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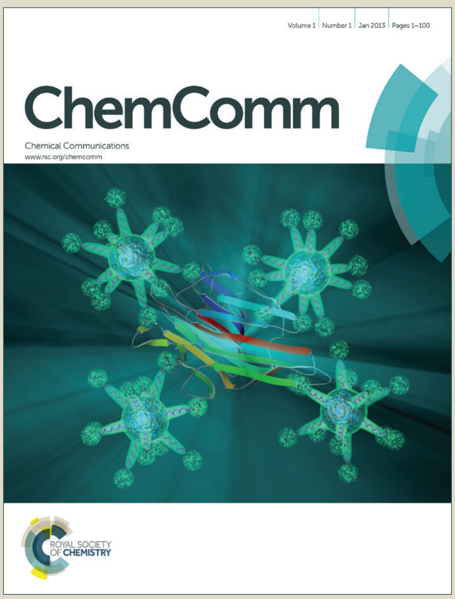

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Enantioselective N-Alkylation of Isatins and Synthesis of Chiral N-Alkylated Indoles

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Asymmetric N-alkylations of isatins with enals were shown to be feasible via a prolinol-catalyzed iminium activation, and N-alkylated isatins were obtained in good yields and with excellent enantioselectivity. The biologically useful N-alkylated isatins also served as valuable synthetic precursors, and could be readily converted to chiral N-alkylated indole derivatives. The described method provides a novel entry to access optically enriched N-alkylated isatin and indole derivatives.

Functionalized chiral indole derivatives are extremely important structural units that are widely present in natural products and bioactive molecules.[1] Consequently, enormous efforts have been devoted to the development of new reactions for asymmetric functionalizations of indoles.[2] Indoles most commonly act as a carbon nucleophile at the C3 position, and numerous reactions were focused on the asymmetric C3 alkylation of indoles.[3] Recently, a number of approaches on enantioselective C2 alkylation of indoles were also developed.[4] Chiral N-alkylated indoles are molecular architectures of great significance (Figure 1).[5] However, catalytic enantioselective reactions at the indole N1 position have been investigated to a much less extent due to the low acidity of NH proton. Hartwig reported an iridium-catalyzed regioselective and enantioselective N-allylation of indoles.[6a] Trost disclosed a palladium catalyzed dynamic kinetic asymmetric alkylation of vinyl aziridines with substituted indoles.[6b] You designed an iridium-catalyzed allylic alkylation/oxidation of indolines to realize asymmetric N-allylation of indoles.[6c] A copper-catalyzed cascade C2-alkylation/N-hemiacetalization reaction of 3-substituted indoles was reported by Chen and Xiao.[6d] Very recently, Hartwig uncovered an iridium-catalyzed intermolecular hydroamination reaction of indoles with unactivated olefins.[6e] In addition to the above transition metal-mediated methods for indole N1 functionalizations, a handful of non-metal based methods also appeared. Intramolecular aza-Michael additions of indoles catalyzed by a phase-transfer-catalyst and a chiral phosphoric acid were reported by Bandini[7a] and You,[7b] respectively. There are a few reports dealing with more challenging non-metal-based intermolecular functionalization of N1 positions of indoles. Chen employed Morita–Baylis–Hillman (MBH) carbonates for asymmetric N-allylic alkylation of indoles, and in situ generated basic *tert*-butoxide is believed to deprotonate the NH of an indole substrate.[7c] By installing an electron-withdrawing indole-2-carbaldehyde, Enders[7d] and Wang[7e] independently developed organocatalytic domino reactions to enantioselectively functionalize indole N1 position. Apparently, the necessity of in situ generated strong base and pre-installation of an aldehyde for activation in the above examples limited broad applications of the above methods. We thus set out to develop a mild and general organocatalytic approach to access chiral N-alkylated indoles.

