Organocatalysis

DOI: 10.1002/anie.200703668

Asymmetric Brønsted Acid Catalysis: Enantioselective Nucleophilic Substitutions and 1,4-Additions**

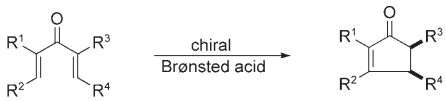
Magnus Rueping, Boris J. Nachtsheim, Stefan A. Moreth, and Michael Bolte*

Dedicated to Professor Dr. Dieter Seebach on the occasion of his 70th birthday

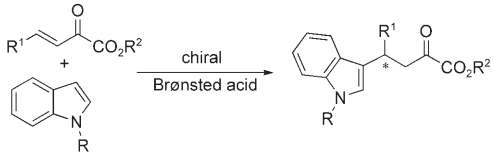
Asymmetric alkylations of electron-rich arenes such as indoles are of great importance for the synthesis of many natural products and pharmaceuticals.[1] Hence, different approaches have been undertaken to develop catalytic enantioselective additions of indoles to α,β-unsaturated carbonyl compounds. To date, these have been based on the application of chiral transition-metal complexes[2] or secondary amines, the latter of which function through covalent activation, forming intermediary iminium ions.[3] In this context the use of β,γ-unsaturated α-keto esters is of particular interest since they not only exhibit a higher reactivity but also can be functionalized readily to the corresponding amino acids or α-hydroxy acids.

Given the frequent occurrence of the indole core structure in biologically active substances and natural products[4] together with the possibility of activating carbonyl functionalities with chiral Brønsted acids,[5–6] the development of an enantioselective, metal-free, noncovalently catalyzed Friedel–Crafts alkylation of indoles appeared to be of great significance. This would not only be the first example of such an organocatalyzed transformation, but more importantly it would give simple and direct access to optically pure α-keto and α-amino acids. We report here on the development of such a reaction, a highly enantioselective Brønsted acid catalyzed addition of indoles to α,β-unsaturated carbonyl compounds.

In continuing studies on the Bønsted acid catalyzed asymmetric Nazarov cyclization of divinyl ketones[5] [Eq. (1)], we assumed that an enantioselective Friedel–Crafts alkylation of indoles through the noncovalent activation of α-keto esters using *N*-triflylphosphoramides [Eq. (2)] should also be feasible.

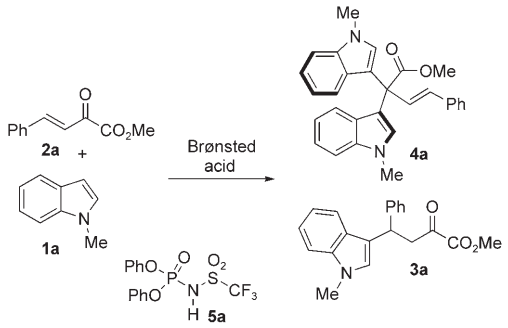


(1)



(2)

Therefore, our investigations started with the examination of the Brønsted acid catalyzed addition of *N*-methylindole (**1a**) to the α-keto ester **2a**. While no reaction was observed when weak Brønsted acids, such as carbonic acids or diphenyl phosphate, were used, catalytic amounts of *N*-triflylphosphoramide **5a** resulted in product formation. However, in addition to the desired 1,4-addition product **3a**, the bisindole **4a** was isolated as the main product (Scheme 1).



Scheme 1. Brønsted acid catalyzed reaction of *N*-methylindole (**1a**) with α-keto ester **2a** to form bisindole **4a**.

