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Enantioselective Organocatalytic Intramolecular Ring-Closing Friedel–Crafts-Type Alkylation of Indoles

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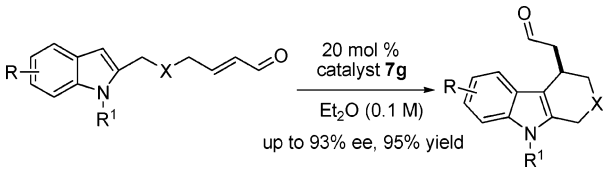
ABSTRACT



An enantioselective organocatalytic intramolecular ring-closing Friedel–Crafts-type alkylation of indolyl α,β-unsaturated aldehydes has been developed. This powerful new strategy allows enantioselective access to THPIs and THBCs in a straightforward and atom-economical manner.

Catalytic transformations of direct C−H bond functionalization involving the indole framework are still a challenging area of intense interest and would be particularly attractive to both academic and industrial chemists.[1] Over the past few years, considerable research efforts have been directed toward the development of new and efficient catalytic routes to polycyclic indoles through both Lewis acid and transition-metal-catalyzed intramolecular alkylations of indoles (IMAI),[2,3] among which high levels of enantiocontrol are achieved in some cases.[2a,d,3h,i] Surprisingly, however, organocatalytic IMAI has remained largely unexplored. Only chiral thiourea and phosphoric acid catalyzed Pictet−Spengler reactions have been reported by Jacobsen[4] and List,[5] respectively, to the best of our knowledge. In addition, few catalytic asymmetric transformations have been developed to prepare tetrahydropyrano[3,4-*b*]indoles (THPIs), although this ring system has become widely identified as a common structural component of a broad range of naturally occurring and biologically active molecules.[1d,6] These facts have stimulated us to explore an enantioselective organocatalytic IMAI, which could be employed as a general approach to enantio-riched polycyclic indoles.

With the development of MacMillan's LUMO-lowering activation of α,β-unsaturated aldehydes, a wide range of

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(5) (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. For other typical organocatalytic cyclizations developed by the List group, please see: (b) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785. (c) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (d) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

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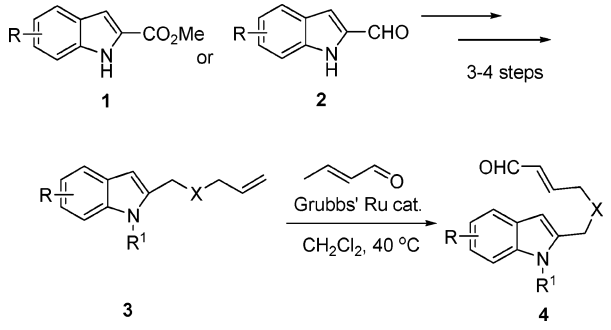
organocatalytic asymmetric reactions have been established.[7] As part of our ongoing project on the enantioselective organocatalysis,[8] we demonstrate that this elegant methodology is amenable to organocatalytic intramolecular ring-closing Friedel−Crafts alkylation of indolyl α,β-unsaturated aldehydes in this communication. Importantly, this strategically new approach allows the construction of THPIs and tetrahydro-β-carbolines (THBCs)[9] from simple substrates.

Starting from methyl 1*H*-indole-2-carboxylate (**1**) or 1*H*-indole-2-carbaldehyde (**2**), the indolyl α,β-unsaturated aldehydes for this study were successfully synthesized using cross metathesis reactions of the corresponding indolyl allyl ethers or amines with crotonaldehyde as the key step in the presence of Grubbs' second-generation catalyst (Scheme 1).[10]

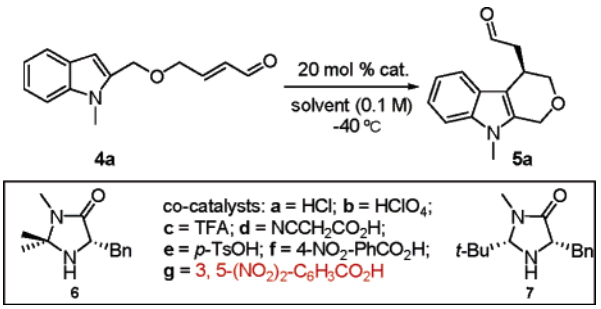
Scheme 1. Synthesis of Indolyl α,β-Unsaturated Aldehydes



By virtue of the ready synthetic availability, indolyl α,β-unsaturated aldehyde (**4a**) was chosen as the model substrate, and a brief survey of IMAI conditions, with a series of catalysts at −40 °C in different solvents, was performed (Table 1).