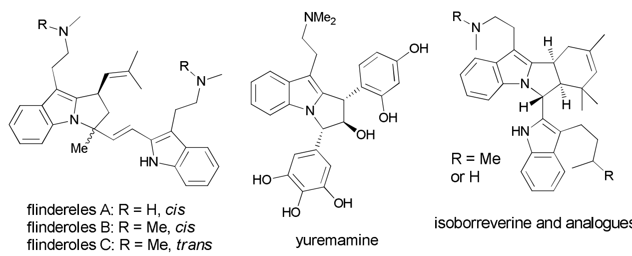
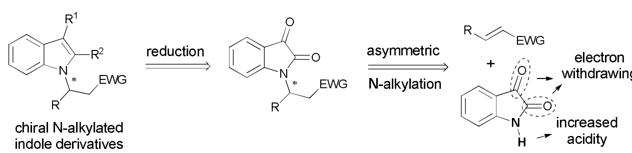


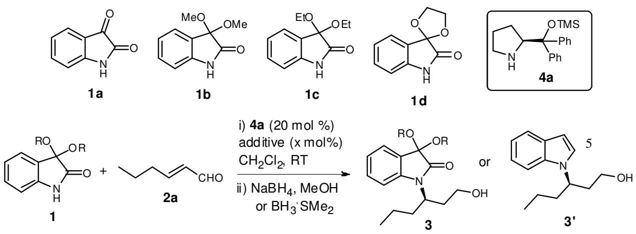
Fig. 1 Bioactive *N*-Alkylated Indole Derivatives



Scheme 1 Isatin as a Precursor to Derive Chiral *N*-Alkylated Indoles

The low nucleophilicity of indole NH is intrinsic, which makes the indole N-alkylation unfavourable, we reasoned judicious selection of an indole precursor may provide an easy solution to this challenging problem. In this context, we considered commercially available isatins as an excellent choice. The presence of the two carbonyl groups at C2 and C3 in isatin structures greatly enhances the acidity of NH group; the pKa value of NH proton is 10.3 for isatin, and that of indole NH is only at 16.2. Whereas C2 and C3 alkylations of indoles are prevailing reaction pathways when N-alkylation is concerned, the N-alkylation of isatins is exclusive. To the best of our knowledge, there was only one example on asymmetric N-allylation of isatins using MBH carbonates.[8] We envisioned such a process may be realized with careful selection of suitable electrophilic partners and efficient catalytic systems. The chiral N-alkylated isatin derivatives can be readily converted to optically enriched N-alkylated indole products via a reduction[9] protocol (Scheme 1). Herein, we describe an enantioselective N-alkylation of isatins, and preparation of chiral N-alkylated indoles.

Table 1 Investigation of N-Alkylation of Isatin Derivatives **1** with Enal **2a** [a]



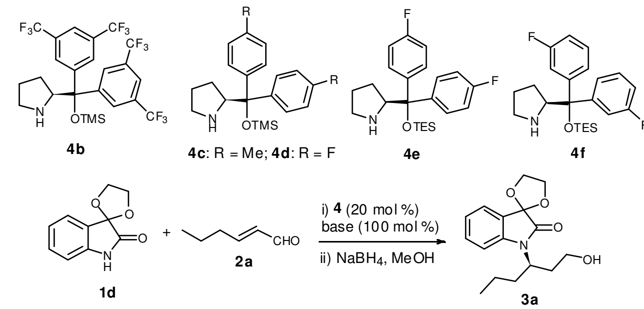
Entry	1	Additive/x	t/h	Product/Yield[%][b]	*ee*[%][c]
1[d]	**1a**	None/-	12	**3'**/21	63
2[d]	**1a**	$PhCO_2H$/20	12	**3'**/trace	-
3[d]	**1a**	Et_3N/20	12	**3'**/25	49
4[d]	**1a**	DBU/20	12	**3'**/27	10
5[d]	**1a**	Et_3N/40	12	**3'**/30	49
6[d]	**1a**	Et_3N/100	12	**3'**/43	47
7[d]	**1a**	Et_3N/150	12	**3'**/41	47
8[e]	**1b**	Et_3N/100	48	**3**/69	78
9[e]	**1c**	Et_3N/100	48	**3**/56	77
10[e]	**1d**	Et_3N/100	48	**3**/78	79

[a] Reactions were performed with **1** (0.2 mmol) and **2a** (0.4 mmol). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $BH_3{\cdot}SMe_2$ was used. [e] $NaBH_4$ was used.

