Organocatalysis

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Enantioselective, Thiourea-Catalyzed Intermolecular Addition of Indoles to Cyclic *N*-Acyl Iminium Ions**

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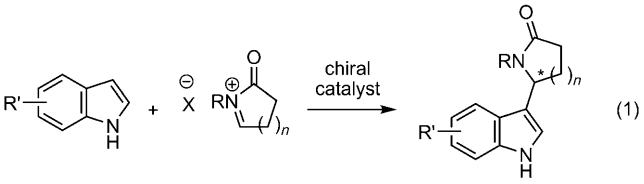
The discovery that chiral hydrogen-bond donors effectively promote highly enantioselective reactions of cationic intermediates has opened a new direction within the field of organocatalysis.[1,2] For example, the development of thiourea-catalyzed enantioselective acyl-Pictet–Spengler-type cyclizations has helped bring *N*-acyl iminium ions into the realm of viable substrates for asymmetric catalysis.[2a–d,f,3] The harnessing of *N*-acyl iminium ions for the enantioselective intermolecular addition of indoles [e.g., Eq. (1)] would enable

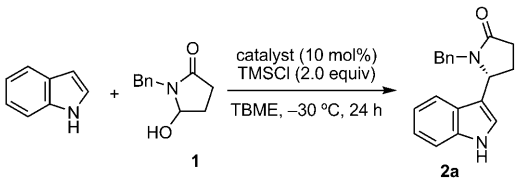


(1)

direct access to functionalized indole frameworks with established biological activity[4] and also provide useful precursors to more complex alkaloid natural product targets.[5] Intermolecular asymmetric catalytic addition reactions of indoles to acyclic imines have been reported.[6] In most cases, the electrophilic partners have been limited to substituted benzaldehyde derivatives, although Deng and coworkers also identified successful reactions with a variety of acyclic aliphatic imines.[6c] Herein we report highly enantioselective intermolecular additions of indoles to hydroxylactam-derived cyclic *N*-acyl iminium ions under the catalysis of a new thiourea Schiff base derivative.

We selected as a model reaction the addition of indole to the succinimide-derived hydroxylactam **1**, a bench-stable, storable compound that was prepared readily and could be handled without difficulty.[7] A variety of thiourea and urea catalyst frameworks were evaluated as potential catalysts under conditions similar to those developed for the related intramolecular acyl-Pictet–Spengler cyclization (Table 1).[2c] A promising lead result was obtained in the reaction

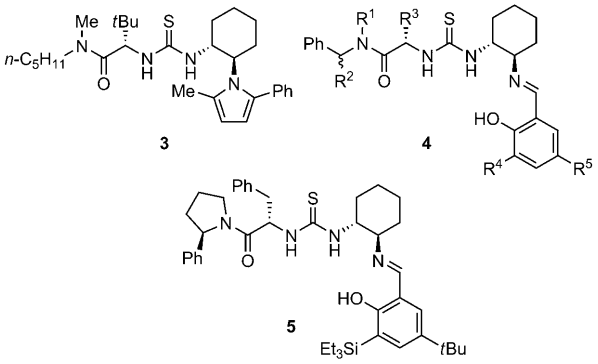
Table 1: Catalyst optimization studies.[a]



1 2a

Entry	Catalyst	R^1	R^2	R^3	R^4	R^5	*ee* [%]
1	**3**	–	–	–	–	–	−14
2	**4a**	Me	H	*t*Bu	*t*Bu	*t*Bu	55
3	**4b**	H	H	*t*Bu	*t*Bu	*t*Bu	35
4	**4c**	Me	H	*t*Bu	*t*Bu	NO_2	13
5	**4d**	Me	H	*t*Bu	*t*Bu	OTIPS	21
6	**4e**	Me	H	*t*Bu	*t*Bu	Cl	40
7	**4f**	Me	H	*t*Bu	Me	*t*Bu	23
8	**4g**	Me	H	*t*Bu	$SiEt_3$	*t*Bu	65
9	**4h**	Me	Me (*S*)	*t*Bu	$SiEt_3$	*t*Bu	75
10	**4i**	Me	Me (*R*)	*t*Bu	$SiEt_3$	*t*Bu	80
11	**4j**	Me	Me (*R*)	CH_2Ph	$SiEt_3$	*t*Bu	89
12	**5**						93

[a] Bn = benzyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.



3 4 5

promoted by Schiff base **4a**[8] in *tert*-butylmethyl ether (TBME) at −30 °C, with adduct **2a** generated with 55 % *ee* and in 30 % yield (Table 1, entry 2). No background reactivity was observed under these conditions in the absence of a catalyst. Interestingly, pyrrole derivative **3**, the optimal catalyst identified for the intramolecular acyl-Pictet–Spengler reaction,[2c] afforded the opposite enantiomer with low enantioselectivity (Table 1, entry 1).

