Asymmetric Synthesis

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Asymmetric Brønsted Acid Catalyzed Isoindoline Synthesis: Enhancement of Enantiomeric Ratio by Stereoablative Kinetic Resolution**

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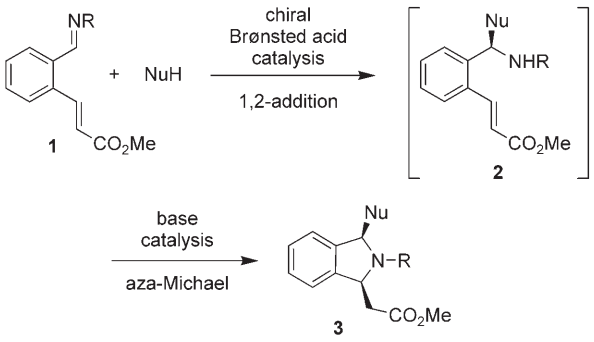
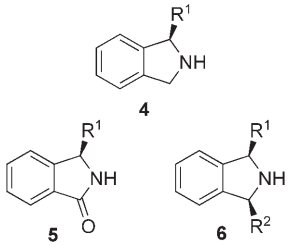
The enantioselective Brønsted acid catalyzed 1,2-addition to imines has emerged as a powerful metal-free method to access functionalized chiral amines.[1] Chiral phosphoric acids have proven to be highly effective catalysts in aza-Friedel–Crafts, hydrocyanation, Mannich, reduction, and other 1,2-addition reactions.[2,3] In a limited number of cases, the resulting amine products have been converted into pharmaceutically relevant or natural product precursors.[2c,f,3o] However, a subsequent tandem or one-pot process using the amine as a nucleophile has rarely been exploited. The research groups of Rueping and Gong independently developed an elegant Brønsted acid catalyzed tandem Mannich/aza-Michael addition of an enolized α,β-unsaturated ketone and imine for the asymmetric synthesis of isoquinuclidines.[3a,e] More recently, chiral piperidines have been prepared by Terada and co-workers in a tandem aza–ene type reaction/cyclization sequence.[3k]

We envisioned that another class of heterocycles, chiral 1,3-disubstituted isoindolines **3**, could be rapidly accessed from bifunctional substrates **1** containing an imine and Michael acceptor (Scheme 1). An ε-iminoenoate **1** could react in a Brønsted acid catalyzed 1,2-addition with a nucleophile (NuH) to afford a chiral amine **2**, which could react further in an intramolecular aza-Michael addition.



Scheme 1. Catalytic enantioselective synthesis of isoindolines using a 1,2-addition/aza-Michael reaction sequence.

Chiral isoindolines, particularly 1-isoindolylcarboxylic acids **4** ($R^1 = CO_2H$) and 1-substituted isoindolin-3-ones **5**,



are common substructures in a variety of natural products[4] and pharmaceuticals.[5] Access to 1- and 1,3-substituted isoindolines **4** and **5** is hampered by the fact that only a limited number of synthetic procedures exist for their preparation.[6] Moreover, few reports describe routes to enantiomerically pure isoindolines. Resolutions[7] and chiral-auxiliary-based methods[8] are dominant avenues to enantiomerically enriched isoindolyl derivatives **4**–**6**. Several articles detail the metal-catalyzed asymmetric synthesis of 1-substituted isoindolines **4** and 1-substituted isoindolin-3-ones **5**.[9] To the best of our knowledge, there are no existing metal- or organocatalyzed asymmetric syntheses of 1,3-disubstituted isoindolines **6**.

We report herein the first catalytic diastereo- and enantioselective synthesis of 1,3-disubstituted isoindolines using a one-pot, two-step process consisting of a chiral Brønsted acid catalyzed aza-Friedel–Crafts reaction and a base-catalyzed intramolecular aza-Michael addition. Moreover, these investigations led to the discovery of a Brønsted acid catalyzed stereoablative kinetic resolution[10] that occurs in tandem to the Friedel–Crafts reaction and amplifies the enantiomeric ratios of the isoindoline products.

