, asymmetric entry to indolic architecture has been largely restricted to the derivatization of enantiopure amino acids[4] or the optical resolution of racemic mixtures.[5]



Having established the capacity of iminium catalysis to mediate the enantioselective coupling of pyrroles and α,β-unsaturated aldehydes (eq 1, 91−99% ee),[6] we recently sought to extend this powerful Friedel−Crafts strategy to indole nucleophiles. Despite structural similarities, it has long been established[7] that the pyrrole π-system is significantly more activated toward electrophilic substitution than the indole framework. Indeed, poor reaction rates and enantioselectivities were observed in the addition of *N*-methylindole to (*E*)-crotonaldehyde using imidazolidinone catalyst **1** (eq 2, 56% ee, 83% yield after 48 h). In an effort to overcome this limitation in indole reactivity, we embarked upon studies to identify a more reactive amine catalyst that might enable less electron-rich heteroaromatics to undergo Friedel−Crafts alkylation. In this context, we report the development of a new imidazolidinone catalyst **2** and its application to the first enantioselective organocatalytic indole alkylation.[8]

Design of Catalyst 2. Preliminary kinetic studies have indicated that the overall rates of iminium-catalyzed reactions are influenced by the efficiency of both the initial iminium formation step and the carbon−carbon bond-forming event. As such, we hypothesized that catalyst **2** (**MM3-2**)[9] should exhibit improved efficiency for iminium formation and hence increased overall rate as the participating nitrogen lone pair is positioned away from structural impediment (cf. **MM3-1**, CH_3-lone pair eclipsing orientation).



Moreover, heteroaromatic nucleophiles that engage the activated-iminium **3** (derived from catalyst **1**) must encounter a retarding interaction with the illustrated methyl substituent. In contrast, the reactive enantioface of iminium ion **4** is free from steric obstruction and, as such, should exhibit increased reactivity toward carbon−carbon bond formation. In terms of our design criteria for enantiocontrol,[10] the catalyst-activated iminium ion **4** was anticipated to selectively populate the (*E*)-isomer to avoid nonbonding interactions between the substrate olefin and the *tert*-butyl group. As a result, the benzyl group on the catalyst framework will effectively shield the *si*-face of the activated olefin, leaving the *re*-face exposed to indole addition.

Catalyst Application. As revealed in Table 1, the enantioselective alkylation of *N*-methylindole with (*E*)-crotonaldehyde using the *tert*-butyl-benzyl imidazolidinone catalysts **2a** and **2b** provided the benzylic substituted indole (*R*)-**5** with high levels of enantioselectivity and reaction efficiency (entries 1 and 2, 1.5−4 h, ≥70% yield, ≥85% ee). An enantioselectivity/temperature profile documents that optimal enantiocontrol is available at −83 °C with catalyst **2a** (entry 5, 84% yield, 92% ee). A survey of solvent additives reveals that the use of *i*-PrOH (15% v/v in CH_2Cl_2) has a dramatic influence on reaction rate without loss in enantiocontrol (entry 6, 92% ee, 19 h). The superior levels of asymmetric induction and efficiency exhibited by **2a** to afford the substituted indole (*R*)-**5**

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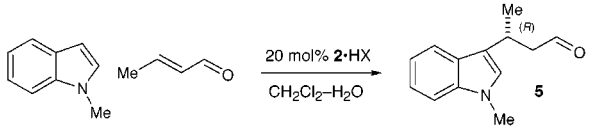
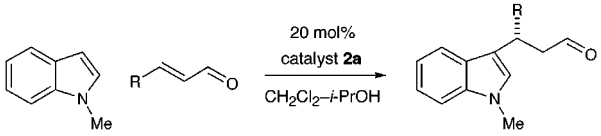
Table 1. Effect of Cocatalyst and Temperature on the Alkylation of *N*-Methylindole with Crotonaldehyde with Catalyst **2**



entry	catalyst	cocatalyst	temp °C	time (h)	% yield	% ee[a,b]
1	**2a**	TFA	−40	1.5	70	85
2	**2b**	*p*-TSA	−40	4	98	88
3	**2c**	2-NO_2PhCO$_2$H	−40	22	88	88
4	**2b**	*p*-TSA	−83	48	15	80
5	**2a**	TFA	−83	31	84	92
6	**2a**	TFA	−83	19	82	92[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration assigned by chemical correlation to a known compound. [c] Reaction conducted with CH_2Cl_2−*i*-PrOH (85:15 v/v) as solvent.