Systematic variation of the catalyst structure around the basic framework of **4** led to substantial improvements in reaction enantioselectivity (Table 1). Diaminocyclohexane-derived catalysts containing different Schiff base, amide, and amino acid side-chain components were examined. The primary amine resulting from hydrolysis of Schiff base **4a**

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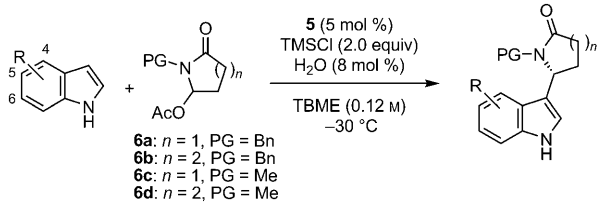
was found to be catalytically active, but afforded the racemic product. Thus, we recognized that it would be essential to maintain the integrity of the Schiff base throughout the reaction to observe high enantioselectivity. After extensive experimentation, it was found that catalyst **4g**, in which R^4 is a triethylsilyl group and R^5 is a *tert*-butyl group, promoted the formation of **2a** with slightly higher enantioselectivity than that observed with catalyst **4a** (65 versus 55% *ee*).

The introduction of a stereochemical element at the benzylic position of the amide led to a further improvement in enantioselectivity: the catalyst **4i**, in which R^2 is a methyl group and the adjacent stereogenic center has the *R* configuration, provided **2a** with 80% *ee* (Table 1, entry 10). Whereas the majority of effective thiourea catalysts identified to date contain a *tert*-leucine backbone ($R^3 = t$Bu),[9] catalyst **4j** derived from phenylalanine proved substantially more enantioselective than the *tert*-leucine analogue **4i** (89 versus 80% *ee*; Table 1, entry 11). Finally, the constraint of the chiral amide component in a cyclic framework, as in catalyst **5**, led to additional improvement in enantioselectivity, with the generation of **2a** with 93% *ee* (Table 1, entry 12).[10–12]

Despite the high enantioselectivity observed with catalyst **5**, the efficiency of product formation with hydroxylactam **1** was quite modest (30–40% conversion with 10 mol% catalyst). This low conversion was attributable, at least in part, to the poor solubility of **1** under the reaction conditions; therefore, several derivatives of the hydroxylactam substrate were prepared with the aim of discovering a more suitable *N*-acyl iminium ion precursor. The acetyl derivative **6a**, prepared by acylation of **1**, displayed improved solubility and underwent conversion into **2a** with 93% *ee* and in 71% yield (Table 2).

Table 2: Alkylation of electron-rich indole substrates.[a]

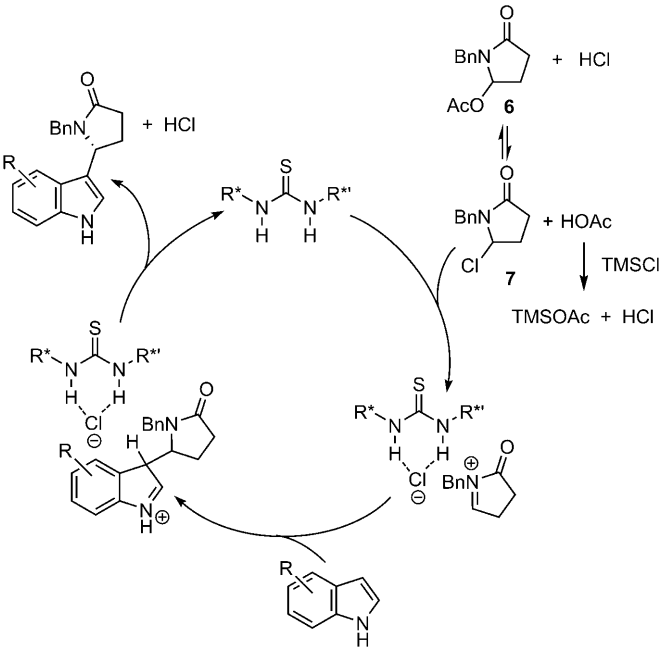


Entry	R	6	*t* [h]	Product	Yield [%][b]	*ee* [%]
1[c]	H	**6a**	24	**2a**	90	93 (99)[d]
2	H	**6c**	24	**2b**	93	86
3	4-Me	**6a**	24	**2c**	86	95
4	5-Me	**6a**	24	**2d**	79	90 (91)[d]
5	5-CH=CH$_2$	**6a**	24	**2e**	82	90
6	6-OMe	**6a**	24	**2f**	80	80 (98)[d]
7	H	**6d**	48	**2g**	60	92
8	H	**6b**	48	**2h**	70	93
9	5-OMe	**6b**	48	**2i**	86	90
10	5-Me	**6b**	48	**2j**	93	94
11	5-CH=CH$_2$	**6b**	48	**2k**	92	91
12	6-OMe	**6b**	48	**2l**	76	88

[a] Unless noted otherwise, reactions were carried out on a 0.3 mmol scale. [b] Yield after chromatographic purification. [c] The reaction was carried out on a 3 mmol scale. [d] The *ee* value of the product after purification by trituration with Et_2O is given in parentheses.