The Lewis or Brønsted acid catalyzed formation of bisindoles starting from aldehydes, ketones, and 1,2-diketones is well known,[7] and several naturally occurring alkaloids contain this structural element.[8] However, the remarkable regioselectivity observed in the reaction of indoles with β,γ-unsaturated α-keto esters favoring the 1,2-addition with the generation of bisindole **4a** has not previously been reported. Figure 1 shows the X-ray crystal structure of **4a**. In contrast to all previously reported bisindoles, **4a** exhibits atropisomerism as a result of the rotation barrier about the bonds to the quaternary carbon bond. The bisindole atropisomers are not only observed in the X-ray crystal structure but can also be

[*] Prof. Dr. M. Rueping, B. J. Nachtsheim, S. A. Moreth
Degussa Endowed Professorship
Institute of Organic Chemisty and Chemical Biology
Johann Wolfgang Goethe-Universität Frankfurt am Main
Max-von-Laue Strasse 7, 60438 Frankfurt am Main (Germany)
Fax: (+49) 69-798-29248
E-mail: M.rueping@chemie.uni-frankfurt.de
Dr. M. Bolte
Institute of Inorganic and Analytical Chemistry
Universität Frankfurt
Marie-Curie-Strasse 11, 60439 Frankfurt (Germany)

[**] The authors acknowledge Degussa GmbH and the DFG (Schwerpunktprogramm Organokatalyse) for financial support as well the Fonds der Chemischen Industrie for a stipend given to B.J.N.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

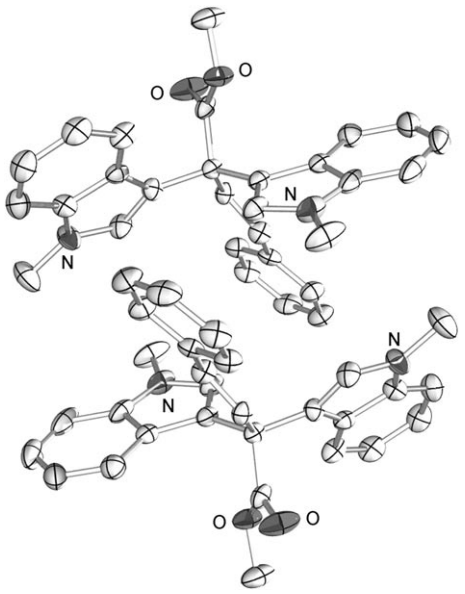
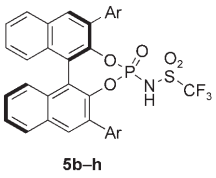


Figure 1. X-ray crystal structure of bisindole **4a**; elemental cell consisting of two atropisomers (ellipsoids drawn at the 50% probability level).

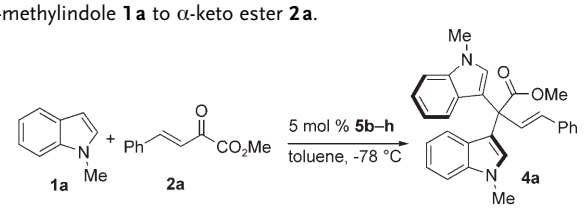
separated chromatographically which additionally demonstrates their stability in solution.[9]



5b–h

Based on the observation that these new bisindoles display atropisomerism, we decided to examine the chiral *N*-triflylphosphoramides **5b–5h**[10] in the addition of *N*-methylindole to β,γ-unsaturated α-keto esters (Table 1). Indeed, after optimizing the reaction by varying the temperature, solvent, catalyst loading, and concentration, we succeeded in obtaining bisindole **4a** in an atropisomeric ratio of 81:19 when 5 mol% of Brønsted acid **5f** was used (Table 1, entry 5).

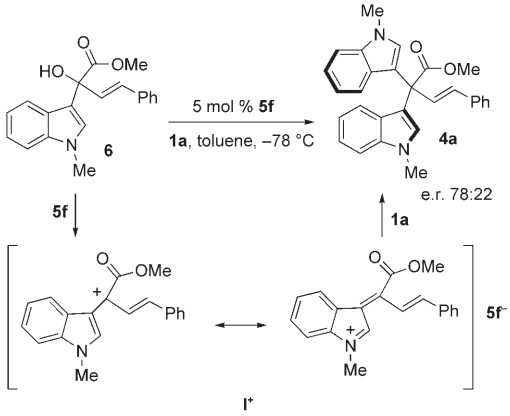
Table 1: Different *N*-triflylphosphoramides in the 1,2-addition of *N*-methylindole **1a** to α-keto ester **2a**.



