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O-TMS-α,α-diphenyl-(*S*)-prolinol Modified with an Ionic Liquid Moiety: A Recoverable Organocatalyst for the Asymmetric Michael Reaction between α,β-Enals and Dialkyl Malonates

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O-TMS-α,α-diphenyl-(*S*)-prolinol derivative bearing an ionic liquid fragment was synthesized for the first time and proven to be an efficient catalyst for the asymmetric Michael reaction of aromatic α,β-unsaturated aldehydes with dialkyl malonates. The prepared catalyst can be recovered four times and used in the same reaction without a decrease in activity or a decrease in the enantioselectivity of the reaction.

Introduction

The organocatalytic asymmetric 1,4-conjugate addition of nucleophilic reagents to electron-deficient alkenes is one of the most powerful tools for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds,[1] which is widely applied for the synthesis of biologically active compounds and natural products.[2] The reaction is efficiently catalyzed by a number of organocatalysts in particular by (*S*)-proline,[3] imidazolidine,[4] and thiourea[5] derivatives, and by some other chiral compounds.[1] α,α-Diarylprolinol silyl ethers are among the most active and enantioselective catalysts.[6] Yet, these compounds synthesized from proline in several synthetic steps[7,8] are usually lost during the isolation of Michael adducts like a majority of other organocatalysts. Therefore, the development of immobilized versions of α,α-diarylprolinol ethers is an important issue both from economical and from green chemistry standpoints.

Recoverable organocatalysts bearing an (*S*)-proline unit at the active site have been well documented and reviewed.[9] There are successful examples of supported prolinol-type catalysts with a free OH group mainly applied for α,β-enone reductions.[10] Though only a few immobilized catalysts containing prolinol silyl ether moieties to include compounds modified with perfluoroalkyl,[11a] dendritic,[11b] or polymeric[11c] groups have been reported so far. These catalysts have certain drawbacks. The recovery of a fluorinated catalyst could only be achieved by means of expensive fluorinated silica gel.[11a] A weak point of a dendritic catalyst is its sophisticated synthesis,[11b] and a polymer-supported catalyst becomes deactivated after the first regeneration.[11c]

In this paper we report a synthesis of the first representative of a new family of recoverable prolinol-type organocatalysts modified with ionic liquid (IL) moieties. IL-supported α-amino acid derivatives with unmodified carboxylic groups were applied earlier as recoverable organocatalysts for asymmetric aldol reactions.[12] Yet, to the best of our knowledge, this approach has never been used to regenerate compounds with a prolinol unit.

Results and Discussion

α,α-Diphenylprolinol derivatives **4a**–**c** with an imidazolium cation and bromide or hexafluorophosphate anions were synthesized by a sequence of reactions, which includes the esterification of (3*R*,5*S*)-1-benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-ol (**1**)[13] with 5-bromopentanoic acid in the presence of DCC/DMAP, alkylation of 1-methylimidazole with bromoester **2**, catalytic hydrogenation of imidazolium salt **3**, followed by the transformation of bromide **4a** into hexafluorophosphate **4b** or its O-TMS derivative **4c** by anion metathesis and silylation reactions (Scheme 1). Total yields of compounds **4a**–**c** were 68–77%.

Prepared compounds **4a**–**c** were examined in a reaction of α,β-unsaturated aldehydes with dialkyl malonates, which is used for synthesizing chiral biologically active compounds.[14] It should be mentioned that the immobilized *O*-TMS-α,α-diphenylprolinol derivatives were only applied as catalysts for epoxidation reactions[11c] and for 1,4-addition reactions between aldehydes and nitroalkenes[11a–11c] pro-

