Tetrahedron: *Asymmetry* 19 (2008) 2088–2091

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of a new organocatalyst for Michael reactions

David Díez *, Ana B. Antón, Pilar García, Narciso M. Garrido, Isidro S. Marcos, Pilar Basabe, Julio G. Urones

Dpto. de Química Orgánica, Facultad de Ciencias Quimicas, Universidad de Salamanca, 37008 Salamanca, Spain

ARTICLE INFO

Article history:
Received 29 July 2008
Accepted 22 August 2008

ABSTRACT

A new, easily tunable organocatalyst has been synthesized and applied in the Michael reaction of cyclohexanones to nitrostyrenes.

1. Introduction

In the last few years large developments in organocatalysis were seen.[1] Among the reactions that have caused more interest using an organic catalyst is the Michael addition.[2] One of these reactions is the addition of carbonyl compounds to nitrostyrenes. Apart from proline,[3] Ley's tetrazole analogue **1**[4] (Fig. 1) has been used in the addition of cyclohexanone to *trans*-β-nitrostyrene. Similarly, some diamines have been found to work as catalysts, such as the one described by Barbas, **2**,[5] or that reported by Alexakis **3**.[6] Wang used catalyst **4**,[7] while our group developed an analogue of it.[8] Recently, catalysts **5** and **6** have been used by Cheng[9] in this reaction and Kotsuki et al. have developed catalyst **7**.[10] More recently Chandrasekhar et al. have obtained catalyst **8**,[11] Xiao et al. have developed several catalysts containing a thiourea group as **9**,[12] while Xu et al. have combined the pyrrolidine with a thioimidazole **10**.[13]

Recently, we have been involved in the synthesis of chiral pyrroles[14] and organocatalysts.[8] With the aim of obtaining more versatile organocatalysts that could be easily tuneable, we decided to obtain catalyst **15** (Scheme 1). The diol intermediate **13** can be manipulated into catalyst **15**, but can also be transformed into many other derivatives (by changing the *O*-substituents) that could serve as organocatalysts, since the primary and secondary hydroxyl groups can be differentiated.

2. Results and discussion

The synthesis of catalyst **15** required four steps from the commercially available material, aldehyde **11**. The synthesis of **15**

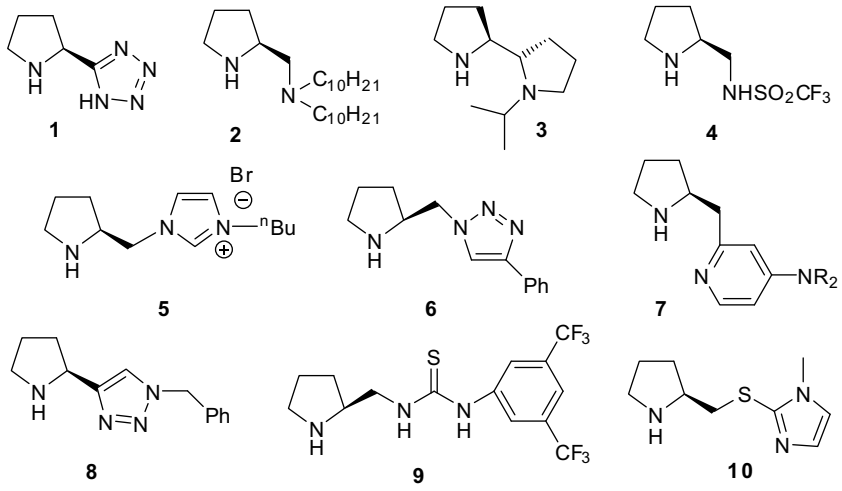
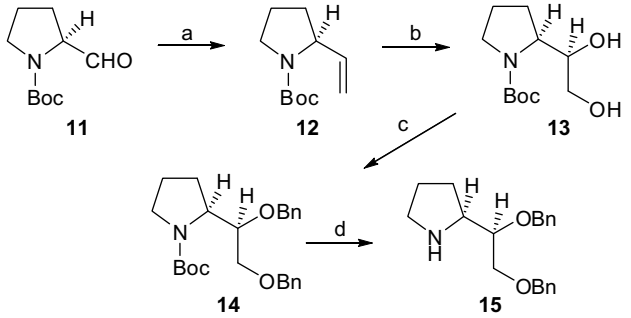


Figure 1.

* Corresponding author. Tel.: +34 923 294474; fax: +34 923 294574.
E-mail address: ddm@usal.es (D. Díez).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.08.025

starts when **11** is submitted to a Wittig reaction to obtain the known olefin **12**.[15] This olefin was submitted to a Sharpless asymmetric dihydroxylation[16] to give diol **13**, which in turn was benzylated under the usual conditions[17] to give the protected pyrrolidine **14**, in excellent yield. When **14** was deprotected,[18] it gave the desired pyrrolidine **15** (Scheme 1).



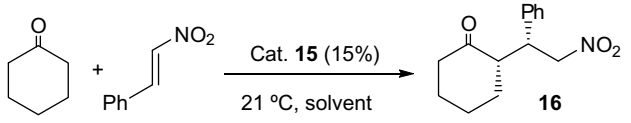
Scheme 1. Reagents and conditions: (a) Ref. 15; (b) *tert*-BuOH/H_2O 2:1, AD-mixβ, $MeSO_2NH_2$, 92%; (c) BnCl, NaH, THF, TBAI, 95% **14**; (d) HCl, 6M, 70%.

With compound **15** in hand, we started to investigate, in detail, the influence of the solvent in the 'Michael addition' of cyclohexanone to *trans*-β-nitrostyrene. As can be seen in Table 1, the reaction yields varied significantly in the solvents tested. It can be seen that toluene is the solvent of choice, while the yields in the more polar solvents, such as DMSO and ^{i}PrOH, are very low or zero; the yields are also very low in solvents such as DCM and chloroform. The THF solvent gave no reaction. Toluene was the solvent of choice as it gives the best yield with very good diastereo- and enantioselectivity (Table 1, entry 9). We then decided to test the addition of an acid in order to increase the enantiomeric excess and reaction rate.

As can be seen, the optimal reaction conditions are in toluene or hexane and using benzoic acid as an additive. When the reaction was carried out at 0 °C (Table 1, entry 16), a slight increase in enantiomeric excess occurred, but led to a dramatic reduction in the reaction rate, so we decided that the best conditions are as follows (Table 1, entry 13): to a suspension of catalyst **15** and cyclohexanone in toluene, are added *trans*-β-nitrostyrene and benzoic acid (15%), and stirred at 21 °C for 12 h.

With the optimal conditions in hand, we probed the scope of the reaction with a variety of nitroolefins and ketones obtaining yields that vary from no reaction to high yields showing in all cases good diastereo- and enantioselectivity (Table 2).

Table 1
Solvent and acid effects on the asymmetric Michael addition of cyclohexanone to *trans*-β-nitrostyrene



Entry[a]	Solv.	Additive	*t* (h)	Yield[b] (%)	dr[c] (%)	ee[d] (%)
1	DMSO		21	11	>95	68
2	^{i}PrOH		88	—	—	—
3	^{i}PrOH	TsOH	88	28	>95	94
4	MeOH		88	—		
5	MeOH	TsOH	88	10	94	92
6	THF		88	—	—	—
7	CH_2Cl_2		21	25	>95	35
8	$CHCl_3$		21	33	94	27
9	Toluene		88	77	93	80
10	Toluene	TsOH	88	—		
11	Toluene	CF_3COOH	88	—		
12	Toluene	CSA	88	—		
13	Toluene	Benzoic acid	12	88	94	89
14	Toluene	2,4-Dinitro Benzoic acid	140	83	94	86
15	Toluene	Acetic acid	88	86	94	65
16	Toluene[e]	Benzoic acid	48	87	94	91
17	Hexane	Benzoic acid	48	97	94	87

[a] For experimental conditions, see the Section 4.
[b] Yield of the isolated product, the relative and absolute configurations of **16** were determined by comparison with ^{1}H NMR data and specific rotations; see Ref. 20.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Chiralpak AD).
[e] Reaction carried out at 0 °C.

3. Conclusions

In conclusion, a new organocatalyst for the Michael addition of cyclohexanones to β-nitrostyrenes has been obtained. This catalyst works better in very nonpolar solvents such as toluene and hexane that differentiate it from the previous ones (**1**–**10**) that work better in more polar solvents. The catalyst is easily tunable and many analogues can be obtained in a straightforward manner. The other enantiomer can be synthesised by changing the starting material to its commercial enantiomer.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a AVATAR 370 FT-IR Thermo Nicolet spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (*J*) are given in hertz. MS and HRMS were performed in a QSTAR XL spectrometer using electrospray technique. Optical rotations were determined in a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, while dichloromethane was distilled under argon from CaH_2.

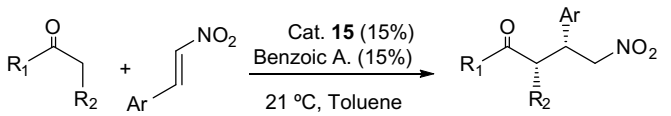
4.1.1. (2*S*)-*N*-*tert*-Butoxycarbonyl-2-[(1′*R*)-1′,2′-dihydroxyethyl]-pyrrolidine, 13

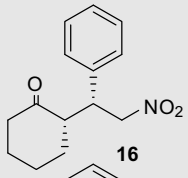
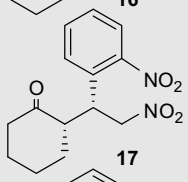
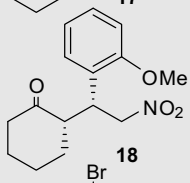
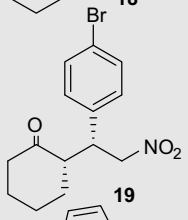
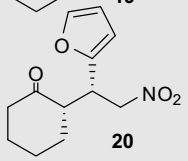
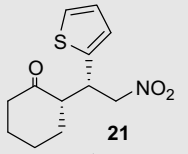
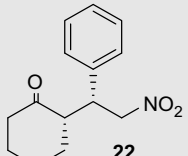
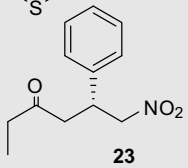
To a solution of *tert*-BuOH (28 mL) and water (14 mL) were added AD mix-β (9.72 g) and methanesulfonamide (593 mg, 6.24 mmol), then stirred magnetically at 21 °C for 20 min. The ensuing mixture was cooled to 0 °C (ice-water bath), treated with olefin **12** (1.23 g, 6.24 mmol) and then stirred vigorously for 72 h. The reaction mixture was quenched, at 0 °C, by addition of Na_2SO_3 (10.1 g), warmed to 21 °C, stirred at this temperature for 0.5 h and then extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (hexane/EtOAc 6:4) to yield 1.32 g (5.7 mmol, 92%) of **13**. $[\alpha]_D^{20} = -42.7$ (*c* 1.1, $CHCl_3$), IR (film) ν (cm^{-1}): 3600–3200, 2975, 2883, 1666, 1478, 1453, 1405, 1367, 1168, 1112, 1066; ^{1}H NMR ($CDCl_3$, 200 MHz, rotamers) δ: 4.08 (2H, m,), 3.84 (1H, m), 3.57 (3H, m), 3.30–3.15 (3H m), 2.05–1.60 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 157.2 (CO), 81.0 (C), 73.1 (CH), 64.4 (CH_2), 58.8 (CH), 47.5 (CH_2), 28.8 ($3CH_3$), 27.9 (CH_2), 23.5 (CH_2). HRMS (ESI): calcd for $C_{11}H_{21}NO_4$, $[M+Na]^+$: 254.1368, found: 254.1376.

4.1.2. (2*S*)-*N*-*tert*-Butoxycarbonyl-2-[(1′*R*)-1′,2′-dibenzyloxyethyl]-pyrrolidine, 14

A suspension of NaH (69 mg, 2.85 mmol) in THF (1 mL) was stirred in an argon atmosphere. Then, a mixture of **13** (300 mg,

Table 2
Substrate scope of the Michael reaction



Entry[a]	Ar	t (h)	Yield[b] (%)	dr[c] (%)	ee[d] (%)
1	 **16**	12	92	94	89
2	 **17**	12	86	88	83
3	 **18**	12	93	94	95
4	 **19**	12	91	90	89
5	 **20**	12	86	79	91
6	 **21**	12	77	80	91
7	 **22**	48	75	82	96
8	 **23** : **24** (3 : 1)	48	84	– / 92	78 / 78

[a] For experimental conditions, see the Section 4.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by chiral high-performance liquid chromatography (HPLC) analysis (Daicel Chiralpak AD).

1.30 mmol), *tert*-butylammonium iodide (97 mg, 0.26 mmol) and BnCl (0.61 mL, 5.19 mmol) was added to the previous solution by canula and left to stir at room temperature for 12 h. The reaction was quenched by the addition of H_2O and then extracted with EtOAc (3 × 70 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. After filtering and evaporating the solvents, the crude mixture was purified by flash chromatography (hexane/EtOAc, 9:1–7:3) to obtain 536 mg (1.2 mmol, 95%) of **14**. $[\alpha]_D^{20} = -70.1$ (*c* 0.72, $CHCl_3$). IR (film) ν (cm^{-1}): 2974, 2930, 2873, 1692, 1454, 1394, 1365, 1168, 1101. ^{1}H NMR ($CDCl_3$, 200 MHz, rotamers) δ: 7.34–7.30 (10H, m), 4.69 and 4.60 (1H each, 2d, J = 11.8, $-CH_2$Ph), 4.30 (1H, m), 4.05 (1H, m), 3.90 (1H, m), 3.58 (2H, m), 3.30 (1H, m), 2.18–1.54 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 154.8 (CO), 138.6 (C), 128.6 (4CH), 128.0 (4CH), 127.7 (2CH), 79.6 (C), 74.0 (CH_2), 73.5 (CH_2), 71.9 (CH_2), 59.0 (CH), 47.3 (CH_2), 28.8 ($3CH_3$), 26.4 (CH_2), 25.7 (CH_2). HRMS (ESI): calcd for $C_{25}H_{33}NO_4$, $[M+Na]^+$: 434.2302, found: 434.2314.

4.1.3. (2*S*)-2-[(1′*R*)-1′,2′-dibenzyloxy-ethyl]-pyrrolidine 15

A solution of **14** in EtOH (410 mg, 1 mmol in 10 mL) was stirred at 0 °C. Then HCl (6M, 1.34 mL) was added over the mixture warmed to 21 °C. The solvent was evaporated and the reaction mixture dissolved in CH_2Cl_2. The resulting mixture was washed with $NaHCO_3$ (concd) and extracted with CH_2Cl_2 (3 times, 30 mL) and dried over anhydrous Na_2SO_4. After filtering, the solvent was evaporated under vacuum to afford after column chromatography (hexane/EtOAc 9:1) 218 mg (0.70 mmol, 70%) of **15**. $[\alpha]_D^{20} = -34.6$ (*c* 0.6, $CHCl_3$). IR (film) ν (cm^{-1}): 3600–3400, 3029, 2922, 2875, 2749, 1453, 1094, 1028, 739. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7,26 (10H, m, Ph), 4.77 (1H, d, J = 5.8, CH_2Ph), 4.60 (1H, d, J = 5.8, CH_2Ph), 4.58 (2H, s, CH_2Bn), 3.67 (2H, m, CH_2O), 3.64 (1H, m, CHO), 3.26 (1H, ddd, J = 6.6, 3.8 and 3.0, CHN), 2.96 (1H, m, H_A-5), 2.86 (1H, m, H_B-5), 1.85 (1H, m, H_A-3), 1.72 (2H, m, CH_2-4), 1.65 (1H, m, H_B-3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.7 (C), 138.2 (C), 128.4 (2CH), 128.3 (2CH), 127.8 (2CH), 127.6 (2CH), 127.5 (2CH), 80.3 (CH), 73.4 (OCH_2Bn), 72.6 (OCH_2Bn), 71.2 (OCH_2), 59.9 (NCH), 46.7 (NCH_2), 27.3 (CH_2-3), 25.5 (CH_2-4). HRMS (ESI): calcd for $C_{20}H_{26}NO_2$, $[M+H]^+$: 312.1958, found: 312.1956.

4.1.4. Typical procedure for the Michael addition reaction

To a mixture of catalyst **15** (8.5 mg, 0.027 mmol, 15%), benzoic acid (3.3 mg, 0.027 mmol, 15%) and *trans*-β-nitrostyrene (27 mg, 0.18 mmol) were added 0.8 mL of toluene and 0.34 mL (3.62 mmol) of cyclohexanone. The resulting mixture was allowed to stir at 21 °C for 12 h, whereupon the reaction was quenched with saturated aqueous ammonium chloride (2 mL), and the aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by flash column chromatography using ethylacetate/hexane.

Compounds **16**[19], **17**[4a], **18**[10], **19**[20], **20**[4a], **21**[10], **22**[7], **23**[6d], and **24**[21] are known.

Acknowledgements

Financial support for this work came from the E.F.S., Spanish MEC (CTQ2006-08296) and Junta de Castilla y León (Spain) (SA007A06). The authors also thank Dr. A. M. Lithgow for the NMR spectra and Dr. César Raposo for the mass spectra. A.B.A. is grateful for a doctoral fellowship to the University of Salamanca.

References

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *116*, 5138; (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8;

(c) *Asymmetric Organocatalysis From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877; (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (c) Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491; (d) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454; (e) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170; (f) Mosseé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559; (g) Lattanzi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 837; (h) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; xu, H.; Cheng, J-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093.
3. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
4. (a) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84; (b) Tori, H.; Nakadai, M.; Ishikara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983; (c) Franckevicius, V.; Knudsen, K. R.; Ladlow, M.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, 889; (d) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, 4287; (e) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831; (f) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66.
5. (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, *9*, 1509; (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527; (c) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.
6. (a) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611; (b) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559; (c) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901; (d) Andrey, O.; Alexakis, A.; Romassini, A.; Bernadinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.
7. Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369.
8. Díez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; García, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2007**, *63*, 740.
9. (a) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J.-P. *J. Org. Chem.* **2005**, *44*, 4212; (b) Luo, S.; Xu, H.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093; See too: (c) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717.
10. Ishi, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.
11. Chandrasekhar, S.; Tiwari, B.; Parida, B. B.; Reddy, Ch. R. *Tetrahedron: Asymmetry* **2008**, *19*, 495–499.
12. Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21.
13. (a) Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.; Wang, Y.-F.; Zhang, S.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2008**, 1049; (b) Xu, D.-Q.; Yue, H.-D.; Luo, S.-P.; Xia, A.-B.; Zhang, S.; Xu, Z.-Y. *Org. Biomol. Chem.* **2008**, *6*, 2054.
14. Díez, D.; Antón, A. B.; García, P.; Nuñez, M. G.; Garrido, N. M.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2006**, *17*, 2260.
15. (a) Molander, G. A.; Romero, J. A. C. *Tetrahedron* **2005**, *61*, 2631; (b) Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240.
16. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
17. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *39*, 3535.
18. Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1999.
19. Juaristi, E.; Beck, A.; Hansen, J.; Matt, T.; Mukhopadhay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.
20. Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *11*, 1829.
21. Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597.