Among the catalysts screened, MacMillan's second-generation imidazolidinone catalyst **7** resulted in better yields and higher enantioselectivities in comparison with the first-generation catalyst **6** and L-proline (Table 1, entries 1−3). The highest enantioselectivity in CH_2Cl_2 was obtained with the use of catalyst **7g**,[11] which provided **5a** in 90% yield

Table 1. Optimization of the Reaction Conditions for the IMAI of **4a**



entry	catalyst/ co-catlyst	solvent	time	yield (%)[a]	ee (%)[b]
1[c]	L-proline	CH_2Cl_2	12.5 days	59	8
2[d]	**6a**	CH_2Cl_2	18 days	51	1
3	**7a**	CH_2Cl_2	82 h	67	12
4	**7b**	CH_2Cl_2	43 h	17	2
5	**7c**	CH_2Cl_2	36 h	71	50
6	**7d**	CH_2Cl_2	36 h	91	84
7	**7e**	CH_2Cl_2	60 h	69	32
8	**7f**	CH_2Cl_2	213 h	92	80
9	**7g**	**CH_2Cl_2**	**32 h**	**90**	**85**
10	**7g**	$CHCl_3$	31 h	72	84
11	**7g**	*i*-PrOH	67 h	83	48
12	**7g**	THF	43 h	76	82
13	**7g**	CH_3CN	24 h	65	80
14	**7g**	**Et_2O**	**27 h**	**85**	**90**
15[e]	**7g**	Et_2O	139 h	91	88
16	**7g**	toluene	22 h	67	88
17[f]	**7g**	toluene	10 days	72	72

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Warmed to 0 °C after 12 days. [d] Warmed to 0 °C after 17.5 days. [e] At −60 °C. [f] At −78 °C.

and 85% ee (Table 1, entry 9). Further examinations on the solvent with **7g** (Table 1, entries 9−17) showed that the solvent played an important role in obtaining both high levels of enantioselectivity and reaction efficiency. An enantioselectivity/solvent profile documented that optimal enantiocontrol was available in diethyl ether with catalyst **7g** (Table 1, entry 14, 85% yield, 90% ee). Decreasing the reaction temperature to −60 °C in diethyl ether did improve the reaction yield but did not improve the enantioselectivity after 139 h (Table 1, entry 15). The superior levels of asymmetric induction and reaction efficiency exhibited by **7g** in diethyl ether prompted us to select this catalyst−solvent combination for further exploration.

Experiments that probe the scope of the indolyl α,β-unsaturated aldehyde substrates are summarized in Table 2. The reaction appears quite tolerant with respect to the steric and electronic contribution of substituents on the indole ring (Table 2, entries 1−11). Incorporation of methyl and methoxyl substituents at the C-5 position of the indole revealed that electronic and steric modification could be accomplished with no obvious influence on the reaction selectivity (Table 2, entries 10 and 11, ≥ 58% yield, 92% ee). As shown in entries 4, 6, and 8 in Table 2, we could also use electron-deficient indole architecture in the context

(7) For selected references, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (c) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (d) Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157. (e) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.

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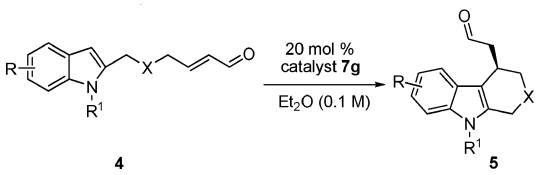
(10) Please see the Supporting Information for details.

(11) The catalyst **7g** was prepared in situ by mixing the equal amount of MacMillan's catalyst **7** with 3,5-dinitrobenzoic acid.