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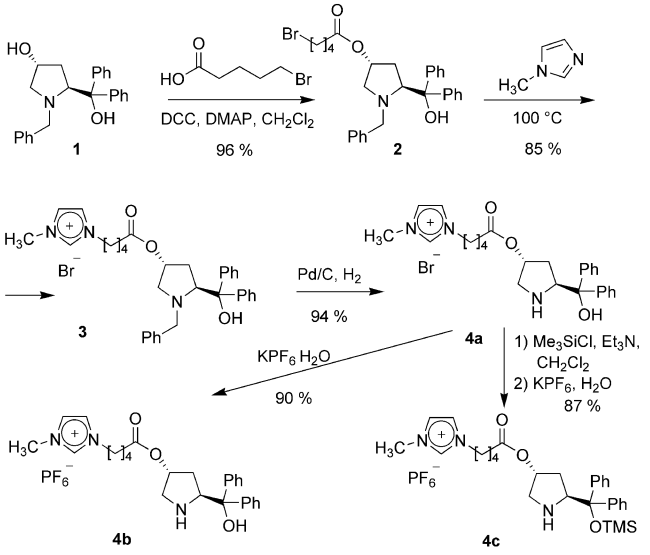
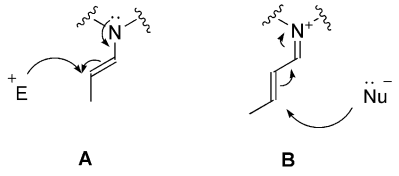


Scheme 1. Synthesis of α,α-diphenylprolinol derivatives **4a**–**c** bearing an ionic liquid fragment.

ceeding via the formation of enamine-type intermediates comprised of a catalyst and an aldehyde donor[1c,15] (Scheme 2, **A**).



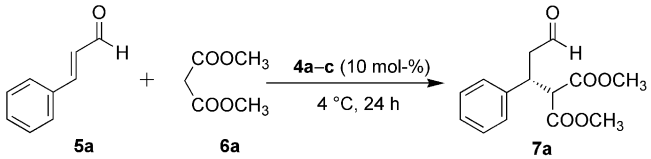
Scheme 2. Enamine **A** and iminium **B** intermediates in organocatalytic reactions of carbonyl compounds.

The immobilized catalysts have never been employed in reactions that involve iminium ion **B** formation from a chiral catalyst and an aldehyde acceptor[15] – the reaction class where unimmobilized prolinol ether organocatalysts exhibit high efficacy.[6a,14,15d]

First of all, we examined compounds **4a**–**c** in a reaction of *trans*-cinnamaldehyde (**5a**) with dimethyl malonate (**6a**) where unimmobilized α,α-diaryl-(*S*)-prolinol exhibited good activity and enantioselectivity.[14] The reactions were carried out in the presence of 1–10 mol-% of catalyst at 4 °C for 24 h in 96% EtOH. It was found that in the presence of compounds **4a** and **4b** with free hydroxy groups the yield of adduct **7a** did not exceed 26% (Table 1, Entries 1 and 2, respectively), whereas in the presence of **4c**, 93% yield was attained along with 96%*ee* (Table 1, Entry 3). Remarkably, the unimmobilized analogue of compound **4c** gave comparable results only after a noticeably longer reaction time (96 h).[14] By decreasing the loading of catalyst **4c** to 1 mol-%, a lower conversion of **6a** was observed (47%; Table 1, Entry 4).

We examined next a reaction between compounds **5a** and **6a** in water and under neat conditions in the presence of catalyst **4c**, which exhibited higher efficacy in 96% EtOH.

Table 1. Catalysts screening in the reaction between dimethyl malonate **6a** and *trans*-cinnamaldehyde (**5a**).[a]



Entry	Catalyst	Solvent	Conversion[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	**4a**	EtOH	26	–	–
2	**4b**	EtOH	15	–	–
3	**4c**	EtOH	>99	93 (85[e], 90[f])	96 (94[e], 96[f])
4[g]	**4c**	EtOH	47	–	–
5	**4c**	H_2O (50 equiv.)	96	92	92
6	**4c**	neat	80	73	92

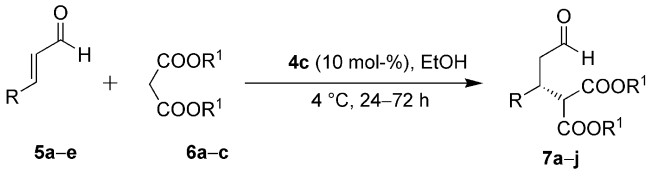
[a] Unless otherwise specified, all reactions were carried out with *trans*-cinnamaldehyde (**5a**; 1 mmol), dimethyl malonate (**6a**; 0.5 mmol), and the solvent (0.5 mL) in the presence of the catalyst (10 mol-%) at 4 °C for 24 h. [b] The conversion of **6a** into **7a** was estimated by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Determined by chiral HPLC analysis of the isolated product. [e] Yield according to ref.[14] [f] Yield according to ref.[16] [g] The reaction was carried out in the presence of 1 mol-% of **4c**.