To provide a validation of our proposal, we chose enal as an electrophile to examine the potential NH functionalization of isatins. An enantioselective conjugate addition of isatins **1** to enal **2a** via iminium activation[10] was performed, and the results are summarized in Table 1. Prolinol **4a**[11] is a well-established effective catalyst in asymmetric enamine/iminium catalysis, we thus selected **4a** to investigate projected addition of isatins to enals in our initial studies. Unprotected isatin **1a** was first employed in the reaction. In the presence of 20 mol % of **4a**, the desired product was obtained with moderate enantioselectivity, but only in poor yield (entry 1). Addition of benzoic acid turned out to be detrimental to the reaction, and only trace amount of the product was detected (entry 2). Effects of adding base additives were next examined. With catalytic amount of the base, a slight increase in chemical yield and a decrease in enantioselectivity were observed (entries 3–4). Increasing the amount of base resulted in limited improvement of the reaction (entries 5–7). Suspecting the high electrophilicity of the 3-carbonyl group of isatins may pose problems to the reaction, we then employed protected isatins for further investigations. Gratifyingly, isatin 3-ketals were found to be superior donors, much improved chemical yields and enantioselectivities were attainable, although the reactivities were lower than that of isatin (entries 8–10). When ethylene glycol protected isatin **1d** was employed, the desired product was obtained in good chemical yield and high enantioselectivity.

Having established the feasibility of the projected N-alkylation of isatins, we next focused on optimizing the reaction conditions to make the process highly enantioselective, and the results are summarized in Table 2. Solvent screening revealed that chloroform was the solvent of choice (entries 1–5). A number of prolinol silyl ethers were prepared and their catalytic effects were examined. Catalyst **4b** containing 3,5-CF_3-Ph substituents was less effective (entry 6). Prolinols with mono-substituted phenyl rings showed similar catalytic activities, and catalyst **4f** was chosen since it led to slightly better results (entries 7–10). Different bases were also examined as additives. While organic bases efficiently promoted the reaction (entries 10–12), inorganic bases were tested for further improvements. By adding $NaHCO_3$, the desired product was obtained with high enantioselectivity, however, the yield was low (entry 14). With the employment of Na_2CO_3, the N-alkylation product was obtained in 73% yield and with 91% ee (entry 15).

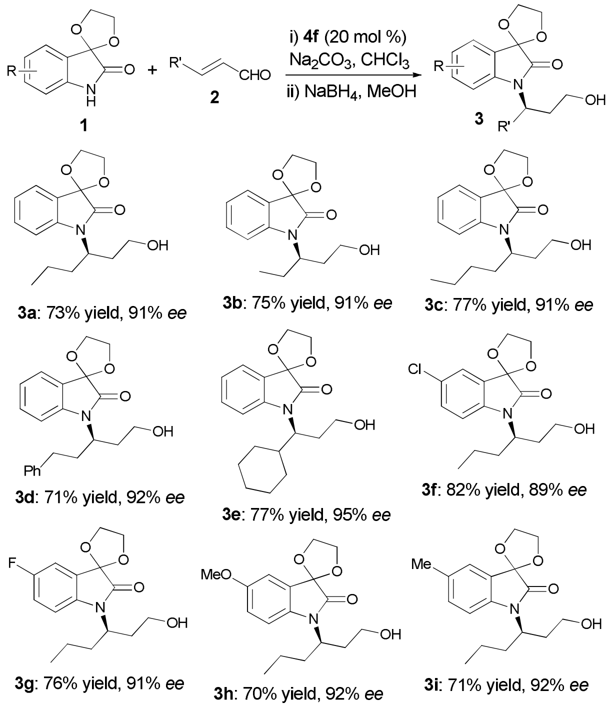
Table 2 Chiral Prolinol Silyl Ether-catalyzed Conjugate Addition of Isatin **1d** to Enal **2a** [a]