Entry[a]	Catalyst	Ar	e.r.[b]
1	**5b**	phenyl	58:41
2	**5c**	4-$NO_2C_6H_4$	52:49
3	**5d**	1-naphthyl	65:35
4	**5e**	2-naphthyl	52:49
5	**5f**	9-phenanthryl	81:19
6	**5g**	anthracyl	72:29
7	**5h**	3,5-(CF_3)-phenyl	54:47

[a] Reaction conditions: **2a**, 5 mol% **5b–h**, **1a** (1.5 equiv). [b] Determined by HPLC analysis using a Chiralcel OD-H column.

This Brønsted acid catalyzed transformation to form enantiomerically enriched bisindoles is not only mechanistically of great interest but also provides enantioselective access to these atropisomers. To obtain more information about the mechanism, we prepared the racemic compound **6**[11] and converted this into **4a** under the reaction conditions used previously (Scheme 2). Bisindole **4a** was obtained in an



Scheme 2. Brønsted acid catalyzed enantioselective nucleophilic substitution to give the enantiomerically enriched bisindole **4a**.

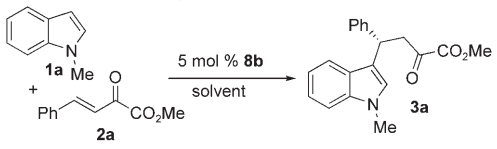
enantiomeric ratio of 78:22. With regard to the reaction mechanism, we conclude that **6** undergoes a Brønsted acid catalyzed nucleophilic substitution, starting with the elimination which results in the formation of the ion pair $\mathbf{I}^+\mathbf{5f}^-$. Subsequent reaction with *N*-methylindole (**1a**) then leads to enantiomerically enriched bisindole **4a**.

We were also interested in product **3a**, which may be derived from a Brønsted acid catalyzed 1,4-addition (Scheme 1). Given that in the presence of catalytic quantities of *N*-triflylphosphoramide **5b–h**, **3a** was obtained only as a side product with a yield less than 10% and low enantioselectivities, we decided to prepare the silylated *N*-triflylphosphoramides **8a** and **8b**, Brønsted acids with improved steric and electronic properties.[12]

Analogous to the *N*-triflylphosphoramides **5a–h**, the catalyst **8a** provided predominantly bisindole **4a**, while **8b** resulted in the formation of the addition product **3a.** This may be attributed to the steric properties of the catalyst. The 3,3′-C–Si bond is longer than the corresponding C–C bond in catalysts **5b–h**, and the spherically arranged phenyl groups on the silicon atoms increase the steric demand at the catalytic center, resulting in better shielding of the carbonyl groups in the activation process and giving rise to the preferred regioselective addition of indole in 4-position.

Following the initial results with the new Brønsted acid **8b** we again examined the reaction conditions (Table 2). The enantioselective Brønsted acid catalyzed indole addition can be conducted in diethyl ether as well as in various chlorinated

Table 2: Optimization of the reaction conditions for the Brønsted acid catalyzed enantioselective 1,4-addition.



Entry[a]	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	e.r.[c]
1	Et_2O	RT	24	62	53:47
2	Et_2O	−40	36	–	–
3	toluene	RT	16	44	65:34
4	toluene	−40	20	72	76:21
5	toluene	−78	18	58	84:15
6	CH_2Cl_2	−40	16	82	83:16
7	CH_2Cl_2	−75	15	62	94:6
8[d]	CH_2Cl_2	−75	16	44	94:6
9[e]	CH_2Cl_2	−75	24	36	91:9
10	$CHCl_3$	RT	20	53	66:34
11	$CHCl_3$	−40	20	62	70:29
12	$ClCH_2CH_2Cl$	−40	18	67	70:28

[a] Reaction conditions: **2a**, 5 mol% **8b**, **1** (1.5 equiv). [b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a Chiralcel OD-H column. [d] Using 10 mol% **8b**. [e] Using 2 mol% **8b**.

or aromatic solvents (Table 2). The best enantioselectivities were obtained in dichloromethane at −75 °C (Table 2, entries 7–9). With regard to the catalyst loading, the best results were achieved with 5 mol% **8b**. Neither higher loadings of **8b** (10 mol%) nor lower loadings (2 mol%) improved the yields and enantioselectivities (Table 2, entries 8 and 9). Under these optimized reaction conditions we subjected various indoles **1** as well as β,γ-unsaturated α-keto esters **2** in the asymmetric Brønsted acid catalyzed 1,4-addition (Table 3). In general the differently substituted α-keto esters **3** were isolated in good yields and in excellent enantiomeric ratios (up to 96:4 e.r.).

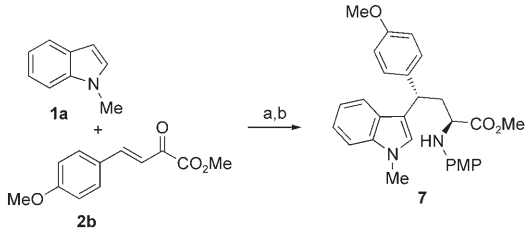
This Brønsted acid catalyzed indole addition reaction provides the corresponding α-keto esters which can be used as precursors for the synthesis of amino acids. Based on our previously reported highly enantioselective Brønsted acid catalyzed reactions,[13] such as the first transfer hydrogenations[14] with Hantzsch dihydropyridine as the hydride source, we assumed that an *N*-triflylphosphoramide-catalyzed reaction sequence consisting of a 1,4-addition followed by a reductive amination should result in the corresponding amino acids (Scheme 3). Thus, the double Brønsted acid catalyzed reaction sequence starting with the reaction of indole **1a** with **2b** gave the intermediate α-keto ester (Table 3, entry 9), which under the reduction conditions previously described was directly transformed into amino acid **7.**

In summary we have reported here on the a Brønsted acid catalyzed enantioselective Friedel–Crafts alkylation of indoles as well as a highly enantioselective 1,4-addition. This efficient method is not only the first example of a

Table 3: Scope of the enantioselective, Brønsted acid catalyzed indole addition.

Entry[a]	R^1	R^2	R^3	*T* [h]	Yield [%][c]	e.r. [%][c]
1	Ph	Me	H	15	62	94:6
2	Ph	Et	H	24	81	93:7
3	Ph	Me	5-Br	24	43	93:7
4	Ph	Me	7-Me	22	78	92:8
5	4-ClC_6H_4	Me	H	22	65	94:7
6	4-BrC_6H_4	Me	H	24	60	95:5
7	4-MeC_6H_4	Me	H	20	69	96:4
8	4-MeC_6H_4	Me	Br	22	55	90:10
9	4-$MeOC_6H_4$	Me	H	18	88	93:7
10	2-naphthyl	Me	H	18	70	95:5

[a] Reaction conditions: **2**, 5 mol% **8b**, **1** (1.5 equiv) at −75 °C. [b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a chiral stationary phase.



Scheme 3. Brønsted acid catalyzed Friedel–Crafts alkylation/reductive amination sequence. a) **2b**, 5 mol% **8b**, **1a** (1.5 equiv), CH_2Cl_2, −75 °C; b) Hantzsch dihydropyridine (1.5 equiv), *p*-anisidine, MS 4 Å (43%, d.r. 1.3:1). PMP = *p*-methoxyphenyl

Brønsted acid catalyzed activation of α,β-unsaturated carbonyl compounds, but it also provides the corresponding α-keto esters **3** in good yields and with excellent enantioselectivities. A double Brønsted acid catalyzed reaction sequence comprising a Friedel–Crafts alkylation followed by a reductive amination enables convenient and direct access to new amino acids. Depending on the selection of the chiral triflylphosphoramide catalyst, it is possible to synthesize previously unknown atropisomeric bisindoles in an unprecedented asymmetric 1,2-addition. Based on the experimental results we propose that the reaction mechanism of the transformation reported here is a Brønsted acid catalyzed enantioselective, nucleophilic substitution. Furthermore, the enantioselective reactions introduced here demonstrate the great potential of the acidic triflylphosphoramides as efficient and highly reactive chiral Brønsted acid catalysts. Moreover, the enantioselective Brønsted acid catalyzed, noncovalent activation of α-keto esters as well as of the unsaturated carbonyl compounds allows further transformations with diverse nucleophiles to be carried out, which is the subject of current studies.