Table 2. Organocatalyzed Intramolecular Ring-Closing Friedel−Crafts-Type Alkylation of Representative Indolyl α,β-Unsaturated Aldehydes



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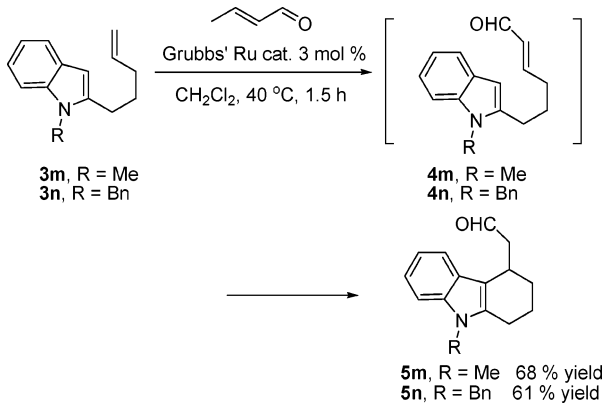
entry	4	R_1	R	X	temp (°C)	time	yield (%)[a]	ee (%)[b]
1	**4a**	Me	H	O	−40	27 h	85 (**5a**)	90
2[c]	**4b**	Bn	H	O	−20	11.5 days	75 (**5b**)	92
3[d,e]	**4c**	DMB	H	O	−30	89 h	48 (**5c**)	80
4	**4d**	Me	5-F	O	−40	23 h	86 (**5d**)	84
5[e,f]	**4e**	Bn	5-F	O	−20	9 days	89 (**5e**)	85
6	**4f**	Me	5-Cl	O	−40	36 h	73 (**5f**)	90
7	**4g**	Me	7-Cl	O	−40	32 h	77 (**5g**)	90
8	**4h**	Me	5-Br	O	−40	72 h	95 (**5h**)	93
9[d]	**4i**	Me	5-MeO	O	0	24 h	57 (**5i**)	80
10	**4j**	Bn	5-MeO	O	−20	7 days	58 (**5j**)	92
11[c]	**4k**	Bn	5-Me	O	−20	11 days	75 (**5k**)	92
12[g]	**4l**	Bn	H	O	0	4.5 days	78 (**5l**)	90

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Warmed to rt after 10 days. [d] DMB: 3,4-dimethoxybenzyl. [e] 0.1 M in toluene. [f] Warmed to rt after 8 days. [g] 0.075 M in toluene.

of 5-F-, Cl-, and Br-substituted indole rings for this organocatalytic IMAI, and the enantioselectivity of the reaction improved in the order of Br > Cl > F under the same conditions. Incorporation of a chloro substituent at the C-5 and C-7 positions showed little influence on the reaction selectivity and efficiency (Table 2, entries 6 and 7). Importantly, such Cl- and Br-substituted THPIs should be valuable for some transition-metal-catalyzed transformations,[12] and the fluorine-containing THPIs could be useful in the fields of medicinal and material sciences.[13] In addition, a variation in the N-substituents (R^1 = Me, Bn, DMB) was possible but would result in significant differences in the reaction rate and selectivity, with the best results being obtained with the *N*-Me substrate (Table 2, entries 1−3). To demonstrate the utility of this methodology to other polycyclic indoles in addition to THPIs, the reaction of **4l** (X = NTs) was performed under the optimized conditions to afford the corresponding THBC **5l** in 90% ee and 78% isolated yield (Table 2, entry 12).

When X was a methylene group, the α,β-unsaturated aldehydes (**4m** and **4n**) could not be isolated from the cross-metathesis (CM) reaction system. The ring-closing alkylation occurred readily under the CM reaction conditions to afford the corresponding tetrahydrocarbazoles **5m** and **5n**, respectively (Scheme 2). In addition, the reaction of the indolyl α,β-unsaturated ketone, (*E*)-5-((1-methyl-1*H*-indol-2-yl)-methoxy)pent-3-en-2-one (**4o**), was performed at room

Scheme 2. Reactions of **3m** and **3n** in the Presence of Grubbs' Catalyst

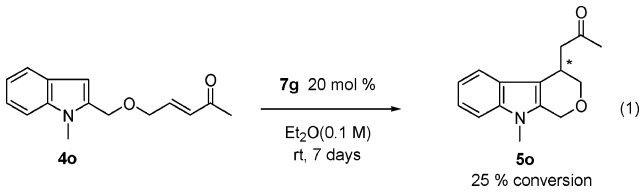


3m, R = Me
3n, R = Bn

4m, R = Me
4n, R = Bn

5m, R = Me 68 % yield
5n, R = Bn 61 % yield

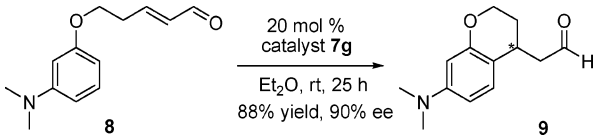
temperature; however, this reaction was very sluggish, and only 25% conversion was observed after 7 days (eq 1).[10]



4o **5o** 25 % conversion (1)

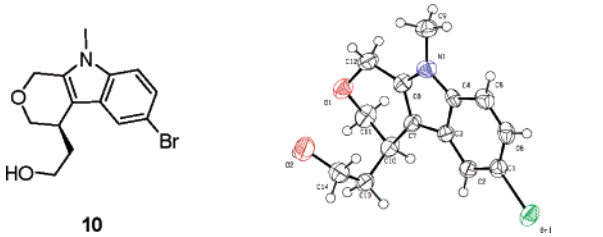
To examine the generality of this chemistry, phenoxyl-substituted α,β-unsaturated aldehyde **8** was synthesized and subjected to **7g** in diethyl ether at room temperature for 25 h (Scheme 3). To our great delight, the intramolecular ring-

Scheme 3. Organocatalyzed Intramolecular Ring-Closing Friedel−Crafts-Type Alkylation of **8**



8 **9**

closing alkylation works very well to afford the corresponding chroman-4-yl acetaldehyde **9** in 90% ee and 88% yield.



10

Figure 1. X-ray crystal structure of (*R*)-2-(6-bromo-9-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl)ethanol (**10**).

(12) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852 and references cited therein. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

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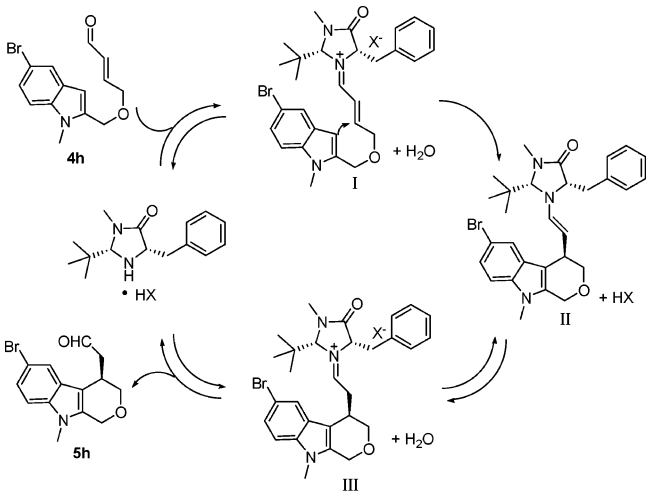
To determine the absolute configuration of the product, we have prepared the corresponding alcohol **10** through the reduction of 2-(6-bromo-9-methyl-1,3,4,9-tetrahydropyrano-[3,4-*b*]indol-4-yl)acetaldehyde (**5h**). The absolute configuration of **5h** was determined to be *R* by X-ray crystallography[10] of **10** (Figure 1). The other products could be tentatively assigned by assuming an analogous enantioinduction (Scheme 4).

Scheme 4. Possible Mechanism of IMAI



A possible mechanism of IMAI is outlined in Scheme 4. Exposure of α,*β*-unsaturated aldehyde **4h** to the imidazolidinone catalysts woud generate activated iminium ion **I**, in which the benzyl group on the catalyst framework could effectively shield the *si* face of the activated olefin. The nucleophilic attack of the indole species approaches from the *re* side, leading to the formation of a (*R*)-configured stereocenter in the enamine II. Hydrolysis of the resulting iminium III releases the catalysts and the alkylation product (*R*)-**5h**.

In conclusion, we have developed a powerful new enantioselective organocatalytic variant of the intramolecular indole alkylation. This method allows enantioselective access to THPIs and THBCs in a straightforward and atom-economical manner. Further studies to expand the scope of this methodology are in progress.

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Supporting Information Available: Experimental details and chromatographic and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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