Entry	4	solvent	base	t/d	Yield[%][b]	*ee*[%][c]
1	**4a**	$CHCl_3$	Et_3N	2	72	84
2	**4a**	DCE	Et_3N	2	64	79
3	**4a**	toluene	Et_3N	2	55	84
4	**4a**	THF	Et_3N	2	trace	n.d.
5	**4a**	MeOH	Et_3N	2	trace	n.d.
6	**4b**	$CHCl_3$	Et_3N	2	42	67
7	**4c**	$CHCl_3$	Et_3N	2	70	84
8	**4d**	$CHCl_3$	Et_3N	2	75	85
9	**4e**	$CHCl_3$	Et_3N	2	77	86
10	**4f**	$CHCl_3$	Et_3N	2	77	87
11	**4f**	$CHCl_3$	DIPEA	2	78	83
12	**4f**	$CHCl_3$	$n$$Bu_3N$	2	75	75
13	**4f**	$CHCl_3$	proton sponge	2	<20	n.d.
14	**4f**	$CHCl_3$	$NaHCO_3$	4	37	91
15	**4f**	$CHCl_3$	Na_2CO_3	3	73	91
16	**4f**	$CHCl_3$	K_2CO_3	3	<20	n.d.
17	**4f**	$CHCl_3$	Cs_2CO_3	1	messy	n.d.

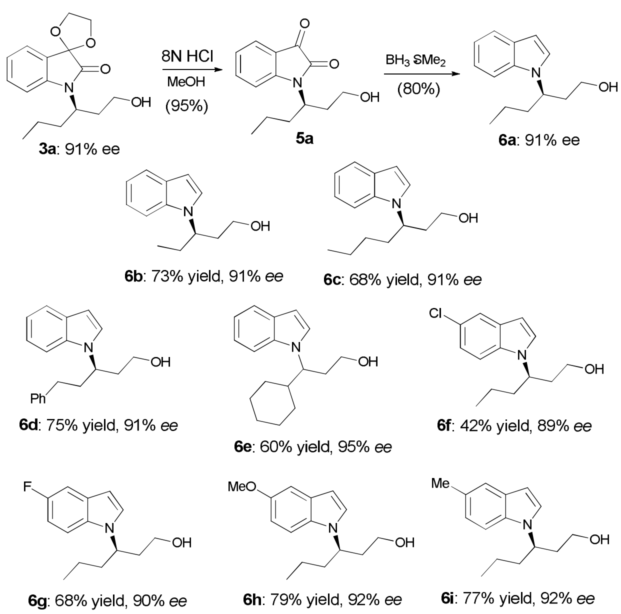
[a] Reactions were performed with **1d** (0.2 mmol) and **2a** (0.4 mmol). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

The generality of the reaction was next evaluated by employing various enals and isatin 3-ketals (Scheme 2). Aliphatic enals with a linear chain were well tolerated (**3a**–**3c**). Aryl substituted linear enal and branch enal were also suitable substrates (**3d**–**3e**). Different substitutions on 5-positon of isatin motif also worked well, and the products were obtained in high yields and with high ee values (**3f**–**3i**). However, aryl enals were found to be unsuitable for the reaction.[12]