Table 2. Organocatalyzed Alkylation of *N*-Methylindole with Representative α,β-Unsaturated Aldehydes



entry	R	temp °C	time (h)	% yield	% ee[a]
1	Me	−83	19	82	92[b]
2	Pr	−60	6	80	93
3	*i*-Pr	−50	32	74	93
4	CH_2OBz	−83	18	84	96[b]
5	Ph	−55	45	84	90
6	CO_2Me	−83	21	89	91

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation.

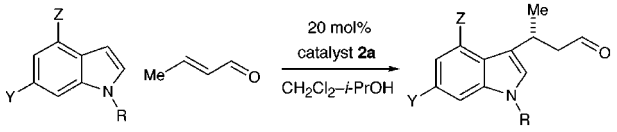
in 92% ee and 82% yield prompted us to select this catalyst for further exploration.

Experiments that probe the scope of the α,β-unsaturated aldehyde substrate are summarized in Table 2. The reaction appears quite tolerant with respect to the steric contribution of the olefin substituent (R = Me, Pr, *i*-Pr, CH_2OBz, entries 1−4, ≥74% yield, ≥92% ee). As revealed in entries 5 and 6, the reaction can accommodate electron-deficient aldehydes that do not readily participate in iminium formation (R = CO_2Me, 91% ee) as well as stabilized iminium ions that might be less reactive toward Friedel−Crafts alkylation (R = Ph, 90% ee). To demonstrate preparative utility, the addition of *N*-methylindole to crotonaldehyde was performed on a 25 mmol scale with catalyst **2a** to afford (*R*)-**5** in 92% ee and 81% yield.

This amine-catalyzed conjugate addition is also general with respect to indole architecture (Table 3). Variation in the *N*-substituent (R = H, Me, CH_2Ph, allyl, entries 1−4) is possible without significant loss in yield or enantioselectivity (≥70% yield, 89−92% ee). Incorporation of alkyl and alkoxy substituents at the C(4)-indole position reveals that electronic and steric modification of the indole ring can be accomplished with little influence on reaction selectivity (entries 5 and 6, ≥90% yield, 94% ee). As revealed in entry 7, we have successfully utilized electron-deficient nucleophiles in the context of a 6-chloro substituted indole (73% yield, 97% ee). Such halogenated indole adducts should prove to be valuable synthons for use in conjunction with organometallic technologies (e.g., Buchwald or Hartwig,[11] Stille[12] couplings).

A demonstration of the utility of this organocatalytic alkylation is presented in the synthesis of the indolobutyric acid **6** (eq 3), a COX-2 inhibitor developed in association with the Merck rofecoxib campaign.[13] As outlined in eq 3, organocatalytic alkylation of the 5-methoxy-2-methylindole **7** with crotonaldehyde followed by oxidation of the formyl moiety provides the COX-2 inhibitor **6** in 87% ee and in 82% yield over two steps. This operationally trivial

Table 3. Enantioselective Organocatalyzed Alkylation of Representative Indoles with (*E*)-Crotonaldehyde



	indole substituents						
entry	R	Y	Z	temp (°C)	time (h)	% yield	% ee[a]
1	Me	H	H	−87	19	82	92[b]
2	H	H	H	−60	22	72	91[b]
3	allyl	H	H	−72	20	70	92
4	CH_2Ph	H	H	−60	120	80	89[b]
5	H	H	Me	−60	3	94	94[c]
6	Me	H	OMe	−87	19	90	96[c]
7	H	Cl	H	−60	13	73	97[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation. [c] Reaction conducted with (*E*)-BzOCH_2CH=CHCHO.

procedure reveals that complex enantioenriched drug leads can be rapidly accessed using this new organocatalytic protocol.

In summary, we have further established LUMO-lowering organocatalysis as a broadly useful concept for asymmetric synthesis in the context of Friedel−Crafts indole alkylation. A full account of this survey will be forthcoming.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (PDF). See any current masthead page for ordering information and Web access instructions.

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