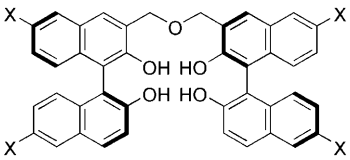
Asymmetric Mannich Reaction

Direct Catalytic Asymmetric Mannich-Type Reactions of *N*-(2-Hydroxyacetyl)pyrrole as an Ester-Equivalent Donor**

Shinji Harada, Shinya Handa, Shigeki Matsunaga, and Masakatsu Shibasaki**

The catalytic in situ generation of metal enolates and enamines from donor substrates in asymmetric carbon–carbon bond-forming reactions has recently received much attention.[1] Although tremendous progress has been made in this area in the last five years with various metal catalysts and organocatalysts,[2] room for improvement remains. For example, in metal catalysis, the donor substrates are mostly limited to ketones.[3,4] The use of donor substrates with the oxidation state of carboxylic acid is still a formidable task since the pK_a value of the α proton in carboxylic acid derivatives is much higher than that in ketones. A few landmark studies addressing this issue were recently reported.[5] In particular, Evans et al. achieved a highly enantioselective aldol reaction utilizing *N*-acyl thiazolidinethione donors and a chiral Ni catalyst.[5a] The reaction proceeded with excellent yield and selectivity; however, stoichiometric amounts of the silylating reagent and amine base were required to facilitate catalyst turnover. The development of a suitable ester-equivalent donor and/or a new asymmetric catalyst to achieve both high enantioselectivity and conversion without additional stoichiometric reagents is desirable. Herein, we report that an *N*-acylpyrrole moiety is an effective achiral template for the in situ generation of metal enolates. New complexes composed of $In(OiPr)_3$ and (*S*,*S*)-linked-binol **1** were used to catalyze the



X=H: (*S*,*S*)-linked-binol **1a**
X=$(CH_3)_3Si$: (*S*,*S*)-6,6',6'',6'''-TMS-linked-binol **1b**

asymmetric Mannich-type reaction of *N*-(2-hydroxyacetyl)-pyrrole and *ortho*-tosylimines, which proceeded through simple proton transfer to give β-amino-α-hydroxy carboxylic acid derivatives in high enantioselectivity (91–98% *ee*, major diastereomer) and good yield (65–98%).

We selected *N*-acylpyrrole as a donor substrate for investigation and as an achiral template for the following reasons. Evans et al. reported the unique properties of *N*-acylpyrrole.[6] We subsequently demonstrated the utility of the *N*-acylpyrrole moiety as an ester surrogate in catalytic asymmetric conjugate additions, in which an α,β-unsaturated *N*-acylpyrrole substrate was used as an activated, monodentate electrophile.[7] Because the lone pair on the nitrogen atom in the pyrrole ring is delocalized in an aromatic system, the properties of the carbonyl group are similar to those of a phenyl ketone. We supposed that *N*-acylpyrrole would also be useful as an ester-equivalent donor because the aromaticity would assist enolate formation. Since the coordination mode of the *N*-acylpyrrole donor is similar to that of an aromatic ketone, the chiral environment optimized for ketone donors would be applicable for *N*-acylpyrrole. Based on our previous report that the complex Et_2Zn/linked-binol **1a** is suitable for the formation of an enolate from an aromatic hydroxyketone,[2c] we used *N*-(2-hydroxyacetyl)pyrrole **2** (Figure 1) and complexes composed of a metal and linked-binol **1a** in the preliminary evaluations of the potential of the *N*-acylpyrrole moiety for the catalytic in situ generation of metal enolates.

The results of the initial screening in the Mannich-type reaction with **2** are shown in Table 1. When the Et_2Zn/**1a**

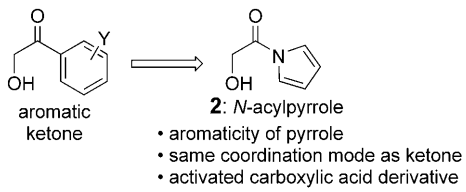


Figure 1. Structure and properties of *N*-acylpyrrole (**2**).