Indoles **8** and *N*-tosyliminoenoates **9** were selected as the nucleophilic and electrophilic components, respectively, for this reaction (Scheme 2). In the first instance, indole (**8a**) and iminoenoate **9a** were exposed to several chiral binaphthol-(BINOL)-derived phosphoric acids (e.g. **7a**, X = OH). These catalysts were found to be completely inert, even though they are known to readily promote the Friedel–Crafts reaction of indoles **8** and a variety of imines (Table 1, entry 1).[3h,i,o] This indicates that the *ortho*-enoate substituent has a profound

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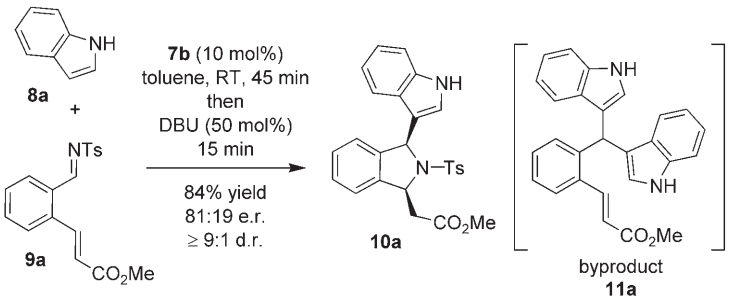
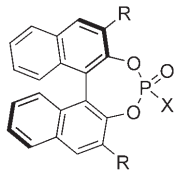


Scheme 2. One-pot Friedel–Crafts/aza-Michael reaction.



7a, R = 3,5-$(CF_3)C_6H_4$, X = OH
7b, R = 3,5-$(CF_3)C_6H_4$, X = NHTf
7c, R = 2-naphthyl, X = NHTf
7d, R = 4-biphenyl, X = NHTf
7e, R = $SiPh_3$, X = NHTf
7f, R = 4-$(NO_2)C_6H_4$, X = NHTf

Table 1: Catalyst screening for the synthesis of isoindoline **10a**.[a,b]

Entry	Cat.	Time[c]	Yield [%][d]	e.r.[e]
1	**7a**	>120 h	0	n.d.
2	**7b**	45 min	84	81:19
3	**7c**	15 min	92	86:14
4	**7d**	5 min	89	70:30
5	**7e**	30 min	72	86:14
6	**7f**	10 min	93	90:10

[a] Reaction conditions: A mixture of 0.3 mmol imine **9a**, 3 equiv indole (**8a**), and 10 mol% catalyst **7** was stirred at room temperature in 2.0 mL toluene; DBU (50 mol%) was added and the reaction mixture was stirred for a further 15 min. [b] Diastereomeric ratio (d.r.) was 9:1 as determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Refers to the reaction time prior to addition of DBU. [d] Refers to inseparable mixture of diastereomers obtained after flash chromatography. [e] Determined by HPLC analysis on a chiral stationary phase.

effect on the reactivity of the imine moiety within substrate **9a**.

BINOL-derived phosphoric acids have recently been derivatized into more acidic *N*-triflyl phosphoramides, which are more active in several chemical reactions.[11] Therefore, BINOL-derived *N*-triflyl phosphoramide **7b** was synthesized and found to rapidly catalyze the Friedel–Crafts reaction (Scheme 2). Following exposure of the reaction mixture to a catalytic quantity of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), isoindoline **10a** was isolated in good yield and diastereo- and enantioselectivity. Notably, the Friedel–Crafts reaction was highly chemoselective as the 1,4-addition of indole (**8a**) to the Michael acceptor of ε-iminoenoate **9a** was not observed.[12] Bis-indole byproduct **11a** was also formed in small amounts during the acid-catalyzed step.[13]

A series of *N*-triflyl phosphoramides **7b–f** (X = NHTf) were then synthesized. All of these catalysts were active, and isoindoline **10a** could be prepared in high yields and diastereoselectivities (Table 1, entries 2–6). The best catalyst, **7f** (R = 4-$NO_2C_6H_4$, X = NHTf), was capable of providing good levels of asymmetric induction (90:10 e.r.). Thus, further reaction optimization was conducted with this compound.

Many aromatic and chlorinated solvents were good reaction media, and isoindoline **10a** was formed in good to excellent enantioselectivities (89:11 to 95:5 e.r., Table 2, entries 1–6). Lowering the reaction temperature had a negligible or negative effect on the stereoselectivity: Therefore, all further experiments were conducted at room temperature.