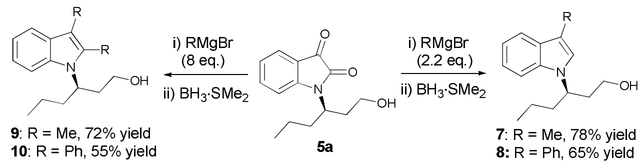
Scheme 2 *N*-Alkylated Isatin Derivatives

We then established effective conversion of chiral N-alkylated isatin 3-ketal to optically enriched indole derivative. Isatin **3a** was first deprotected to the corresponding isatin **5a** under acidic condition. N-Alkylated indole derivative **6a** was readily obtained in high yield after reduction of isatin **5a** with borane. The ee value was maintained throughout the deprotection–reduction process. With this protocol in hand, a range of chiral N-alkylated indole derivatives were readily prepared, in moderate to good chemical yields and excellent enantiomeric excesses (Scheme 3).



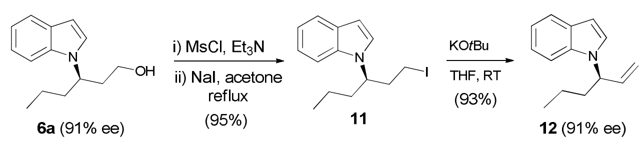
Scheme 3 Preparation of Chiral *N*-Alkylated Indoles

In addition to simple indole derivatives, the N-alkylated isatins can also be derived into various C2/C3-substituted N-alkylated indole derivatives (Scheme 4). When isatin **5a** was treated with 8 equivalents of Grignard reagent, nucleophilic additions to both carbonyl groups of isatin took place, and 2,3-disubstituted N-alkylated chiral indole products were obtained. Alternatively, if 2.2 equivalents of Grignard reagent were employed, the nucleophilic addition only occurred at the more electrophilic C3 position, subsequent reduction then afforded 3-mono-substituted indoles bearing an N-alkyl group (Scheme 4).



Scheme 4 Facile Synthesis of 2,3-Substituted Indoles from Isatin **5a**

Since optically enriched N-allylated indoles create an entry into bioactive indole derivatives,[13] we illustrated an easy manipulation of our products to such useful structural motifs (Scheme 5). Indole **6a** was converted to iodide **11** in high yield, and N-allyl indole derivative **12** was obtained in excellent yield upon the elimination of iodide. The absolute configuration of **12** was determined to be *R* by comparison with the known compound reported in the literature[6c] (see the Supporting Information for details).



Scheme 5 Preparation of Branched *N*-Allyl Indole.

In summary, we devised a novel approach to access chiral N-alkylated isatins and indole derivatives. We demonstrated that isatin 3-ketals could undergo efficient N-alkylations with enals via prolinol-catalyzed iminium activation to afford N-alkylated isatins in good yields and excellent enantioselectivities. The N-alkylated isatins are not only biologically significant molecules,[14] but also could serve as useful synthetic intermediates, and were readily converted to (2,3-disubstituted) chiral indole derivatives bearing an N-alkyl group in high yields. It is noteworthy that this is the first time that isatins are used as activated indole precursors for the preparation of chiral N-alkylated indoles. Given the readily availability of isatins, as well as enormous value of indole derivatives in biological sciences and medicinal chemistry, the described approach should have immediate, general applications, and we are currently investigating along this line.

Notes and references

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Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

1 (a) M. Inman and C. J. Moody, *Chem. Sci.,* 2013, **4**, 29; (b) A. J. Kochanowska-Karamyan, *Chem. Rev.,* 2010, **110**, 4489; (c) T.

Kawasaki and K. Higuchi, *Nat. Prod. Rep.,* 2007, **24**, 843; (d) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.,* 2005, **22**, 761; (e) M. Somei and F. Yamada, *Nat. Prod. Rep.,* 2005, **22**, 73; (f) M. Somei and F. Yamada, *Nat. Prod. Rep.,* 2004, **21**, 278; (g) R. J. Sundberg, *Indoles,* Academic Press, San Diego, 1996.