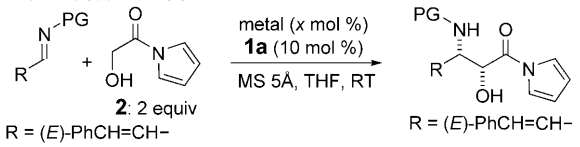
[*] S. Harada, S. Handa, Dr. S. Matsunaga, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp

[**] This work was supported by a Grant-in-Aid for Specially Promoted Research and a Grant-in-Aid for Encouragement of Young Scientists (B) (for S.M.) from JSPS and MEXT.

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

 DOI: 10.1002/ange.200501180 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1: Direct catalytic asymmetric Mannich-type reaction of *N*-(2-hydroxyacetyl)pyrrole (**2**).[a]



2: 2 equiv
R = (*E*)-PhCH=CH–
PG = *p*-Ts: **3a**, *o*-Ts: **4a**
R = (*E*)-PhCH=CH–

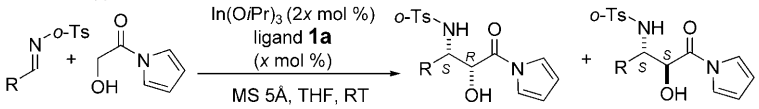
Entry	Imine	Metal (*x* mol %)	Prod.	*t* [h]	Yield [%]	*syn*/*anti*	*ee* [%]
1	**3a**	Et_2Zn (40)	**5a**	96	11	40:60	–
2	**3a**	$In(OiPr)_3$ (20)	**5a**	96	61	86:14	93
3	**4a**	$In(OiPr)_3$ (20)	**6a**	96	94	91:9	96

[a] PG = protecting group, MS 5Å = molecular sieves 5 Å, RT = room temperature.

complex was used for *para*-tosylimine **3a**, a Mannich adduct was obtained in only low yield (Table 1, entry 1, 11%), probably due to the low Brønsted basicity of the Zn catalyst in the formation of the zinc enolate from **2**. Screening of other metal sources revealed that $In(OiPr)_3$ was the most effective.[16] When a 2:1 complex of $In(OiPr)_3$ and **1a** was used, the reaction of **2** and **3a** in THF proceeded at room temperature to give the Mannich adduct in 61% yield and 93% *ee* (Table 1, entry 2). The reaction of *ortho*-tosylimine **4a** under the same conditions gave **6a** with improved yield (94%), diastereoselectivity (*syn*/*anti* = 91:9), and enantioselectivity (96% *ee* (*syn*); Table 1, entry 3).[8,9] In this reaction, we assumed that either an indium alkoxide or an indium phenoxide functions as a Brønsted base and deprotonates **2** at the α position to form the indium enolate in situ. Although there are many reports on Lewis acidic indium catalysts ($In(OTf)_3$, $InCl_3$, $InBr_3$, etc.),[10] the Brønsted basic property of indium chiral catalysis was utilized for the first time in organic synthesis. Furthermore, the present reaction using an α-hydroxy-substituted donor complements the reports by Evans and Shair,[5] in which α-alkyl-substituted donors were used.[11]

The substrate scope of the present reaction is summarized in Tables 2 and 3. The diastereomeric ratio depended on the imines used. As shown in Table 2, alkenyl imines **4a–d** afforded *syn* adducts in good diastereoselectivity (88:12–91:9) and high enantioselectivity (93–97% *ee* (*syn*) Table 2, entries 1–4). The *syn* selectivity of the reactions of imines **4e** and **4f**, which have an unsubstituted and *para*-substituted aromatic ring, respectively, was only modest (Table 2, entries 5 and 6).[12] At present, this reaction with the In-$(OiPr)_3$/(*S*,*S*)-linked-binol complex is limited to sp^2-hybridized imines; however, subsequent functionalization of the C–C double bond in the Mannich adducts obtained from alkenyl imines **4a–d** can afford β-alkyl-substituted β-amino-α-hydroxy carboxylic acid derivatives (see below). Further trials to expand the substrate scope of the reaction to aliphatic imines are ongoing. On the other hand, imines **4g–k**, which contain *ortho*-substituted aromatic rings, and cyclopropyl imine **4l** gave products with *anti* selectivity[8] in high *ee* (92–98% *ee*, *anti*; Table 3). Both electron-withdrawing (Cl, Br) and electron-donating substituents (Me, MeO) on the aromatic ring were applicable. For less reactive substrates, an increased amount of the chiral ligand (15 mol%) was required to obtain products in good yield (Table 3, entries 1, 2, and 5–7). Use of a modified linked-binol ligand **1b** resulted

Table 2: Mannich-type reaction of imines **4a–f** with **2**.