Received: August 10, 2007

Keywords: alkylation · atropisomers · Michael addition · nucleophilic substitution · organocatalysis

[1] Reviews: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; b) M. Bandini, A. Eichholzer, A. Umani-Ronchi, *Mini-Rev. Org. Chem.* **2007**, *4*, 115; c) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550.

[2] Asymmetric Friedel–Crafts alkylations of α,β-unsaturated carbonyl compounds: Copper-catalyzed: a) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 160; b) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; c) K. A. Jørgensen, *Synthesis* **2003**, 1117; d) M. Bandini, M. Fagioli, M. Garavelli, A. Melloni, V. Trigari, A. Umani-Ronchi, *J. Org. Chem.* **2004**, *69*, 7511; e) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; f) Y. X. Jia, S. F. Zhu, Y. Yang, Q. L. Zhou, *J. Org. Chem.* **2006**, *71*, 75; g) S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739; h) R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099. Scandium-catalyzed: i) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780; j) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942; k) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029.

[3] Asymmetric Lewis base catalyzed Friedel–Crafts alkylation of α,β-unsaturated carbonyl compounds: a) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894; d) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955; e) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; f) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; g) W. Zhou, L.-W. Xu, L. Li, L. Yang, C.-G. Xia, *Eur. J. Org. Chem.* **2006**, 5225; h) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.

[4] M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278.

[5] M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097.

[6] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626.

[7] Selected more recent examples: a) J. S. Yadav, B. V. S. Reddy, S. Sunitha, *Adv. Synth. Catal.* **2003**, *345*, 349; b) T. J. K. Gibbs, N. C. O. Tomkinson, *Org. Biomol. Chem.* **2005**, *3*, 4043; c) D. G. Gu, S. J. Ji, Z. Q. Jiang, M. F. Zhou, T. P. Loh, *Synlett* **2005**, 959; d) S. M. Ma, S. C. Yu, *Org. Lett.* **2005**, *7*, 5063; e) V. Nair, K. G. Abhilash, N. Vidya, *Org. Lett.* **2005**, *7*, 5857; f) H. M. Li, Y. Q. Wang, L. Deng, *Org. Lett.* **2006**, *8*, 4063; g) S. Shirakawa, S. Kobayashi, *Org. Lett.* **2006**, *8*, 4939.

[8] a) E. Fahy, B. C. M. Potts, D. J. Faulkner, K. Smith, *J. Nat. Prod.* **1991**, *54*, 564; b) R. Bell, S. Carmeli, N. Sar, *J. Nat. Prod.* **1994**, *57*, 1587; c) G. Bifulco, I. Bruno, R. Riccio, J. Lavayre, G. Bourdy, *J. Nat. Prod.* **1995**, *58*, 1254; d) T. R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H. Yukawa, *J. Nat. Prod.* **2000**, *63*, 596.

[9] Atropisomerism of bisindoles has not been reported to date. We are currently conducting experiments to determine the stability, rotation barriers, etc.

[10] *N*-Triflylphophoramides **5b**–**h** have been prepared in analogy to the procedure described in references [5] and [6].

[11] The preparation of **6** is described in the Supporting Information.

[12] The synthesis of the new *N*-triflylphophoramides **8a** and **8b** will be described separately.

[13] a) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; b) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832; c) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Köckritz, A. Pews Davtyan, N. Nemati, M. Beller, *Org. Lett.* **2007**, *9*, 1065; d) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2007**, 144; e) M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759; f) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903.

[14] a) M. Rueping, C. Azap, E. Sugiono, T. Theissmann, *Synlett* **2005**, 2367; b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; c) M. Rueping, T. Theissmann, A. P. Antonchick, *Synlett* **2006**, 1071; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; f) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562.