No reaction was observed in the absence of TMSCl or another acidic additive, and the comparison of different TMS-X reagents revealed that the chloride counteranion was uniquely effective for the promotion of high enantioselectivity.[13,14] The use of BCl_3 as an additive in place of TMSCl led to complete substrate conversion after only 8 hours, albeit with slightly diminished enantioselectivity (91 versus 93% *ee*).

The presence of controlled amounts of added water in the TMSCl-promoted reactions also had a pronounced beneficial effect on reactivity.[15] The best results were obtained when the reaction was carried out with catalyst **5** (5 mol%), TMSCl (2 equiv), and water (8 mol%) in anhydrous TBME at −30 °C for 24 hours. Under these conditions, adduct **2** was generated reproducibly with 93% *ee* and isolated in 84% yield. The synergistic effect of TMSCl and catalytic H_2O[16] suggests that acetoxylactam **6** reacts with HCl generated in situ to form chlorolactam **7**, and that this equilibrium is driven by trapping of the acetic acid by-product with TMSCl.[17] We propose that the racemic chlorolactam **7** is the actual substrate in the alkylation, and that the reaction proceeds through an S_N1-type anion-binding mechanism analogous to that proposed for related thiourea-catalyzed acyl-Pictet–Spengler and oxocarbenium-ion-alkylation reactions (Scheme 1).[2c–e]

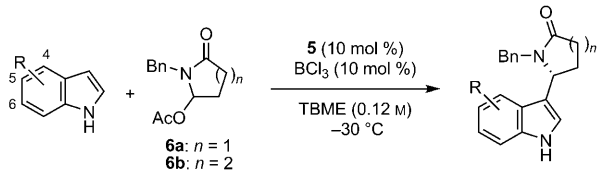


Scheme 1. Proposed catalytic cycle.

Having developed a reliable protocol, we investigated the scope of the reaction. Under the optimized conditions, a variety of electron-rich indoles underwent addition to both succinimide- and glutarimide-derived electrophiles with high enantioselectivity (Table 2).[18] Consistent results were obtained upon a ten-fold increase in the scale of the reaction (Table 2, entry 1). In several cases, we found that the enantiomeric enrichment of the products could be increased simply by trituration.[19]

Encouraged by the scope of the addition with electron-rich indoles, we also examined electron-deficient indoles. Under the optimized conditions with TMSCl, these substrates were converted into the corresponding adducts with high enantioselectivity, but in low yield. In contrast, for halogenated indole substrates, the use of BCl_3 (10 mol%) in the presence of **5** (10 mol%) led to the formation of products **2m–2u** in useful yields and with high enantioselectivity (Table 3).

Table 3: Alkylation of electron-deficient indoles.



Entry	R	*n*	*t* [days]	Product	Yield [%][a]	*ee* [%]
1	4-F	1	1.5	**2m**	57	96 (99)[b]
2	4-Br	1	5	**2n**	47	97
3	5-F	1	2	**2o**	87	94
4	5-Br	1	5	**2p**	80	93
5	6-F	1	3	**2q**	75	96
6	6-Cl	1	4	**2r**	81	96
7	4-Br	2	5	**2s**	12	85
8	6-F	2	3	**2t**	75	96
9	6-Cl	2	5	**2u**	40	92

[a] Yield of the isolated product. [b] The *ee* value of the product after purification by trituration from Et_2O is given in parentheses.

In summary, we have developed a highly enantioselective addition of indoles to cyclic *N*-acyl iminium ions with a chiral thiourea Schiff base catalyst. Both electron-rich and electron-poor indole nucleophiles can be used as substrates. The products are synthetically useful intermediates that can be elaborated readily: for example, cleavage of the benzyl protecting group with Na/NH_3 proceeds without erosion of enantiomeric excess.[19] Efforts to apply anion-binding principles to other reactions involving cationic intermediates are underway.

Experimental Section

The indole (0.040 g, 0.343 mmol) and catalyst **5** (0.012 g, 0.017 mmol) were placed in a 10 mL flame-dried round-bottomed flask, which was then sealed with a rubber septum. The flask was flushed with N_2, and anhydrous TBME (1.6 mL) was added. The resulting yellow solution was cooled to −78 °C, and a solution of acetoxylactam **6a** in TBME (0.65 mL, 0.34 mmol, 0.53 M) was added. Next, solutions in TBME of TMSCl (0.43 mL, 0.69 mmol, 1.6 M) and H_2O (0.20 mL, 0.03 mmol, 0.14 M) were added sequentially, and the mixture was warmed to −30 °C and stirred for 24 h. The heterogeneous reaction mixture was quenched by the addition of a solution of NaOEt in EtOH (0.2 mL, 21 wt%), followed by the immediate addition of water (1 mL). The mixture was allowed to warm to room temperature and was diluted with EtOAc until all solids had dissolved (the amount of EtOAc added (ca. 5–10 mL) depends on the product). The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification procedures for individual products, as well as the BCl_3 protocol for electron-deficient indoles, are provided as Supporting Information.

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[1] For recent general reviews of chiral H-bond catalysts, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.

[2] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; b) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858–6862; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700–6704; c) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405; d) I. T. Raheem, P. S. Thiara, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 1577–1580; e) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199; f) P. C. Pan, B. List, *Chem. Asian J.* **2008**, *3*, 430–437; g) for a review of anion-binding thiourea organocatalysis, see: Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.

[3] For seminal applications of *N*-acyl iminium ions in aluminum-catalyzed Reissert reactions, see: a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; b) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801–6808; c) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785; d) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809.

[4] I. R. Baldwin, P. Bamborough, J. A. Christopher, J. K. Kerns, T. Longstaff, D. D. Miller, WO 2005067923A1.

[5] a) B. Atta-ur-Rahman, *Indole Alkaloids*, Harwood Academic, Chichester, **1998**; b) M. Amat, S. Hadida, N. Llor, S. Sathyanarayana, J. Bosch, *J. Org. Chem.* **1996**, *61*, 3878–3882; c) S. Shimizu, K. Ohori, T. Arai, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1998**, *63*, 7547–7551.

[6] a) M. Johannsen, *Chem. Commun.* **1999**, 2233–2234; b) Y. X. Jia, J. H. Xie, H. F. Duan, L. X. Wang, Q. L. Zhou, *Org. Lett.* **2006**, *8*, 1621–1624; c) Y. Q. Wang, J. Song, R. Hong, L. H. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157; d) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609–2611; e) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661–5663; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565–5567; f) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485; g) M. Terada, S. Yokoyama, K. Sorimachi, D. Uraguchi, *Adv. Synth. Catal.* **2007**, *349*, 1863–1867; h) Q. Kang, X.-J. Zheng, S.-L. You, *Chem. Eur. J.* **2008**, *14*, 3539–3542.

[7] J. C. Hubert, J. B. P. A. Wunberg, W. N. Speckamp, *Tetrahedron* **1975**, *31*, 1437–1441.

[8] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

[9] For important exceptions, see: a) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661; b) R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2009**, *11*, 887–890.

[10] For an efficient asymmetric synthesis of 2-phenylpyrrolidines, see: K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.

[11] The diastereomer of catalyst **5**, prepared from (*R*)-2-phenylpyrrolidinone, D-phenylalanine, and (*S*),(*S*)-diaminocyclohexane provided product **2** with −79% *ee*.

[12] Thiourea catalysts derived from 2-aryl pyrrolidines were also applied successfully to enantioselective alkylation reactions of oxocarbenium ions; see reference [2e].
[13] Adduct **2** was obtained with 26% *ee* when TMSBr was used with catalyst **4a**, and as a racemate when TMSI was used.
[14] It has been established previously that thioureas interact much more strongly with chloride than with bromide or iodide: a) S. Kondo, M. Nagamine, Y. Tano, *Tetrahedron Lett.* **2003**, *44*, 8801–8804; b) S. Kondo, M. Sato, *Tetrahedron* **2006**, *62*, 4844–4850.
[15] Very poor reactivity was observed under strictly anhydrous conditions. Elevated levels of added water (>20 mol%) led to diminished enantioselectivity.
[16] Reactions carried out with HCl alone proceeded with comparable enantioselectivity but were substantially slower.
[17] The conversion of **6a** into chlorolactam **7** was established and monitored by ^{1}H NMR spectroscopy. Spectra (^{1}H and ^{13}C NMR) of **7** and of related compounds are provided in the Supporting Information.
[18] The absolute configuration of addition products was determined by single-crystal X-ray analysis of the addition product **2s** (Table 3); the configuration of all other products was assigned by analogy. CCDC 736017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[19] See the Supporting Information for complete details.