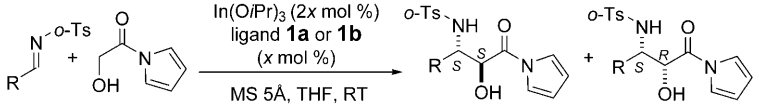


4a–f **2**: 2 equiv *syn*-**6a–f** *anti*-**6a–f**

Entry	**4**, R	Lig. **1a** [*x* mol %]	Prod.	*t* [h]	Yield [%]	d.r. *syn*/*anti*	*ee* [%] *syn*, *anti*
1	**4a**, (*E*)-PhCH=CH-	10	**6a**	96	94[a]	91:9	96, 83
2	**4b**, (*E*)-*p*-tol-CH=CH-	10	**6b**	97	86[a]	89:11	95, 76
3	**4c**, (*E*)-*p*-Cl-C_6H_4-CH=CH-	10	**6c**	97	79[a]	88: 12	93, 71
4	**4d**, (*E*)-2-furyl-CH=CH-	10	**6d**	99	80	90:10	97, 81
5	**4e**, Ph	10	**6e**	111	98	61:39	91, 91
6	**4f**, *p*-Cl-C_6H_4-	10	**6f**	89	97	59:41	96, 94

[a] Yield of isolated product after conversion into the corresponding benzoate.

Table 3: Mannich-type reaction of **4g–l** with **2**.



4g–l **2**: 2 equiv *anti*-**6g–l** *syn*-**6g–l**

Entry	**4**, R	Ligand (*x* mol %)	Prod.	*t* [h]	Yield [%]	d.r. *anti*/*syn*	*ee* [%] *anti*, *syn*
1	**4g**, 1-naphthyl	**1a** (15)	**6g**	99	86	72:28	90, 87
2	**4g**, 1-naphthyl	**1b** (15)	**6g**	99	87	77:23	94, 89
3	**4h**, *o*-Cl-C_6H_4	**1a** (10)	**6h**	76	87	83:17	93, 81
4	**4i**, *o*-Br-C_6H_4	**1a** (10)	**6i**	89	68	86:14	95, 90[a]
5	**4j**, *o*-Me-C_6H_4	**1a** (15)	**6j**	92	76	76:24	93, 85[a]
6	**4k**, *o*-MeO-C_6H_4	**1a** (15)	**6k**	93	70	77:23	89, 81
7	**4k**, *o*-MeO-C_6H_4	**1b** (15)	**6k**	93	74	77:23	92, 86
8	**4l**, cyclopropyl	**1a** (10)	**6l**	65	83	63:37	96, 91
9	**4l**, cyclopropyl	**1b** (10)	**6l**	65	86	75:25	98, 90

[a] The enantiomeric excess was determined after conversion of the product into the triethylsilyl ether.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

in slightly better stereoselectivity in some cases (Table 3, entries 1, 6, and 8 vs. 2, 7, and 9).

In all entries in Tables 2 and 3, the *syn* and the *anti* adducts were obtained with the same absolute configuration at the β position (*S*), implying that selection of the imine enantioface is identical.[8] Proposed models of the acyclic *anti*-periplanar transition state are shown in Figure 2. Imines **4a–f**

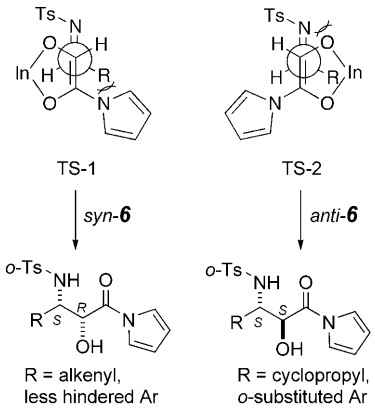
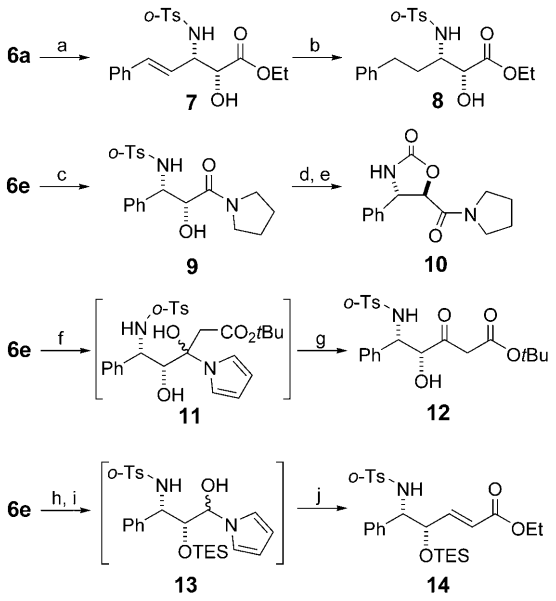