2 For recent reviews, see: (a) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem. Int. Ed.,* 2004, **43**, 550; (b) M. Bandini, S. Tommasi and A. Umani-Ronchi, *Synlett,* 2005, 1199; (c) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.,* 2008, **108**, 2903; (d) M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.,* 2009, **48**, 9608; (e) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.,* 2009, **38**, 2190; (f) M. Zeng and S.-L. You, *Synlett,* 2010, 1289; (g) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.,* 2010, **39**, 4449.

3 For selective examples of C3 alkylations of indoles, see: (a) M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi and A. Umani-Ronchi, *J. Am. Chem. Soc.,* 2006, **128**, 1424; (b) B. M. Trost and J. Quancard, *J. Am. Chem. Soc.,* 2006, **128**, 6314; (c) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.,* 2010, **132**, 11418; (d) Y.-Q. Wang, J. Song, R. Hong, H. Li and L. Deng, *J. Am. Chem. Soc.,* 2006, **128**, 8156; (e) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, *Angew. Chem. Int. Ed.,* 2007, **46**, 5565; (f) M. Terada and K. Sorimachi, *J. Am. Chem. Soc.,* 2007, **129**, 292; (g) Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.,* 2007, **129**, 1484; (h) K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2001, **40**, 160; (i) J. Zhou and Y. Tang, *J. Am. Chem. Soc.,* 2002, **124**, 9030; (j) D. A. Evans, K. R. Fandrick. H.-J. Song, K. A. Scheidt and R. Xu, *J. Am. Chem. Soc.,* 2007, **129**, 10029; (k) J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem. Int. Ed.,* 2008, **47**, 4016; (l) M. Rueping, B. J. Nachtsheim, S. A. Moreth and M. Botle, *Angew. Chem. Int. Ed.,* 2008, **47**, 593; (m) M. Ganesh and D. Seidel, *J. Am. Chem. Soc.,* 2008, **130**, 16464; (n) A. J. Boersma, B. L. Feringa and G. Roelfes, *Angew. Chem. Int. Ed.,* 2009, **48**, 3346; (o) H. Huang and R. Peters, *Angew. Chem. Int. Ed.,* 2009, **48**, 604; (p) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem. Int. Ed.,* 2009, **48**, 7428; (q) L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong and E. Meggers, *Angew. Chem. Int. Ed.,* 2013, **52**, 14021.

4 For selective examples of indole C2 alkylations, see: (a) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2004, **126**, 10558; (b) J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc.,* 2006, **128**, 1086; (c) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem. Int. Ed.,* 2007, **46**, 7485; (d) I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2007, **129**, 13404; (e) S. Lee and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2007, **129**, 15438; (f) M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.,* 2009, **48**, 9533; (g) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.,* 2009, **131**, 10796.

5 (a) F. Tillequin, M. Koch, M. Bert and T. Sevenet, *J. Nat. Prod.,* 1979, **42**, 92; (b) E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double and M. C. Bibby, *J. Med. Chem.,* 1989, **32**, 1612; (c) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck and D. Jasserand, *J. Med. Chem.,* 1995, **38**, 669; (d) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn and V. M. Avery, *Org. Lett.,* 2009, **11**, 329.

6 (a) L. M. Stanley and J. F. Hartwig, *Angew. Chem. Int. Ed.,* 2009, **48**, 7841; (b) B. M. Trost, M. Osipov and G. Dong, *J. Am. Chem. Soc.,* 2010, **132**, 15800; (c) W.-B. Liu, X. Zhang, L.-X. Dai and S.-L. You, *Angew. Chem. Int. Ed.,* 2012, **51**, 5183; (d) H.-G. Cheng, L.-Q. Liu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen and W.-J. Xiao, *Angew. Chem. Int. Ed.,* 2013, **52**, 3250; (e) C. S. Sevov, J. Zhou and J. F. Hartwig, *J. Am. Chem. Soc.,* 2014, **136**, 3200.

7 (a) M. Bandini, A. Eichholzer, M. Tragni and A. Umani-Ronchi, *Angew. Chem. Int. Ed.,* 2008, **47**, 3238; (b) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem. Int. Ed.,* 2010, **49**, 8666; (c) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang and Y.-C. Chen, *Angew. Chem. Int. Ed.,* 2009, **48**, 5737; (d) D. Enders, C. Wang and G. Raabe, *Synthesis* 2009, **24**, 4119; (e) L. Hong, W. Sun, C. Liu, L. Wang and R. Wang, *Chem. Eur. J.,* 2010, **16**, 440.

8 M.-X. Zhao, M.-X. Chen, W.-H. Tang, D.-K. Wei, T.-L. Dai and M. Shi., *Eur. J. Org. Chem.,* 2012, 3598.

9 (a) W. Wierenga, J. Griffin and M. A. Warpehoski, *Tetrahedron Lett.,* 1983, **24**, 2437; (b) S. J. Garden, R. B. da Silva and A. C. Pinto, *Tetrahedron,* 2002, **58**, 8399.

10 For selected reviews on iminium catalysis, see: (a) G. Lelais and D. W. C. MacMillan, *Aldrichimica Acta,* 2006, **39**, 79; (b) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.,* 2007, **107**, 5416. For chiral secondary amine catalyzed asymmetric addition of *N*-nucleophiles to enals, see: (c) Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2006, **128**, 9328; (d) P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2007, **46**, 1983; (e) Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu and J. Zhou, *Org. Lett.,* 2009, **11**, 1999; (f) C. Appayee and S. E. Brenner-Moyer, *Org. Lett.,* 2010, **12**, 3356; (g) G.-L. Zhao, S. Lin, A. Korotvička, L. Deiana, M. Kullberg and A. Córdova, *Adv. Synth. Catal.,* 2010, **352**, 2291. For a chiral amine catalyzed C3 selective alkylation of indole with enals, see: (h) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2002, **124**, 1172.

11 For the initial reports on prolinol silyl ether, see: (a) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem. Int. Ed.,* 2005, **44**, 4212; (b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2005, **127**, 18296.

12 Reaction between cinnamaldehyde and **1d** in the presence of **4a** was examined under various conditions as described in Table 1 (entries 1–4). However, no desired N-alkylation product was observed, probably due to inability of current catalytic system to activate thermodynamically more stable cinnamaldehyde.

13 (a) P. S. Turnbull and R. Cadilla, PCT Int. Appl., WO 2014013309, 2014; (b) S. Hitchcock, H. Monenschein, H. Reichard, H. Sun, S. Kikuchi, T. Macklin and M. Hopkins, PCT Int. Appl., WO 2014014951, 2014; (c) Y.-P. Liu, Y.-L. Zhao, T. Feng, G.-G. Cheng, B.-H. Zhang, Y. Li, X.-H. Cai and X.-D. Luo, *J. Nat. Prod.,* 2013, **76**, 2322; (d) D. Thotala, J. M. Craft, D. J. Ferraro, R. P. Kotipatruni, S. R. Bhave, J. J. Jaboin and D. E. Hallahan, *PLoS One,* 2013, **8**, e69688.

14 (a) M. S. Gil-Turnes, M. E. Hay and W. Fenical, *Scinece,* 1989, **246**, 116; (b) S. E. Webber, J. Tikhe, S. T. Worland, S. A. Fuhrman, T. H. Hendrickson, D. A. Matthews, R. A. Love, A. K. Patick, J. W. Meador, R. A. Ferre, E. L. Brown, D. M. DeLisle, C. E. Ford and S. L. Bindord, *J. Med. Chem.,* 1996, **39**, 5072; (c) R. F. Kester, PCT Int. Appl., US 2012/0142705, 2012.