Product **7a** was obtained in aqueous media in 92% yield, but the enantioselectivity appeared to be slightly lower (92%*ee*; Table 1, Entry 5). In contrast to compound **4c**, α,α-diphenyl(or hexyl)-(*S*)-prolinol silyl ethers without IL groups catalyzed this reaction in water only in the presence of acidic additives,[8,16] which indicates an important role of the IL moiety. Under neat conditions, product **7a** was prepared in as low as 73% yield after 24 h, whereas the enantioselectivity remained at the same level (92%*ee*; Table 1, Entry 6).

The most efficient procedure (**4c**: 10 mol-%, 96% EtOH, 4 °C) was applied in reactions of *trans*-cinnamaldehyde (**5a**) and its derivatives **5b**–**e** bearing donor (i.e., **5d**) or acceptor (i.e., **5b**,**c**,**e**) groups in the aromatic ring with dimethyl, diethyl, and dibenzyl malonates (i.e., **6a**,**b**,**c**, respectively; Table 2). In most cases, corresponding adducts **7a**–**j** were produced in yields (up to 98%) higher than those produced in the presence of the known catalysts[8,14,16] and with comparable *ee* values (up to 96%*ee*). Furthermore, catalyst **4c** increased the yield (from 72 to 94%) and enantiomeric excess (from 86 to 96%*ee*) of fluorinated adduct **7j**, which is the key intermediate for the synthesis of the prospective antidepressant (–)-paroxetine, as compared with the reported data[14] (Table 2, Entry 10).

The recoverability of catalyst **4c** was studied in a reaction of **5a** with **6a** (Table 3). Upon completion of the reaction, EtOH was evaporated, the products were extracted with Et_2O, and fresh portions of reagents **5a**, **6a**, and ethanol were added to the residue. The catalyst could be recovered three times and used in the same reaction without any decrease in its activity or decrease in the enantioselectivity of the reaction. Yet, upon the fourth regeneration (fifth cycle), the conversion after 24 h dropped down to 70%, and at the sixth cycle it was necessary to extend the reaction time to

Table 2. Enantioselective Michael reactions between dialkyl malonates **6a**–**c** and substituted *trans*-cinnamaldehydes **5a**–**e** catalyzed by **4c**.[a]



5a–e 6a–c 7a–j

Entry	R	R^1	Time [d]	Product, yield[b] [%]	*ee*[c] [%]
1	Ph	Me	1	**7a**, 93 (85[e], 90[f])	96 (94[e], 96[f])
2	Ph	Et	2	**7b**, 98 (42[e])	95 (89[e])
3	Ph	Bn	3	**7c**, 81 (80[e], 93[f], 77[g])	92 (91[e], 95[f], 96[g])
4	4-ClC_6H_4	Me	2	**7d**, 97	91
5	4-ClC_6H_4	Bn	3	**7e**, 95 (85[e])	88 (86[e])
6[d]	4-$O_2NC_6H_4$	Bn	3	**7f**, 97	82
7	4-$MeOC_6H_4$	Me	2	**7g**, 97 (73[e], 81[f])	76 (90[e], 91[f])
8	4-$MeOC_6H_4$	Bn	3	**7h**, 98 (93[e], 88[f], 74[g])	89 (92[e], 96[f], 99[g])
9	4-FC_6H_4	Me	2	**7i**, 95 (78[f])	92 (97[f])
10	4-FC_6H_4	Bn	3	**7j**, 94 (72[e])	96 (86[e])

[a] Unless otherwise specified, reactions were carried out by using substituted *trans*-cinnamaldehyde **5** (0.664 mmol), dialkyl malonate **6** (0.332 mmol), and EtOH (0.3 mL) in the presence of catalyst **4c** (10 mol-%) at 4 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis of the isolated product. [d] The reaction was carried out by using 0.6 mL of EtOH. [e] Yield according to ref.[14] [f] Yield according to ref.[16] [g] Yield according to ref.[8]

96 h to reach the same conversion as that obtained in the fifth cycle. Despite the deactivation of the catalyst, the enantioselectivity of the reaction remained the same or ever slightly increased (up to 98%*ee*). Possibly, the catalyst deactivation could be explained by its leaching into the organic solvent (Et_2O) or by its transformation into catalytically inactive or less-active compounds (e.g., into compound **4b** through hydrolysis of the TMS group[11c]). We suppose that optimization of the catalyst structure (substituents in the pyrrolidine ring, IL cation and anion) would allow these undesirable processes to be suppressed, which would extend the catalytic system operation period.

Table 3. Recycling of catalyst **4c** in the asymmetric Michael reaction between dimethyl malonate (**6a**) and *trans*-cinnamaldehyde (**5a**).[a]

Cycle	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	24	>99	95
2	24	>99	94
3	24	>99	94
4	24	96	95
5	24	70	98
6	96	70	98

[a] Unless otherwise specified, all reactions were carried out with *trans*-cinnamaldehyde (**5a**; 0.332 mmol), dimethyl malonate (**6a**; 0.166 mmol), and EtOH (0.15 mL) at 4 °C in the presence of **4c** (10 mol-%). After the indicated time catalyst **4c** was separated from the products by the addition of ether (2 × 1 mL) and reused. [b] The conversion of **6a** into **7a** was estimated by ^1H NMR spectroscopy. [c] Determined by chiral HPLC analysis of the isolated product.

Conclusions

In summary, we have proposed a new promising approach to the development of recoverable organocatalysts for asymmetric Michael reactions, involving iminium ion formation, by modifying α,α-diarylprolinol silyl ethers with ionic liquid moieties. In the presence of synthesized catalyst **4c** the reaction of dialkyl malonates **6a**–**c** with *trans*-cinnamaldehyde (**5a**) and its derivatives **5b**–**e** proceeded under mild conditions to afford the respective adducts in high yields (up to 98%) and high enantioselectivities (up to 98%*ee*). Unlike the known prolinol-type catalysts, compound **4c** could be used four times without any decrease in its activity or decrease in the enantioselectivity of the reaction.

Experimental Section

General Procedure for the Michael Reactions: A mixture of catalyst **4a**–**c** (0.03 mmol, 10 mol-%), α,β-unsaturated aldehyde **5a**–**e**[17] (0.66 mmol, 2 equiv.), dialkyl malonate **6a**–**c** (0.33 mmol, 1 equiv.), and 96% EtOH (0.3 mL) was stirred at 4 °C for the indicated time (Table 2). The solvent was evaporated under reduced pressure; the products were extracted with Et_2O (2 × 1 mL). The combined extract was evaporated under reduced pressure. Compounds **7** were isolated by column chromatography (TLC monitoring by using 2,4-diphenylhydrazine for visualization). If appropriate, the catalyst was reused.

Catalyst Recycling: A solution of compounds **5a** (88 mg, 0.66 mmol) and **6a** (44 mg, 0.33 mmol) in 96% EtOH (0.3 mL) was added to the catalyst, which remained after the extraction of product **7a**, and the reaction was carried out as described above.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and analytical data of compounds **1**–**7**.

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[1] a) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; b) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; e) B. R. Buckley, *Annu. Rep. Prog. Chem. Sect. B* **2007**, *103*, 90–106.

[2] a) R. M. Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; b) Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu, J. Zhou, *Org. Lett.* **2009**, *11*, 1999–2002; c) Z.-H. Ming, Sh.-Zh. Xu, L. Zhou, M.-W. Ding, J.-Y. Yang, Sh. Yang, W.-J. Xiao, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3938–3940; d) Y. Nishikawa, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 1987–1990.

[3] a) S. Hanessian, S. Govindan, J. S. Warrier, *Chirality* **2005**, *17*, 540–543; b) L. Gua, G. Zhaoa, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632; c) D. Enders, Sh. Chow, *Eur. J. Org. Chem.* **2006**, 4578–4584; d) D.-Q. Xu, L.-P. Wang, Sh.-P. Luo, Y.-F. Wang, Sh. Zhang, Zh.-Y. Xu, *Eur. J. Org. Chem.* **2008**, 1049–1053.

[4] a) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897–3900; b) G. Szántó, P. Bombicz, A. Grün, I. Kádas, *Chirality* **2008**, *20*, 1120–1126.

[5] a) W.-M. Zhou, H. Liu, D.-M. Du, *Org. Lett.* **2008**, *10*, 2817–2820; b) K. L. Kimmel, M. T. Robak, J. A. Ellman, *J. Am. Chem. Soc.* **2009**, *131*, 8754–8755; c) F.-Zh. Peng, Zh.-H. Shao, B.-M. Fan, H. Song, G.-P. Li, H.-B. Zhang, *J. Org. Chem.* **2008**, *73*, 5202–5205; d) P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.* **2008**, *10*, 1389–1391; e) P. Li, Sh. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753–756.

[6] a) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948; b) S. Belot, A. Massaro, A. Tenti, A. Mordini, A. Alexakis, *Org. Lett.* **2008**, *10*, 4557–4560; c) Y. Hayashi, M. Toyoshima, H. Gotoh, H. Ishikawa, *Org. Lett.* **2009**, *11*, 45–48; d) B.-Ch. Hong, R. Y. Nimje, A. A. Sadani, J.-H. Liao, *Org. Lett.* **2008**, *10*, 2345–2348; e) Q. Zhu, Y. Lu, *Org. Lett.* **2008**, *10*, 4803–4806; f) G. Luo, Sh. Zhang, W. Duan, W. Wang, *Tetrahedron Lett.* **2009**, *50*, 2946–2948; g) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem. Int. Ed.* **2009**, *48*, 3699–3702; h) A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *15*, 1562–1565.

[7] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) R. M. de Figueiredo, R. Froehlich, M. Christmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 1450–1453.

[8] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.

[9] a) M. Gruttadauria, Fr. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688; b) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525–1533; c) R. Sebesta, I. Kmentova, S. Toma, *Green Chem.* **2008**, *10*, 484–496; d) K. Bica, P. Gaertner, *Eur. J. Org. Chem.* **2008**, 3235–3250; e) B. Ni, Q. Zhang, K. Dhungana, A. D. Headley, *Org. Lett.* **2009**, *11*, 1037–1040; f) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211–1214.

[10] a) S. Goushi, K. Funabiki, M. Ohta, K. Hatano, M. Matsui, *Tetrahedron* **2007**, *63*, 4061–4066; b) G. Wang, Ch. Zheng, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2074–2081; c) G.-Y. Wang, X.-T. Liu, G. Zhao, *Synlett* **2006**, *8*, 1150–1154; d) R. J. Kell, P. Hodge, P. Snedden, D. Watson, *Org. Biomol. Chem.* **2003**, *1*, 3238–3243; e) Z. Dalicsek, F. Pollreisz, A. Go1mo1ry, T. Soos, *Org. Lett.* **2005**, *7*, 3243–3246; f) Q. Chu, M. S. Yu, D. P. Curran, *Org. Lett.* **2008**, *10*, 749–752; g) M. Lombardo, M. Chiarucci, C. Trombini, *Chem. Eur. J.* **2008**, *14*, 11288–11291.

[11] a) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131–5134; b) Y. Li, X.-Y. Liu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2034–2039; c) M. C. Varela, S. M. Dixon, K. S. Lam, N. E. Schore, *Tetrahedron* **2008**, *64*, 10087–10090.

[12] a) D. E. Siyutkin, A. S. Kucherenko, M. I. Struchkova, S. G. Zlotin, *Tetrahedron Lett.* **2008**, *49*, 1212–1216; b) D. E. Siyutkin, A. S. Kucherenko, S. G. Zlotin, *Tetrahedron* **2009**, *65*, 1366–1372; c) W. Miao, T. H. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1711–1718; d) M. Lombardo, S. Easwar, F. Pasi, C. Trombinia, *Adv. Synth. Catal.* **2009**, *351*, 276–282; e) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xua, J.-P. Cheng, *Tetrahedron* **2007**, *63*, 1923–1930; f) Zh. Chen, Y. Li, H. Xie, Ch.-G. Hu, X. Dong, *Russ. J. Org. Chem.* **2008**, *44*, 1807–1810.

[13] G. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712–7713.

[14] S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309.

[15] a) P. Diner, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122–127; b) D. Seebach, U. Groselj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999–2034; c) J.-Q. Zhao, L.-H. Gan, *Eur. J. Org. Chem.* **2009**, 2661–2665; d) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.

[16] A. Ma, Sh. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075–3077.

[17] All *trans*-cinnamaldehydes were prepared according to the procedure: G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett.* **2003**, *5*, 777–780.

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