Figure 2. Postulated transition-state model of Mannich-type reactions.

with a planar configuration would favor the TS-1 to minimize *gauche* interactions. On the other hand, imines **4g–l** have a twisted configuration due to steric (**4g–k**) and stereoelectronic (**4l**) effects. Thus, steric repulsion between imine substituents R and the pyrrole ring of the indium enolate would become more predominant, and the *anti*-periplanar TS-2 would be more favorable than TS-1. For a more precise understanding of the diastereoselectivity evidenced in Table 2 and Table 3 and the effects of the modified ligand **1b**, further mechanistic studies including clarification of the structure of the complex of $In(OiPr)_3$ and (*S*,*S*)-linked-binol **1** are required.

Finally, the utility of the *N*-acylpyrrole unit as an ester surrogate was demonstrated through several transformations of Mannich adducts (Scheme 1).[13] The *N*-acylpyrrole unit of **6a** was readily transformed into an ethyl ester unit by treatment with NaOEt at room temperature for 5 min, affording **7** in quantitative yield. Hydrogenation of the C–C double bond in **7** gave **8** in 92% yield, which corresponds to the β-amino-α-hydroxy ester accessible from an aliphatic imine. Substitution with amine also proceeded smoothly. Amide **9** was obtained in quantitative yield by the treatment of Mannich adduct **6e** with pyrrolidine and DBU at 40 °C for 1 h. Neither epimerization nor racemization was observed during substitution. After conversion of **9** into the cyclic carbamate (94% yield), the *o*-Ts group was removed under mild reduction conditions (Mg powder, room temperature, 20 min)[14] to give **10** in 81% yield. In addition to substitution reactions with alcohols and amines, reaction of **6e** with a lithium enolate followed by treatment with DBU provided keto ester **12** in 62% yield. Protection with a triethylsilyl (TES) group followed by reduction with $LiBH_4$ afforded the pyrrole carbinol **13** as a stable intermediate. Under Masamune–Roush conditions,[15] the aldehyde moiety was generated in situ from the crude pyrrole carbinol **13**, and the α,β-unsaturated ester **14** was obtained in 67% yield (in two steps from the TES-protected Mannich adduct).



Scheme 1. Transformations of Mannich adducts. Reaction conditions: a) NaOEt, EtOH, 0 °C→RT, 5 min, quant. yield; b) Pd/C, H_2, MeOH, RT, 30 min, 92%; c) pyrrolidine, DBU, THF, 40 °C, 1 h, quant. yield; d) triphosgene, py, CH_2Cl_2, −78 °C→RT, 1 h, 94%; e) Mg powder, MeOH, RT, 20 min, 81%; f) LDA, *t*Bu acetate, THF, −78 °C, 10 min; g) DBU, CH_2Cl_2, RT, 5 min, 62% (2 steps); h) TESCl, imidazole, DMF, 0 °C, 30 min, 87%; i) $LiBH_4$, THF, RT, 30 min; j) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN, RT, 7 h, 67% (2 steps). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, py = pyridine.

In summary, we have demonstrated the utility of *N*-acylpyrrole **2** as an ester-equivalent donor in a direct Mannich-type reaction. A catalytic amount of a chiral complex composed of $In(OiPr)_3$ and the (*S*,*S*)-linked-binol **1** was effective in generating the indium enolate in situ from **2**. The reaction is formally a simple proton transfer, and high enantioselectivity (up to 98% *ee*) was achieved at ambient temperature. Mechanistic studies of indium catalysis, trials to improve the unsatisfactory reaction rate and diastereoselectivity, and further application of the *N*-acylpyrrole moiety as an ester-equivalent donor in other reactions are ongoing.