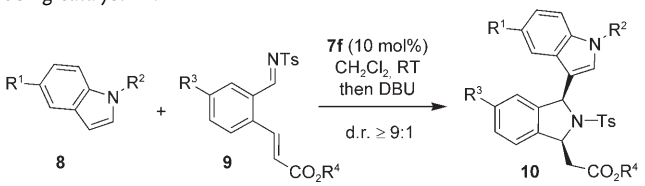
Table 2: Optimization of reaction conditions (solvent, time, and temperature) for the synthesis of isoindoline **10a** using catalyst **7f** (R = 4-$NO_2C_6H_4$, X = NHTf).[a,b]

Entry	Solvent	*T* [°C]	Time[c]	Yield [%][d]	e.r.[e]
1	toluene	RT	10 min	93	90:10
2	benzene	RT	1 min	97	92:8
3	PhCl[f]	RT	1 min	90	92:8
4	$CHCl_3$	RT	10 min	90	95:5
5	DCE[g]	RT	15 min	87	95:5
6	CH_2Cl_2	RT	10 min	94	95:5
7	CH_2Cl_2	0	10 min	86	95:5
8	CH_2Cl_2	−78	22 h	73	89:11

[a–e] See corresponding footnotes of Table 1. [f] PhCl = chlorobenzene. [g] DCE = 1,2-dichloroethane.

The substrate scope of the reaction was examined, and varying substitution patterns within the imine **9** and indole **8** were found to be tolerated (Table 3). For all cases, the yields ranged from good to excellent (71–99%) and the process

Table 3: Substrate scope for the synthesis of various isoindolines **10a–j** using catalyst **1f**.[a,b]



Entry	**10**	R^1	R^3	R^4	Time[c]	Yield [%][d]	e.r.[e]
1	**a**	H	H	Me	10 min	94	95:5
2	**b**	Br	H	Me	20 min	99	94:6
3	**c**	OMe	H	Me	90 min	93	76:24[f]
4[g]	**d**	H	H	Me	30 min	86	61:39
5	**e**	CO_2Me	H	Me	240 min	71	86:14
6	**f**	H	F	Me	30 min	75	91:9
7	**g**	OMe	F	Me	60 min	95	88:12[f]
8	**h**	H	H	*t*Bu	20 min	75	88:12
9	**i**	Br	H	*t*Bu	10 min	85	91:9
10	**j**	OMe	H	*t*Bu	70 min	97	90:10

[a–e] See corresponding footnotes of Table 1; reaction performed in 2.0 mL CH_2Cl_2; R^2 = H unless otherwise noted. [f] Determined after reduction of the ester to the corresponding alcohol. [g] R^2 = Me.

occurred in a diastereoselective fashion (9:1 d.r.).[14] The enantioselectivity of the one-pot Friedel–Crafts/aza-Michael addition was generally high. The enantiomeric ratios of isoindolines **10a–j** showed little dependence on the substitution patterns of the imine and indole substrates. Moreover, *tert*-butyl ester containing substrates **10h–j** were compatible with the acidic reaction conditions of this method (Table 3, entries 7–9). A limitation of the scope occurred with *N*-methylindole **8d** ($R^1 = H$, $R^2 =$ Me), which reacted in lower enantioselectivity (61:39 e.r., Table 3, entry 4).

NMR and X-ray crystallographic analysis of isoindolines **10** established the relative and absolute stereochemistry. Thus, the intramolecular Michael addition was *cis*-selective and (*S*,*S*)-configured isoindolines **10** were formed (Figure 1).[15]

The enantioselectivity of the reaction was found to change when the reaction time was varied. Further investigation led to a remarkable discovery:

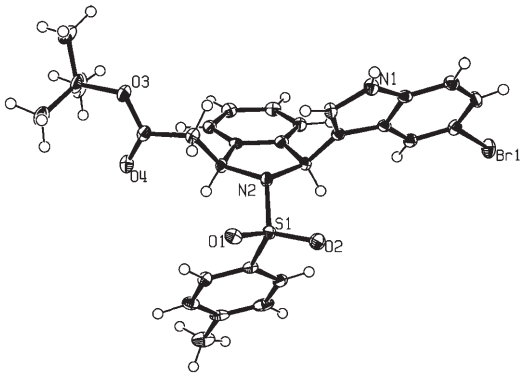
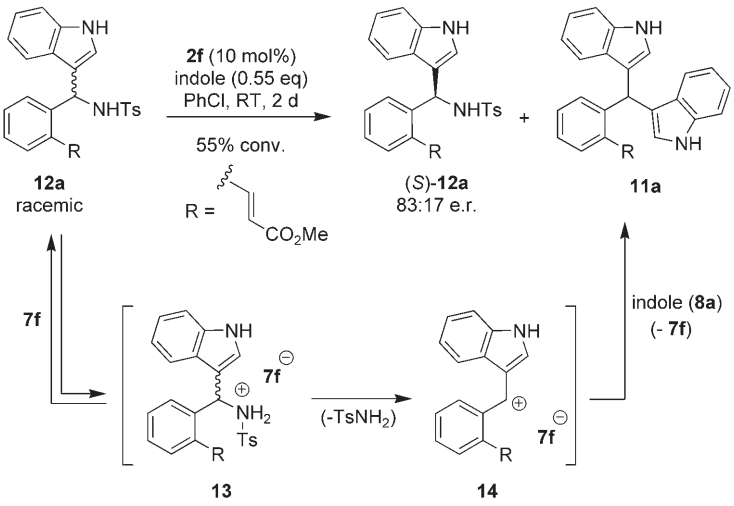


Figure 1. X-ray crystal structure of isoindoline **10i** (ORTEP view, ellipsoids drawn at the 50% probability level, CCDC 682470).

the enantiomeric ratio of isoindoline **10a** increased when the Friedel–Crafts reaction was run for a longer time. At the same time, the yield of isoindoline **10a** decreased and higher amounts of achiral bis-indole **11a** were formed. This indicated that a stereoablative kinetic resolution[10] was occurring during the Brønsted acid catalyzed step. To confirm this, a racemic sample of Friedel–Crafts adduct **12a** was exposed to indole (**8a**) in the presence of catalyst **7f** (Scheme 3).[16]

When the reaction was stopped prior to completion, the unreacted Friedel–Crafts adduct **12a** was found to be enantiomerically enriched (83:17 e.r.). The stereochemical outcome of the stereoablative kinetic resolution was the same as that for the Brønsted acid catalyzed Friedel–Crafts reaction: both processes led to enantiomerically enriched (*S*)-**12a**. Thus, the stereoablation destroys the minor enantiomer formed during the Friedel–Crafts reaction. This suggested that these processes could be coupled in a tandem reaction leading to an increase in enantiomeric ratios of isoindolines **10**. To achieve this, the reaction time of the Brønsted acid catalyzed reaction was extended (Table 4). This



Scheme 3. Stereoablative kinetic resolution of Friedel–Crafts adduct **12a**.

Table 4: Tandem Friedel–Crafts addition/stereoablative kinetic resolution for the synthesis of isoindolines **10a**,**b**,**f**,**h**,**j**.[a,b]

Entry	**10**	R^1	R^3	R^4	Time[c]	Yield [%][d]	e.r.[e]
1	**a**	H	H	Me	16 h	71	98:2
2[f]	**b**	Br	H	Me	10 d	57	>99:1
3[f]	**f**	H	F	Me	5 d	52	>99:1
4	**h**	H	H	*t*Bu	2 d	31	99:1
5	**j**	OMe	H	*t*Bu	2 d	34	99:1

[a] Reaction conditions (unless otherwise noted): A mixture of 0.3 mmol imine **9**, 1.5 equiv indole **8**, and 10 mol% catalyst **7f** in 2.0 mL PhCl was stirred at room temperature for 1–10 d. The isolated Friedel–Crafts adducts **12** were cyclized with DBU (50 mol%). [b–e] See corresponding footnotes of Table 1. [f] Performed in a mixture of $PhCl/CHCl_3$ (1:1).

simple procedural modification allowed isoindoline **10a** to be prepared in excellent enantiomeric ratio with minor loss in yield (Table 4, entry 1). Extension of the method to additional imines and indoles demonstrated that various isoindolines **10b**,**f**,**h**,**j** could be prepared in moderate yields (31–71%) and excellent enantiomeric ratios (99:1 e.r., Table 4, entries 2–5).

A reasonable mechanism can be proposed for the stereoablation. Assuming rapid and reversible protonation of both enantiomers of **12**, preferential dissociation of tosylamide ($TsNH_2$) from one of the diastereomeric ion pairs **13** occurs (Scheme 3). The resultant carbocation **14** then reacts irreversibly with indole (**8a**).[17]

In conclusion, we report the first catalytic asymmetric synthesis of 1,3-disubstituted isoindolines. The method described herein is based on a metal-free one-pot Brønsted acid catalyzed Friedel–Crafts/base-catalyzed aza-Michael addition reaction of bifunctional ε-iminoenoates and indoles. Chiral BINOL-derived *N*-triflyl phosphoramides catalyzed the initial Friedel–Crafts reaction and the isoindoline products were obtained in high yields and excellent diastereo- and enantiomeric ratios. Moreover, a Brønsted acid catalyzed stereoablative kinetic resolution was found to occur in tandem to the Friedel–Crafts reaction, thus enhancing the isoindoline enantiomeric ratios to excellent levels.

Experimental Section

General procedure: A solution of imine **9a–c** (0.29 mmol) and *N*-triflyl phosphoramide **7b–g** (0.029 mmol, 10 mol%) in CH_2Cl_2 (2.0 mL) was charged with 4 Å molecular sieves (10 beads, 0.12–0.14 g) and indole **8a–e** (0.873 mmol, 3.00 equiv). The reaction vessel was stoppered and stirred at room temperature for 10 to 90 min. DBU (22 μL, 0.15 mmol, 50 mol%) was added, and the reaction mixture was stirred for an additional 15 min. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography (pentane/ether, dry loaded) to afford isoindoline **10a–j**.

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[1] For reviews on Brønsted acid catalysis, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; c) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013–4016; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; f) J. D. McGilvra, V. B. Gondi, V. H. Rawal in *Enantioselective Organocatalysis: Reactions and Procedures* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**, pp. 189–254.

[2] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; c) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805; d) T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523–1526; e) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590–7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; f) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360–9361; g) G. B. Rowland, H. L. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696–15697; h) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583–2585; i) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783; j) M. Rueping, C. Azap, E. Sugiono, T. Theissmann, *Synlett* **2005**, 2367–2369; k) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312–2315; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254–2257; l) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679–2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617–2619; m) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903–6907; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751–6755.

[3] a) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996–7999; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832–7835; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; c) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087; d) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071; e) H. Liu, L. F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Org. Lett.* **2006**, *8*, 6023–6026; f) M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759–764; g) M. Terada, S. Yokoyama, K. Sorimachi, D. Uraguchi, *Adv. Synth. Catal.* **2007**, *349*, 1863–1867; h) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292–293; i) Q. Kang, Z. A. Zhao, S. L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485; j) G. L. Li, Y. X. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831; k) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336–10337; l) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman, J. C. Antilla, *Chem. Commun.* **2007**, 4477–4479; m) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Kockritz, A. Pews-Davtyan, N. Nemati, M. Beller, *Org. Lett.* **2007**, *9*, 1065–1068; n) G. B. Rowland, E. B. Rowland, Y. X. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609–2611; o) G. L. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065–4068; p) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2007**, 1441–1445.

[4] E. Valencia, A. J. Freyer, M. Shamma, V. Fajardo, *Tetrahedron Lett.* **1984**, *25*, 599–602.

[5] a) B. Portevin, C. Tordjman, P. Pastoureau, J. Bonnet, G. De Nanteuil, *J. Med. Chem.* **2000**, *43*, 4582–4593; b) T. L. Stuk, B. K. Assink, R. C. Bates, D. T. Erdman, V. Fedij, S. M. Jennings, J. A. Lassig, R. J. Smith, T. L. Smith, *Org. Process Res. Dev.* **2003**, *7*, 851–855.

[6] a) T. Kurihara, K. Fukunaga, T. Sakaguchi, H. Hirano, *J. Heterocycl. Chem.* **1975**, *12*, 989–993; b) P. J. Kukkola, N. A. Bilci, T. J. Ikeler, *Tetrahedron Lett.* **1996**, *37*, 5065–5068; c) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941; d) M. Bao, H. Nakamura, A. Inoue, Y. Yamamoto, *Chem. Lett.* **2002**, 158–159; e) O. Gaertzen, S. L. Buchwald, *J. Org. Chem.* **2002**, *67*, 465–475; f) H. Miyabe, K. Yoshida, Y. Kobayashi, A. Matsumura, Y. Takemoto, *Synlett* **2003**, 1031–1033; g) G. Stajer, F. Csende, *Curr. Org. Chem.* **2005**, *9*, 1277–1286; h) Q. Shi, P. L. Ornstein, K. Briner, T. I. Richardson, M. B. Arnold, R. T. Backer, J. L. Buckmaster, E. J. Canada, C. W. Doecke, L. W. Hertel, N. Honigschmidt, H. M. Hsiung, S Husain, S. L. Kuklish, M. J. Martinelli, J. T. Mullaney, T. P. O'Brien, M. R. Reinhard, R. Rothhaar, J. Shah, Z. Wu, C. Xie, J. M. Zgombick, M. J. Fisher, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2341–2346; i) M. Buchert, S. Meinke, A. Prenzel, N. Deppermann, W. Maison, *Org. Lett.* **2006**, *8*, 5553–5556.

[7] L. A. Carpino, *J. Chem. Soc. Chem. Commun.* **1966**, 858–859.

[8] a) R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar, *J. Org. Chem.* **1988**, *53*, 5381–5383; b) A. I. Meyers, B. Santiago, *Tetrahedron Lett.* **1995**, *36*, 5877–5880; c) D. Enders, V. Braig, G. Raabe, *Can. J. Chem.* **2001**, *79*, 1528–1535; d) R. T. Backer, I. Collado Cano, O. De Frutos-Garcia, C. W. Doecke, M. J. Fisher, S. L. Kuklish, V. Mancuso, M. Martinelli, J. T. Mullaney, P. L. Ornstein, C. Xie, Eli Lilly & Co.), WO 2003/061660, **2003**; e) J. Clayden, C. J. Menet, *Tetrahedron Lett.* **2003**, *44*, 3059–3062; f) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron: Asymmetry* **2008**, *19*, 111–123.

[9] a) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133–6135; b) Y. Sato, T. Nishimata, M. Mori, *Heterocycles* **1997**, *44*, 443–457; c) Z. Q. Wang, C. G. Feng, M. H. Xu, G. Q. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 5336–5337; d) T. Ogata, A. Ujihara, S. Tsuchida, T. Shimizu, A. Kaneshige, K. Tomioka, *Tetrahedron Lett.* **2007**, *48*, 6648–6650.

[10] Enantioselective stereoablative reactions afford enantiomerically enriched compounds by destroying a stereogenic element within a molecule. For a review, see: J. T. Mohr, D. C. Ebner, B. M. Stoltz, *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

[11] a) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627; b) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143–2146; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097–2100; c) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 2445–2447; *Angew. Chem. Int. Ed.* **2008**, *47*, 2411–2413.

[12] For asymmetric Brønsted acid-catalyzed Michael additions of indoles, see: a) W. Zhou, L. W. Xu, L. Li, L. Yang, C. G. Xia, *Eur. J. Org. Chem.* **2006**, 5225–5227; b) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603–606; *Angew. Chem. Int. Ed.* **2008**, *47*, 593–596.

[13] For examples of Brønsted and Lewis acid catalyzed formation of bis-indoles from imines, see: a) W. H. Xie, K. M. Bloomfield, Y. F. Jin, N. Y. Dolney, P. G. Wang, *Synlett* **1999**, 498 – 500; b) G. Babu, N. Sridhar, P. T. Perumal, *Synth. Commun.* **2000**, *30*, 1609 – 1614; c) J. Hao, S. Taktak, K. Aikawa, Y. Yusa, M. Hatano, K. Mikami, *Synlett* **2001**, 1443 – 1445; d) X. L. Mi, S. Z. Luo, J. Q. He, J. P. Cheng, *Tetrahedron Lett.* **2004**, *45*, 4567 – 4570.

[14] Potassium carbonate and activated neutral alumina also facilitated the aza-Michael addition of the Friedel–Crafts adduct **12a** in comparable yield and diastereoselectivity; however, the reaction times were longer.

[15] For an example of 1,3-*cis*-selective intramolecular hetero-Michael addition to form a five-membered ring, see: G. Mandville, C. Girard, R. Bloch, *Tetrahedron: Asymmetry* **1997**, *8*, 3665 – 3673.

[16] In CH_2Cl_2, the reaction of the Friedel–Crafts adduct **12a** and indole (**8a**) to form bis-indole **11a** was slow (< 5% conversion after 24 h). In chlorobenzene, the Friedel–Crafts adduct **12a**, although only sparingly soluble, underwent reaction with indole (**8a**) to form the bis-indole **11a**.

[17] Racemic Friedel–Crafts adduct **12a** was exposed to *N*-triflyl phosphoramide **7h** in the absence of indole for 2 d. Following cyclization with DBU, isolindoline **10a** was isolated in nearly quantitative yield and as a racemate. This provides further evidence that the enhancement of enantiomeric ratio is a result of a stereoablative nucleophilic displacement reaction: in the absence of a nucleophile, no enhancement occurs.

