Asymmetric Synthesis

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One-Pot Synthesis of Chiral α-Substituted β,γ-Epoxy Aldehyde Derivatives through an Asymmetric Aldol Reaction of Chloroacetaldehyde

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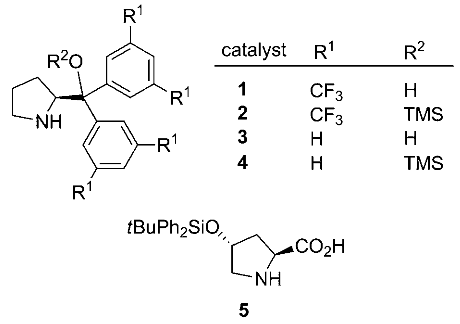
Epoxides are among the most important functional groups in organic synthesis,[1] and there are many reliable synthetic methods for the preparation of chiral epoxides. The asymmetric catalytic epoxidation of the corresponding alkene is one of the well-established methods, which include the Katsuki–Sharpless epoxidation,[2] the chiral salen-mediated epoxidation developed independently by Jacobsen[3] and Katsuki,[4] Shi's epoxidation using a sugar-derived ligand,[5] and Yamamoto's chiral epoxidation of homoallylic alcohols mediated by a vanadium reagent.[6] Asymmetric epoxidation of α,β-unsaturated carbonyl compounds is also a well-investigated reaction.[7] In addition to enantioselective epoxidation through oxidation of the corresponding alkene, there is also a method for the formation of an epoxide that involves the generation of a new carbon–carbon bond.[8]

Since the discovery of the proline-mediated intermolecular aldol reaction reported by List et al.,[9] the field of organocatalysis[10] has been developing very rapidly. The asymmetric cross-aldol reaction of two different aldehydes was first reported by MacMillan and co-workers.[11] When an α-halo aldehyde acts as an electrophilic aldehyde and reacts with an enamine, which is generated from another aldehyde, a β-hydroxy-γ-halo aldehyde is formed, which can be treated with a base and transformed into a β,γ-epoxy aldehyde. To our knowledge, the synthesis of a chiral β,γ-epoxy aldehyde through a one-pot process has not been described yet. As chloroacetaldehyde is commercially available as a hydrated form in an aqueous solution (40%), it would be a synthetic advantage to employ the aqueous solution directly from a commercial source without removal of water, in the presence of which the aldol reaction is necessarily performed.[12] Because we have already described an organocatalyst-mediated aldol reaction in the presence of water or in water,[13,14] we expected that the aldol reaction would proceed using an aqueous solution of chloroacetaldehyde directly. With these scenarios in mind, we investigated the aldol reaction of aqueous chloroacetaldehyde. During the preparation of this manuscript, Mahrwald and co-workers reported a histidine-mediated aldol reaction, in which there is one example using chloroacetaldehyde.[15]

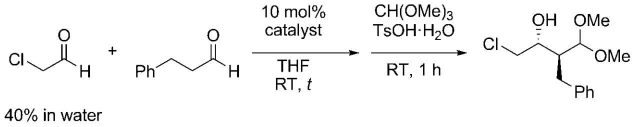


catalyst	R^1	R^2
1	CF_3	H
2	CF_3	TMS
3	H	H
4	H	TMS

Scheme 1. Organocatalysts investigated in the present study. TMS = trimethylsilyl.

First, the reaction of chloroacetaldehyde and 3-phenylpropanal was investigated with several organocatalysts (Scheme 1). The reaction proceeded, and the product was isolated and characterized after conversion into the corresponding dimethyl acetal by treatment of the reaction mixture

Table 1: The effect of the catalyst and solvent in the aldol reaction of aqueous chloroacetaldehyde and 3-phenylpropanal.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	proline	THF	100	< 5	–	–
2	**1**	THF	82	72	4.9:1	99
3	**1**	CH_2Cl_2	48	< 5	–	–
4	**1**	DMF	60	75	2.8:1	95
5	**1**	MeOH	48	52	3.0:1	94
6	**1**	CH_3CN	60	60	4.0:1	94
7	**2**	THF	100	70	2.9:1	−77
8	**3**	THF	100	53	1.1:1	92
9	**4**	THF	100	57	1.0:1	4
10	**5**	THF	72	41	1.7:1	−7

[a] Unless otherwise shown, the reaction was performed by employing chloroacetaldehyde (0.75 mmol, 123 μL, 40% aqueous solution), 3-phenylpropanal (0.50 mmol), and organocatalyst (0.05 mmol) in the indicated solvent (0.5 mL) at room temperature for the indicated time. After that, $CH(OMe)_3$ (6.0 mmol) and $TsOH{\cdot}H_2O$ (0.1 mmol) were added, and the reaction mixture was stirred for 1 h at room temperature (see the Supporting Information for details). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. DMF = *N*,*N*-dimethylformamide, Ts = 4-toluenesulfonyl.

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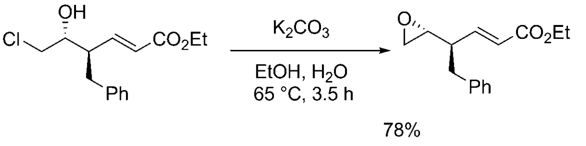
with $CH(OMe)_3$ and a catalytic amount of $TsOH{\cdot}H_2O$. The catalyst and solvent were screened (Table 1). The diarylprolinol derivative with a trifluoromethyl substituent is an effective catalyst,[16] which leads to the aldol product in good yield with good diastereoselectivity and excellent enantioselectivity when tetrahydrofuran (THF) is used as a solvent (Table 1, entry 2). Despite the excellent result obtained with diarylprolinol, its corresponding silyl ether[17] gave a lower stereoselectivity (Table 1, entry 7). A nearly racemic aldol product was obtained when diphenylprolinol **3**, its silyl ether **4**, or siloxyproline **5** were employed as catalysts (Table 1, entries 9 and 10).

Next, the generality of the reaction was investigated using several aldehydes. The aldol product was isolated after conversion not only into the corresponding dimethyl acetal, but also into the α,β-unsaturated ester through a reaction with a Wittig reagent (Table 2). Both dimethyl acetal and α,β-unsaturated ester were obtained with excellent enantioselectivities. Not only propanal, but also butanal, pentanal, and isovaleraldehyde turned out to be suitable aldehydes that led to the aldol products in good yield and with excellent enantioselectivity. In these reactions, two equivalents of the aldehydes have been employed (Table 2, entries 1–4, 8–11). When the nucleophilic aldehyde is expensive or precious, it should be used in a lower amount than the inexpensive chloroacetaldehyde. The reaction also proceeds efficiently even though chloroacetaldehyde and nucleophilic aldehydes such as 3-phenylpropanal, (*Z*)-5-octenal, and 5-trimethylsilyl-4-pentynal were used at 1.5 and 1.0 equivalents, respectively, to afford the aldol products with excellent enantioselectivity (Table 2, entries 5–7, 12, 13). Double bonds and triple bonds do not interfere with the reaction and the *Z*/*E* isomerization of double bond is not observed.

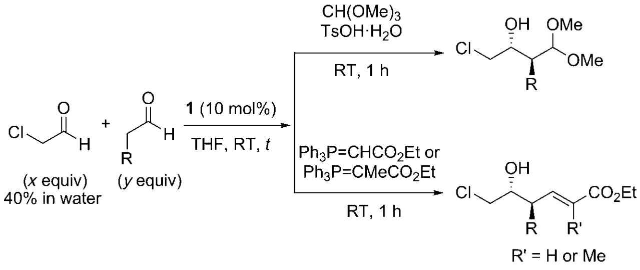
Because the aldol product possesses a β-chloro hydroxy moiety, the synthetically useful epoxide would be prepared through treatment with a base. When ethyl 6-chloro-5-hydroxy-2-hexenoate, the isolated product derived from the sequential aldol and Wittig reactions, was treated with several bases, the corresponding epoxide was found to be obtained in good yield (78 %) by treatment with K_2CO_3 at 65 °C [Eq. (1)].

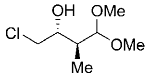
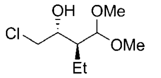
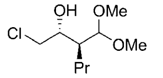
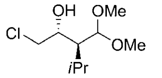
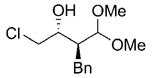
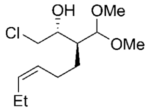
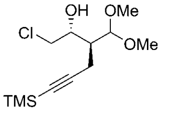
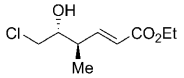
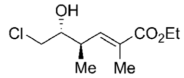
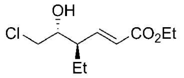
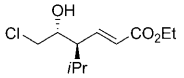
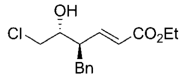
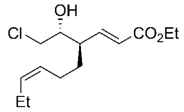


(1)

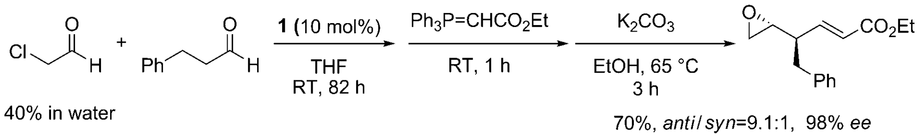
The synthesis of the epoxides was carried out from chloroacetaldehyde in a one-pot reaction as follows. After the aldol reaction, a Wittig reagent was added and the reaction mixture was stirred for one hour at room temperature. After addition of EtOH and K_2CO_3 in the same flask, the epoxide was generated in good yield by stirring the reaction mixture at 65 °C for three hours [Eq. (2)]. The enantioselectivity

Table 2: One-pot aldol/acetalization or aldol/Wittig reaction.[a]



Entry	Product	*x* [equiv][b]	*y* [equiv][c]	*t* [h]	Yield [%][d]	*anti*/*syn*[e]	*ee* [%][f]
1		1	2	33	90	5.9:1	95
2		1	2	38	81	9.0:1	97
3		1	2	36	82	5.9:1	98
4[g]		1	2	90	68	9.1:1	97
5		1.5	1	82	72	4.9:1	99
6[g]		1.5	1	46	76	5.9:1	98
7[g]		1.5	1	86	66	3.0:1	90
8		1	2	33	75	4.2:1	95
9		1	2	38	74	5.6:1	94
10		1	2	36	66	5.9:1	99
11[g]		1	2	90	44	8.7:1	98
12		1.5	1	82	70	6.9:1	98
13[g]		1.5	1	46	74	5.9:1	96

[a] Unless otherwise shown, the catalyst **1** was employed in 10 mol% (see the Supporting Information for experimental details). [b] Amount of chloroacetaldehyde. [c] Amount of nucleophilic aldehyde. [d] Yield of isolated product. [e] Determined by ^1H NMR spectroscopy. [f] See the Supporting Information. [g] Catalyst **1** (15 mol%) was employed.

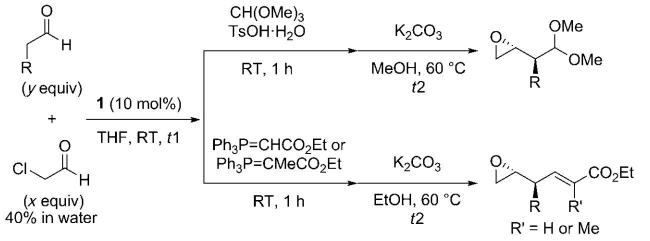


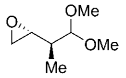
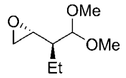
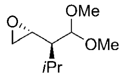
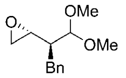
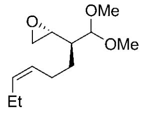
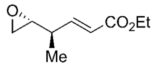
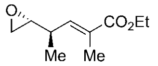
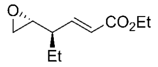
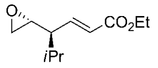
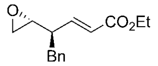
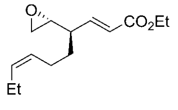
(2)

(98% *ee*) was found to be the same as that of the aldol product.

After establishing the one-pot synthesis of chiral epoxides, the generality of the process was investigated (Table 3). A chiral epoxide with a dimethyl acetal moiety is obtained in good yield with good diastereoselectivity and excellent enantioselectivity through aldol/acetalization/epoxidation reactions. One-pot aldol/Wittig reaction/epoxidation reactions also proceed to provide epoxides with an α,β-unsaturated ester moiety in good yield with good diastereoselectivity and excellent enantioselectivity.

Table 3: One-pot synthesis of epoxide through aldol/acetalization/epoxidation or aldol/Wittig/epoxidation.[a]

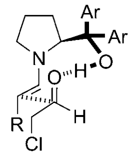


Entry	Product	*x* [equiv][b]	*y* [equiv][c]	*t*1 [h][d]	*t*2 [h][e]	Yield [%][f]	*anti*/*syn*[g]	*ee* [%][h]
1		1	2	33	5	82	4.8:1	95
2		1	2	38	8	80	6.7:1	97
3[i]		1	2	90	10	78	8.3:1	97
4		1.5	1	82	1.5	63	8.3:1	99
5[i]		1.5	1	46	5	82	5.3:1	98
6		1	2	33	6	75	4.8:1	95
7		1	2	33	7	79	5.0:1	94
8		1	2	38	8.5	72	4.6:1	99
9[i]		1	2	90	12	61	6.3:1	98
10		1.5	1	82	3	70	9.1:1	98
11[i]		1.5	1	46	6	78	4.8:1	96

[a] Unless otherwise shown, the catalyst **1** was employed in 10 mol% (see the Supporting Information for experimental details). [b] Amount of chloroacetaldehyde. [c] Amount of nucleophilic aldehyde. [d] Reaction time for the aldol reaction. [e] Reaction time for the treatment with K_2CO_3. [f] Yield of isolated product. [g] Determined by ^{1}H NMR spectroscopy. [h] See the Supporting Information. [i] Catalyst **1** (15 mol%) was employed. Bn = benzyl.

Because the epoxide is a reactive intermediate, its further transformation in a one-pot three-component reaction was investigated. After the aldol and acetalization reaction, a β-chloro hydroxy derivative has been generated, which has reacted with a nucleophile and a base in the same flask, thus affording a highly functionalized chiral alcohol. The successful results are summarized in Table 4. When NaH and MeOH or allyl alcohol were added into the reaction mixture after formation of the acetal, a methoxy or allyloxy alcohol were obtained in good yield with excellent enantioselectivity (Table 4, entries 1 and 2). While azido alcohol was obtained with excellent enantioselectivity by the addition of NaN_3 and K_2CO_3 (Table 4, entry 3), cyanation also proceeded to afford cyano alcohol with excellent enantioselectivity by the reaction of NaCN and K_2CO_3 (Table 4, entry 4). When $LiAlH_4$ was used as a nucleophile, the chiral alcohol was obtained with excellent enantioselectivity (Table 4, entry 5). This reaction is the synthetic equivalent of an asymmetric cross-aldol reaction between acetaldehyde as an electrophile and propanal as a nucleophile—such a reaction is very challenging.

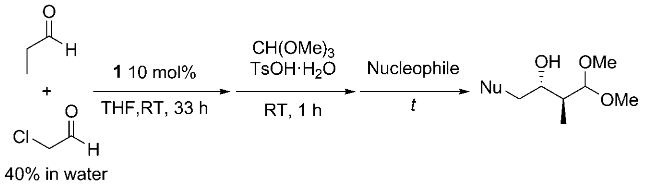
The absolute configuration of the products[18] is reasonably explained by the transition state shown in Scheme 2, which is similar to that proposed for the aldol reaction of ethyl glyoxylate catalyzed by the same diarylprolinol (**1**) catalyst.[16c] Chloroacetaldehyde is activated by the coordination to the proton of the hydroxy group of the catalyst through hydrogen bonding.

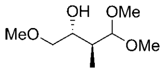
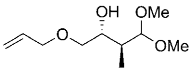
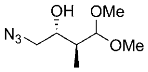
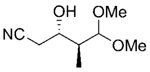
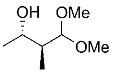


Scheme 2. The transition state of intermediate enamine and chloroacetaldehyde. Ar = 3,5-bis(trifluoromethyl)phenyl.

In conclusion, we have developed a one-pot synthesis of α-substituted β,γ-epoxy aldehyde derivatives through uninterrupted sequential reactions that include either an asymmetric, direct aldol reaction of chloroacetaldehyde catalyzed by diarylprolinol **1**, acetalization, and epoxide formation, or an asymmetric aldol reaction, Wittig reaction, and epoxide formation. There are several noteworthy features in this process. 1) Synthetically useful chiral epoxides with an acetal moiety or with an α,β-unsaturated ester moiety have been prepared in a single flask with good *anti* selectivity and excellent enantioselectivity. 2) Commercially available aqueous chloroacetaldehyde has been used directly without removal of water prior to use. 3) α,α-Unsubstituted chiral epoxide, a useful synthetic intermediate, has been prepared with excellent enantioselectivity through the formation of a carbon–carbon bond. 4) A three-component coupling reaction led to the formation of a multifunctional alcohol with excellent enantioselectivity (Table 4). 5) This is one of the rare reactions in which a diarylprolinol is successfully used as an efficient catalyst,[16,19] while its silyl ether is widely used as

Table 4: One-pot, three-component coupling reaction through aldol/acetalization/epoxide formation/nucleophilic opening of epoxide.[a]



Entry	Reagents	Product	t [h][b]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	MeOH, NaH		6	66	4.0:1	96
2	allylalcohol, NaH		3	76	3.9:1	95
3	NaN_3, K_2CO_3		20	65	3.5:1	95
4	NaCN, K_2CO_3		16	63	4.6:1	95
5	$LiAlH_4$		4	68	4.3:1	95

[a] Unless otherwise shown, the catalyst **1** was employed in 10 mol% (see the Supporting Information for experimental details). [b] Reaction time of nucleophile. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] See the Supporting Information.

an effective organocatalyst.[17] Because the generated product possesses several functional groups, this method offers an efficient route for the preparation of chiral α-substituted β,γ-epoxy aldehydes with excellent diastereoselectivity and enantioselectivity.

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Keywords: aldol reaction · asymmetric synthesis · diarylprolinol derivatives · epoxidation · organocatalysis

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[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**.
[2] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[3] W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801.
[4] R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345.
[5] Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488.
[6] W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286, and references therein.
[7] Selected references: a) H. Kakei, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 8962; b) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; c) C. A. Lattanzi, *Chem. Commun.* **2009**, 1452; d) O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227.
[8] a) S. Arai, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 2145; b) P. Bakó, K. Vizárdi, Z. Bajorm, L. Tõke, *Chem. Commun.* **1998**, 1193; c) V. K. Aggarwal, J. P. H. Charmant, D. Fuentes, J. N. Harvey, G. Hynd, D. Ohara, W. Picoul, C. Smith, J.-L. Vasse, C. L. Winn, *J. Am. Chem. Soc.* **2006**, *128*, 2105.
[9] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[10] For selected reviews on organocatalysis, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Groger), Wiley-VCH, Weinheim, **2005**; c) Y. Hayashi, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 464; d) B. List, *Chem. Commun.* **2006**, 819; e) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001; f) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; g) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; h) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; i) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; j) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477; k) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; l) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; m) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; n) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.
[11] A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 2204; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
[12] For a Lewis acid catalyzed aldol reaction of chloroacetaldehyde in the presence of water, see: S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, *59*, 3590.
[13] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958; b) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527; c) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103; d) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Commun.* **2007**, 957; e) S. Aratake, T. Itoh, T. Okano, T. Usui, M. Shoji, Y. Hayashi, *Chem. Commun.* **2007**, 2524; f) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246.
[14] For selected reviews on organocatalyst-mediated reactions in the presence of water, see: a) J. Paradowska, M. Stodulski, J. Mlynarski, *Angew. Chem.* **2009**, *121*, 4352; *Angew. Chem. Int. Ed.* **2009**, *48*, 4288; b) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33; c) M. Raj, V. K. Singh, *Chem. Commun.* **2009**, 6687; d) N. Mase, C. F. Barbas III, *Org. Biomol. Chem.* **2010**, *8*, 4043.
[15] M. Markert, U. Scheffler, R. Mahrwald, *J. Am. Chem. Soc.* **2009**, *131*, 16642.
[16] a) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082; b) Y. Hayashi, S. Samanta, T. Itoh, H. Ishikawa, *Org. Lett.* **2008**, *10*, 5581; c) T. Urushima, Y. Yasui, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 2966.
[17] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; c) M. Marigo, D. Fielenbach, A. Braunton, A. Kjasgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794. Review: d) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; e) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.
[18] For the determination of the absolute configuration, see the Supporting Information.
[19] a) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579; b) A. Russo, A. Lattanzi, *Org. Biomol. Chem.* **2010**, *8*, 2633.