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Organocatalytic Asymmetric Friedel–Crafts Alkylation of Indoles with Simple α,β-Unsaturated Ketones

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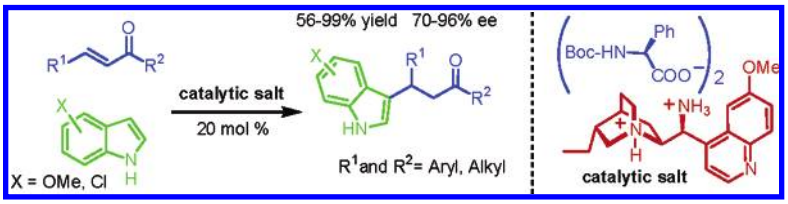
ABSTRACT



The first general and highly enantioselective organocatalytic Friedel–Crafts alkylation of indoles with simple α,β-unsaturated ketones has been accomplished. Central to these studies has been the identification of a new catalyst amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis.

The indole framework represents a privileged structural motif of established value in medicinal chemistry and complex target synthesis.[1] In this regard, the development of effective asymmetric entries to indole architecture constitutes an important research field. Over the past few years, the catalytic enantioselective additions of indoles to unsaturated carbonyl compounds, namely, known as Friedel−Crafts (F−C)-type alkylations, have been the topic of particularly intensive investigations.[2] A number of highly selective metal-catalyzed asymmetric F−C reactions of bidentate chelating carbonyls have been developed,[3] whereas in 2002 MacMillan and co-workers[4] first demonstrated the feasibility of organocatalytic strategies based on LUMO lowering activation of α,β-unsaturated aldehydes via the reversible formation of an iminium ion with chiral imidazolidinones.[5,6] Despite these recent advances, just one efficient metal-catalyzed asymmetric addition of indoles to monochelating ketones has been reported recently by the group of Bandini and Umani-Ronchi, affording the indolyl derivatives in moderate to good optical purity but with important restrictions in substrate scope.[7,8] Thus, the use of simple α,β-unsaturated ketones still remains

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(5) For an excellent review on iminium ion activation, see: Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79−87.

(6) For some leading examples that rely on different organocatalytic strategies, see: (a) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M. S.; Mhadgut, C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086−3089. (b) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576−6579. (c) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156−8157.

(7) (a) Bandini, M.; Fagioli, M.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5846−5849. (b) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511−7518.

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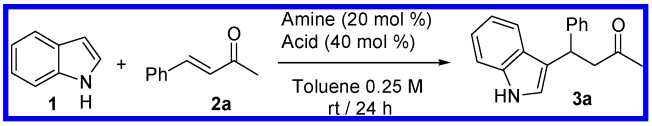
an important challenge for the asymmetric F−C alkylations of indoles.

In this paper, we document the first efficient asymmetric organocatalytic addition of indoles to simple enones,[8] a general and operationally trivial protocol that allows rapid access to a broad range of highly enantioenriched β-indolyl derivatives (up to 96% ee). In particular, the successful application of the iminium ion activation strategy to enone substrates was achieved by developing a new catalytic amine salt, in which both the cation and the anion are chiral.[9]

The proposed organocatalytic F−C alkylation strategy was first examined by reacting indole **1** with *trans*-4-phenyl-3-buten-2-one **2a** in the presence of a series of chiral amine salts as the catalysts (Table 1). Interestingly, secondary

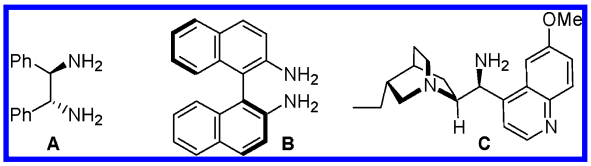
Table 1. Selected Screening Results[a]



entry	amine	acidic additive		conversion (%)[b]	ee (%)[c]
1	L-proline	–		0	–
2	**A**	TFA		85	−16
3	**B**	TFA		73	29
4	**C**	TFA		44	65
5	**C**	TFA[d]		23	61
6	**C**	*p*TSA		20	59
7	**C**	CF_3SO_3H		18	31
		HOOC, NH-PG, R (L)			
8	**C**	R: H	PG: Boc	<5	85
9	**C**	R: Ph	PG: H	0	–
10	**C**	R: *t*-Bu	PG: Boc	7	89
11	**C**	R: Bn	PG: Boc	8	90
12	**C**	R: Bn	PG: Cbz	10	85
13	**C**	R: Bn	PG: Fmoc	<5	86
14	**C**	R: Ph	PG: Boc	16	90
15[e]	**C**	R: Ph	PG: Boc	18	92
16[f]	**C**	R: Ph	PG: Boc	21	93
17[f,g]	**C**	R: Ph	PG: Boc	>95	87

[a] For additional studied catalysts, additives, and conditions, see the Supporting Information. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis. [d] 20 mol % of TFA. [e] Racemic *N*-Boc phenylglycine (Boc−Phg−OH) was used. [f] (D)-Boc−Phg−OH was used. [g] 70 °C reaction temperature.

amines such as L-proline (entry 1) and the MacMillan second-generation imidazolidinone catalyst, which has previously enabled highly enantioselective nucleophilic addition to α,β-unsaturated ketones via iminium ion catalysis,[10] afforded poor results.[8a] Considering the inherent problems of forming congested iminium ions from ketones, we questioned whether primary amines, owing to their reduced steric requirements, might be suitable for enone activation.[11−13]



Preliminary studies confirmed that TFA salts of primary amines **A** and **B** were able to promote the reaction with good catalytic efficiency but with low levels of enantioselectivity (entries 2 and 3). Notably, the use of TFA salts of the easily available 9-amino(9-deoxy)*epi*-hydroquinine **C**, which was very recently described as an effective catalyst for enone activation,[12,13] afforded promising stereoinduction, albeit not yet satisfactory. We speculated that the nature of the counteranion is the crucial factor for the optimization of the catalyst efficiency. With this consideration in mind, a survey of various salts of the chiral primary amine **C** was performed.

An extensive screen of the acidic additives, besides establishing the beneficial effect of a 1:2 ratio of amine **C** to a cocatalyst (entries 4 and 5), revealed that the use of *N*-Boc glycine as an achiral counteranion gave the product **3a** with high enantiomeric excess (85% ee, entry 8) albeit at the expense of reactivity. Considering that asymmetric counterion-directed catalysis (ACDC)[9] has recently been recognized as an efficient strategy for enantioselective transformations, we evaluated the efficiency of catalytic salts derived from the combination of **C** with a series of N-protected L-amino acids. The absence of a protecting group in the amino acid had a deleterious effect on the catalytic activity (entry 9), whereas the variation of the chiral architecture had a substantial impact on reactivity but a minimal impact on stereoselectivity (entries 10−14). Surpris-

(8) For an organocatalytic indole alkylation with enones promoted by an achiral amine, see: (a) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799−801. In this report, an initial attempt to perform an asymmetric version using the MacMillan second-generation imidazolidinone afforded poor selectivity (28% ee). Recently, a low selective (up to 29 % ee) addition of indole to chalcone promoted by D-camphorsulfonic acid was reported. See: (b) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. *Eur. J. Org. Chem.* **2006**, 5225−5227. See also ref 13.

(9) During our studies, the successful application of a similar ACDC tactic for the enantioselective hydrogenation of simple enones was described. See: (a) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369. See also: (b) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193−4195.

(10) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. (b) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662−12663. For selected examples using other secondary chiral amines, see: (c) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955−4957. (d) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272−1276. (e) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787−4790.

(11) For recent use of primary amine salts in asymmetric iminium catalysis with unsaturated ketones, see: Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239−5242. See also ref 9a.

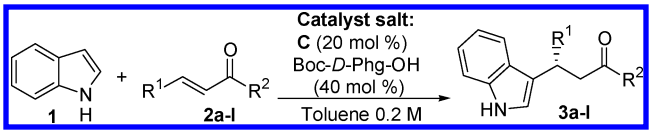
(12) During our studies, the TFA salt of 9-amino(9-deoxy)*epi*-quinine was reported to be an excellent catalyst for the asymmetric conjugate addition of carbon-centered nucleophiles to α,β-unsaturated ketones: (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389−392. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413−415.

(13) After our original submission, the asymmetric alkylation of indoles with unsaturated ketones catalyzed by 30 mol % of the CF_3SO_3H salt of 9-amino(9-deoxy)*epi*-quinine was reported, affording moderate to good levels of enantioselectivity (ee's ranging from 47% to 89%). See: (a) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816−821.

ingly, employing the racemic or the opposite enantiomeric counterion formed the same enantiomeric product **3a** with very similar selectivity although with slightly different reactivity (entries 14−16).[14] On the basis of these studies, D-*N*-Boc phenylglycine was chosen for further investigations as it proved to be superior with regard to enantioselectivity and catalytic efficiency. Interestingly, the ee remained very high even at 70 °C, at which temperature the reaction reached completion after 24 h (entry 17).

After optimizing the standard reaction parameters, the scope of this new organocatalytic F−C indole alkylation was explored using the conditions reported in Table 2: there

Table 2. Organocatalytic Alkylation of Indole **1** with Simple Enones[a]



entry	R^1	R^2	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	Ph	Me, **2a**	70	24	**3a** (90)	88
2[c]	Ph	Me, **2a**	70	60	**3a** (76)	88
3	*p*-ClC_6H_4	Me, **2b**	70	24	**3b** (92)	89
4	2-thienyl	Me, **2c**	70	48	**3c** (92)	84
5	Me	Me, **2d**	40	70	**3d** (98)	87[d]
6	$CH_3(CH_2)_4$	Me, **2e**	rt	96	**3e** (91)	93
7[c]	$CH_3(CH_2)_4$	Me, **2e**	40	90	**3e** (87)	92
8	$Ph(CH_2)_2$	Me, **2f**	rt	96	**3f** (67)	93[d]
9	COOEt	Me, **2g**	50	66	**3g** (99)	95
10		$(CH_2)_3$, **2h**	40	70	**3h** (65)	78
11	Ph	Et, **2i**	70	72	**3i** (56)	95
12	Ph	Ph, **2j**	70	96	**3j** (78)	82
13	Me	Et, **2k**	50	72	**3k** (76)	96
14	Me	Ph, **2l**	70	90	**3l** (94)	70[d]

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 10 mol % of **C** and 20 mol % of Boc-D-Phg−OH were employed. [d] Absolute configuration determined by comparison of the specific optical rotations with those reported in the literature.

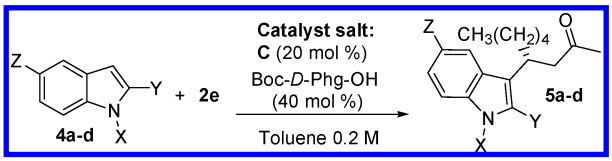
appears to be significant tolerance toward steric and electronic demands of the β-olefin substituent to enable access to a broad variety of highly enantioenriched β-indolyl ketones (entries 1−10).

Importantly, it is possible to decrease the catalyst loading to 10 mol % without affecting the efficiency of the system (entries 2 and 7); the products were isolated in high yield and enantioselectivity, increasing accordingly the reaction time.

Variation in the steric contribution of the R^2 ketone substituents (entries 11 and 13) reveals that the more encumbered ethyl group engenders higher selectivity, albeit with slightly lower reactivity.[15] Notably, our organocatalytic protocol is also effective with aromatic ketones (R^2 = Ph, entries 12 and 14), a class of substrates which, to our knowledge, have not yet been recognized as suitable for iminium ion activation.

The presented organocatalytic tactic is also general with respect to indole architecture, as electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system (Table 3, ee's ranging from 92% to 94%).

Table 3. Organocatalytic Alkylation of Substituted Indoles with **2e**[a]



	indole substituents			temp	time	yield[a]	ee[b]
entry	X	Y	Z	(°C)	(h)	(%)	(%)
1	H	H	H, **1**	rt	96	**3e** (91)	93
2	H	CH_3	H, **4a**	rt	24	**5a** (87)	94
3[c]	H	CH_3	H, **4a**	rt	72	**5a** (84)	94
4	H	H	Cl, **4b**	40	96	**5b** (74)	92
5	H	H	MeO, **4c**	rt	40	**5c** (76)	93
6	CH_3	H	H, **4d**	70	48	**5d** (<5)	62

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 10 mol % of **C** and 20 mol % of Boc-D-Phg−OH were employed.

As a limitation of the approach, it is worth noting that substitution on the indolic nitrogen had a detrimental effect on both reactivity and selectivity (entry 6). This feature has already been observed in other organocatalytic F−C alkylations of indoles believed to proceed via a dual activation mechanism.[6a,b]

In summary, we have disclosed the first general and highly enantioselective organocatalytic Friedel−Crafts alkylation of indoles with simple α,β-unsaturated ketones. Central to these studies has been the identification of a new catalyst amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis. A full account of this survey, providing detailed mechanistic investigations, will be forthcoming.

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Supporting Information Available: Catalysts and conditions screening studies, experimental procedures, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Theoretical studies based on DFT calculations to understand the origin of these phenomena (e.g., the absence of a marked matched−mismatched catalyst ion pair combination) are now underway.

(15) The use of a more encumbered R^2 group resulted in lower reactivity: R^2 = *c*-hexyl, 23% yield, 81% ee after 96 h at 70 °C.