Received: April 4, 2005
Published online: June 7, 2005

Keywords: amino alcohols · asymmetric catalysis · indium · Mannich reaction · pyrroles

[1] A review of the direct Mannich reaction: a) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; a review of the direct aldol reaction: b) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595.

[2] Selected examples of direct Mannich reactions using unmodified ketones and/or aldehydes as donors: with metal catalysts: a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995; b) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338; c) S. Matsunaga, N.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712, and references therein; with organocatalysts: d) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; e) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199; f) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827; g) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842; h) A. Córdova, S.-i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; i) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; j) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476; k) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356, and references therein. For other related examples, see reviews in ref. [1].

[3] See refs [1] and [2a–c]; see also a) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; b) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; c) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169.

[4] For exceptional examples in Mannich-type reactions using readily enolizable substrates with the oxidation state of carboxylic acid, see: with glycine Schiff base as a donor: a) T. Ooi, M. Kameda, J. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397; b) L. Bernardi, R. G. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583; with malonates and ketoesters as donors: c) M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359; d) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525.

[5] Asymmetric aldol reactions: a) D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706; b) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3147; diastereoselective aldol reactions: c) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392; d) D. A. Evans, C. W. Downey, J. T. Shaw, J. S. Tedrow, *Org. Lett.* **2002**, *4*, 1127; racemic aldol reactions: e) G. Lalic, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2003**, *125*, 2852; f) N. Kumagai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 13632.

[6] a) D. A. Evans, G. Borg, K. A. Scheidt, *Angew. Chem.* **2002**, *114*, 3320; *Angew. Chem. Int. Ed.* **2002**, *41*, 3188; for the application of *N*-acylpyrrole as a donor after conversion into enol silane, see: b) D. A. Evans, D. S. Johnson, *Org. Lett.* **1999**, *1*, 595; c) D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am. Chem. Soc.* **2001**, *123*, 4480.

[7] For the use of an α,β-unsaturated *N*-acylpyrrole as an electrophile, see: a) S. Matsunaga, T. Kinoshita, S. Okada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 7559; b) T. Kinoshita, S. Okada, S. Matsunaga, Park, S.-R. *Angew. Chem.* **2003**, *115*, 4828; *Angew. Chem. Int. Ed.* **2003**, *42*, 4680; c) T. Mita, K. Sasaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 514.

[8] For the determination of relative and absolute configurations of Mannich adducts **6a–l**, see the Supporting Information.

[9] The addition of MS 5 Å had beneficial effects on the reaction rate but did not affect the enantiomeric excess. Similar effects of molecular sieves were observed in related reactions using zinc catalysts and hydroxy ketones as donors; see, a) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2582; b) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777, and references therein; see also, refs [2b,c and 3b,c].

[10] Reviews: a) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347; b) J. Podlech, T. C. Maier, *Synthesis*, **2003**, 633.

[11] After submission of this manuscript, an excellent organocatalytic Mannich reaction using α-oxyaldehydes was reported, see: a) I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839; α-oxyaldehydes were also used as donors in organocatalytic aldol (dimerization) reactions, see: b) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 2204; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152; c) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343, and references therein; for related recent work using α-oxyketones as donors, see also: d) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem.* **2005**, *117*, in press; *Angew. Chem. Int. Ed.* **2005**, *44*, in press; for other examples using α-oxyketones, see refs [1, 2], and references therein.

[12] The diastereoselectivity of the reaction with the imine from benzaldehyde was improved by using the bulkier 2,4,6-triisopropylbenzenesulfonyl imine (*syn*/*anti* = 78:22, *syn*: 95% ee); however, reactivity decreased significantly (27% yield).

[13] For conversion of *N*-acylpyrrole units, see refs [6, 7], and references therein.

[14] For the removal of Ts group using Mg powder, see ref. [2a]; see, also: B. Nyasse, L. Grehn, U. Ragnarsson, *Chem. Commun.* **1997**, 1017.

[15] a) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essefeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183; b) D. J. Dixon, M. S. Scott, C. A. Luckhurst, *Synlett* **2003**, 2317.

[16] Note added in proof: since submission of this manuscript we have found that $In(OiPr)_3$ can be purchased from Kojundo Chemical lab (sales@kojundo.co.jp).

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim