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DOI: 10.1002/adsc.201200338

# Chiral Primary Amine Tagged to Ionic Group as Reusable Organocatalyst for Asymmetric Michael Reactions of C-Nucleophiles with $\alpha$ , $\beta$ -Unsaturated Ketones

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Received: April 20, 2012; Revised: July 6, 2012; Published online: November 4, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200338.

**Abstract:** The first primary amine-derived organocatalyst modified with an ionic group for asymmetric Michael reactions of C-nucleophiles with  $\alpha$ , $\beta$ -unsaturated ketones was synthesized. In the presence of this catalyst and an acidic co-catalyst (AcOH), hydroxycoumarin and its sulfur-containing analogue reacted with benzylideneacetone derivatives or cyclohexenone to afford the corresponding Michael adducts in high yields (up to 97%) and with reasonable enantioselectivity (up to 80%). The catalyst could be

### Introduction

Asymmetric organocatalysis is a rapidly developing area of organic chemistry.<sup>[1]</sup> In the presence of lowmolecular organic catalysts, prochiral compounds can be converted to enantiomerically enriched products without using auxiliary chiral groups.<sup>[2]</sup> Moreover, organocatalysts are extremely attractive to pharmacology as they, unlike organometal catalysts, do not cause a contamination leading to the production of medica-tions with toxic metals.<sup>[3]</sup> However, in spite of evident attractiveness, organocatalysts have not been much used in the chemical or pharmaceutical industry so far. Modern organocatalysts based on imidazolidinones,<sup>[4]</sup> alkaloids,<sup>[5]</sup> amino acid derivatives,<sup>[6]</sup> other types of chiral compounds<sup>[7]</sup> are rather expensive. Normally, they are needed in significant amounts (10-20 mol%) which are lost during product isolation, therefore, the development of reusable versions of organocatalysts remains a challenge.<sup>[8]</sup>

Organocatalytic Michael reactions<sup>[9]</sup> along with corresponding aldol reactions<sup>[10]</sup> are extensively used for enantioselective formation of carbon-carbon bonds in organic compounds. Among them, additions of C-nueasily recovered and efficiently reused three times, afterwards, its activity and stereodifferentiating ability gradually declined. The analysis of recovered catalyst samples by ESI-MS allowed us to detect undesirable side reactions that poisoned the catalyst, and propose an approach for its reactivation.

**Keywords:** asymmetric Michael reaction; ESI-MS; hydroxycoumarin; organocatalysis; reusable organocatalysts;  $\alpha$ , $\beta$ -unsaturated ketones; warfarin

cleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds, involving an iminium ion formation step, allow the simple and efficient synthesis of a series of clinically useful medications or key intermediates for their preparation.<sup>[11]</sup> Recently, Hansen, Ni, Pericàs, Schore, Zeitler and our group independently synthesized immobilized forms of the most popular catalysts for these reactions,  $\alpha,\alpha$ -diarylprolinol silyl ethers, by tagging them to polymeric<sup>[12]</sup> or ionic groups.<sup>[13]</sup> Thus prepared catalysts **1** and **2** (Figure 1) could be easily recovered and reused in the same reaction up to 10 times<sup>[14]</sup> without a significant decrease of conversion or enantioselectivity values. In the presence of some



**Figure 1.** Modified organocatalysts of asymmetric Michael reactions between C-nucleophiles and  $\alpha,\beta$ -unsaturated aldehydes (PG=polymeric group, IG=ionic group).



**Figure 2.** Primary 1,2-diamine-derived organocatalysts modified with dendritic, fluorinated or ionic groups (DG=dendritic group, PS=polystyrene,  $R^F = n \cdot C_8 H_{17}$ ).

catalysts, the reaction can be carried out as a continuous flow process.<sup>[15]</sup>

However, bulky  $\alpha, \alpha$ -diarylprolinol-type organocatalysts, being rather efficient in reactions of C-nucleophiles with  $\alpha$ ,  $\beta$ -unsaturated aldehydes, appeared to be nearly inactive in the corresponding reactions involving  $\alpha,\beta$ -unsaturated ketones, presumably, because of special hindrances for iminium ion formation.<sup>[16]</sup> In this case, less special hindered primary amine derivatives, especially compounds bearing a properly located auxiliary H-donor, such as amino<sup>[17]</sup> or hydroxy groups<sup>[18]</sup> (bifunctional catalysis<sup>[19]</sup>), exhibit better catalvtic performance. However, recently reported recoverable catalysts of type 3 (Figure 2), modified with dendritic<sup>[20]</sup> or perfluoroalkyl<sup>[21]</sup> groups, the synthesis of which is rather complicated, have not been used in Michael additions of C-nucleophiles to  $\alpha,\beta$ -unsaturated ketones up to now. Protonated with sulfated polystyrene, the diamine 4 failed to catalyze asymmetric Michael reactions.<sup>[22]</sup>

We assumed that primary  $\beta$ -diamine derivatives **5**, bearing an ionic group remote from the catalytic site, would behave better in asymmetric reactions between C-nucleophiles and  $\alpha$ , $\beta$ -unsaturated ketones (Figure 2). It might be expected that the remote ionic moiety, on the one hand, would reduce solubility of catalyst **5** in organic solvents and facilitate its recovery and, on the other hand, would not significantly change the energy of the transition state and deteriorate the stereochemical outcome of reactions.

#### **Results and Discussion**

To verify this hypothesis, we synthesized 1(R),2(R)-diaminocyclohexane **6** and 1(S),2(S)-diaminodiphenylethane **7** derivatives modified with the 1-methylimidazolium cation, the latter being linked with the nearest stereocenter by a spacer containing four C–C and three C–N bonds (Scheme 1). Starting chiral diamines



Scheme 1. Synthesis of primary amine-derived organocatalysts 6 and 7 modified with the imidazolium cation and  $PF_6^-$  anion.

Adv. Synth. Catal. 2012, 354, 3078-3086

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8 and 9 were obtained by fractional crystallization of corresponding diastereomeric (S)-(+)-tartaric salts.<sup>[23]</sup> Optical purity of compounds 8 and 9 was confirmed by their optical rotations and by HPLC analysis of the corresponding bis-tosylate derivatives (see the Supporting Information). The synthetic strategy was based on selective protection of just one of the two amino groups in diamines 8 and 9. Known methods for mono-protection of compound 8 by the Cbz group are either multi-staged<sup>[24]</sup> or require use of a large access of the precious chiral amine 8, in both cases yields of the target molecule were poor.<sup>[25]</sup> Mono-Cbz-protected 1,2-diaminodiphenylethane 12 was applied<sup>[26]</sup> as starting compound without a description of its synthesis. We synthesized compounds 11 and 12 by treatment of the corresponding trans-diamines 8 and 9 with O-benzyl-O'-phenyl carbonate 10, which had been earlier applied for the acylation of achiral amines.<sup>[27]</sup> The reactions were carried out at ambient temperature to afford high-purity products 11 and 12 (further purification was not needed) in reasonable yields (61–63%). Apparently, this procedure may be useful for the synthesis of other chiral diamine-derived supported organocatalysts. Further synthetic protocols included reactions of amides 11 or 12 with bromovaleroyl chloride and NEt<sub>3</sub>, subsequent alkylation of 1-methylimidazole by the corresponding diamides 13 or 14 followed by metathesis of the anion in bromides 15 or 16 and catalytic deprotection of the resulting hexafluorophosphates 17 or 18 to respective catalysts 6 or 7. Each step of this sequence selectively afforded intermediates or final products in high yields.

We evaluated the catalytic properties of compounds **6** and **7** in the asymmetric reaction of 1-hydroxycoumarin **19a** with benzylideneacetone **20a**. The product of this reaction **21a** is the active substance of the clinically useful anticoagulant warfarin, the (*S*)-enantiomer of which proved to be 2–5 times more active than the (*R*)-enantiomer.<sup>[28]</sup> Recently, several asymmetric syntheses of **21a** from **19a** and **20a** in the presence of chiral organometallic<sup>[29]</sup> or organic catalysts, in particular imidazolidine,<sup>[30]</sup> 1,2-diamino-1,2-diarylethane,<sup>[31]</sup>  $\beta$ -amino alcohol,<sup>[32]</sup> prolinamide<sup>[33]</sup> and 9-amino-9-de-

Table 1. Primary amines 6 or 7-catalyzed reactions between 19a and 20a.<sup>[a]</sup>



| Entry             | Catalyst (mol%) | Solvent        | Additive (equiv.) | Time [h] | Yield [%] <sup>[b]</sup> | ee [%] <sup>[c]</sup>          |
|-------------------|-----------------|----------------|-------------------|----------|--------------------------|--------------------------------|
| 1                 | <b>6</b> (20)   | THF            | _                 | 45       | 60                       | 10 <sup>[d]</sup>              |
| 2                 | 7 (20)          | THF            | _                 | 45       | 73                       | 68                             |
| 3                 | 7 (20)          | THF            | _                 | 100      | 75                       | 54                             |
| 4                 | 7 (20)          | THF            | AcOH (10)         | 45       | 97                       | 72                             |
| 5                 | 7 (20)          | THF            | $PAA^{[e]}(10)$   | 45       | 67                       | 64                             |
| 6                 | 7 (20)          | THF            | $H_2O(10)$        | 45       | 74                       | 66                             |
| 7                 | 7 (20)          | THF            | TFA or HCl (10)   | 45       | trace                    | -                              |
| 8                 | 7 (20)          | DCM            | AcOH (10)         | 45       | 86                       | 70                             |
| 9                 | 7 (20)          | <i>i</i> -PrOH | AcOH (10)         | 45       | 92                       | 69                             |
| 10                | 7 (20)          | neat           | AcOH (10)         | 45       | 35                       | 68                             |
| 11 <sup>[f]</sup> | 7 (20)          | THF            | AcOH (10)         | 70       | 40                       | 79                             |
| 12                | 7 (10)          | THF            | AcOH (10)         | 45       | 49                       | 79                             |
| 13                | 7 (20)          | THF            | AcOH (5)          | 45       | 97                       | 78                             |
| 14                | 7 (20)          | THF            | AcOH (1)          | 45       | 97                       | 72                             |
| 15 <sup>[g]</sup> | 7 (20)          | THF            | AcOH (5)          | 45       | 96                       | <b>80</b> (96 <sup>[h]</sup> ) |

<sup>[a]</sup> The reactions were carried out using **19a** (16.2 mg, 0.10 mmol), **20a** (17.5 mg, 0.12 mmol), catalyst (0.02 mmol), appropriate solvent (0.15 mL) and additive at room temperature.

<sup>[b]</sup> Isolated yield of product **21a** after column chromatography on silica gel.

<sup>[c]</sup> HPLC analysis data (*Chiralpak* AD-H, hexane/*i*-PrOH=70/30, 0.7 mLmin<sup>-1</sup>, 254 nm,  $t_R(R) = 6.2 \text{ min}$ ,  $t_R(S) = 12.5 \text{ min}$ ). Absolute configuration was determined based on the comparison of optical rotations of products (S)-21 and (R)-21 with reported data.

<sup>[d]</sup> Data for (R)-21.

<sup>[e]</sup> Polyacrylic acid (PAA) was used.

<sup>[f]</sup> The reaction was carried out at 5°C.

<sup>[g]</sup> The reaction was carried out in a 1.0-mmol scale.

<sup>[h]</sup> The *ee* value of **21a** after a single crystallization from an acetone/water mixture.

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| Table 2. Asymmetric          | Michael reactions | of compounds | <b>19</b> with | $\alpha,\beta$ -unsaturated | ketones | <b>20</b> in the | presence o | f 7/AcOH | cata- |
|------------------------------|-------------------|--------------|----------------|-----------------------------|---------|------------------|------------|----------|-------|
| lytic system. <sup>[a]</sup> |                   | -            |                | -                           |         |                  | -          |          |       |



| Entry | Х       | $\mathbf{R}^1, \mathbf{R}^2$                            | Time [h] | (21) Yield [%] <sup>[b]</sup> | ee [%] <sup>[c])</sup> |
|-------|---------|---|----------|-------------------------------|------------------------|
| 1     | O (19a) | 4-MeO-C <sub>6</sub> H <sub>4</sub> , Me ( <b>20b</b> ) | 45       | ( <b>b</b> ) 81               | 77                     |
| 2     | O (19a) | $4-Cl-C_6H_4$ , Me ( <b>20c</b> )                       | 45       | (c) 70                        | 77                     |
| 3     | S (19b) | Ph, Me (20a)  | 45       | ( <b>d</b> ) 51               | 76                     |
| 4     | O (19a) | $-(CH_2)_3-(20d)$                                       | 45       | ( <b>e</b> ) 91               | 50                     |

[a] The reactions were carried out using 19 (0.10 mmol), 20 (0.12 mmol), 7 (10.4 mg, 0.02 mmol), THF (0.15 mL) and AcOH (30 μL, 0.50 mmol) at room temperature.

<sup>[b]</sup> Isolated yield of product **21** after column chromatography on silica gel.

<sup>[c]</sup> HPLC analysis data (*Chiralpak* AD-H, hexane/*i*-PrOH=70/30, 0.7 mLmin<sup>-1</sup>, 254 nm).

oxyepiquinine<sup>[34]</sup> derivatives have been developed. However, to the best of our knowledge, immobilized organocatalysts have never been applied in this reaction.

First, we compared the catalytic performance of compounds 6 and 7 under similar conditions (THF, room temperature, 45 h, **19a:20a**=1:1.2, catalyst loading 20 mol%) (Table 1, entries 1 and 2). In the presence of cyclohexane derivative 6, adduct (R)-21a was generated in just 10% ee, whereas the corresponding **7**-catalyzed reaction afforded adduct (S)-**21a** with an enantiomeric enrichment of 68% ee. Therefore, we further studied the reaction between compounds 19a and 20a in the presence of catalyst 7 under various conditions. The enantioselectivity became poorer when the reaction time was increased to 100 h (entry 3). The effect of an acidic additive depended on its structure. Addition of AcOH (10 equiv.) was beneficial allowing us to obtain adduct (S)-21a in nearly quantitative yield with an enantiomeric enrichment of 72% ee after 45 h (entry 4). In the presence of the poorly soluble in THF polyacrylic acid (PAA) or water instead of AcOH, the reaction outcome was similar to that obtained under additive-free conditions (entries 2, 5, 6). Strong acidic co-catalysts (TFA or HCl) prevented the reaction (entry 7). Carrying out the reaction in dichloromethane (DCM) or *i*-PrOH solution or under neat conditions resulted in a reduction of yields and *ees* of adduct **21a** as compared with those in THF (entries 4, 8–10). The enantioselectivity improved to 79% ee when the reaction was carried out at 5°C (entry 11) or in the presence of lower catalyst loading (10 mol%) (entry 12), although at the expense of product yield. The best compromise between selectivity and activity was attained in the catalytic system containing 20 mol% of amine 7 and 5 equivalents of AcOH (entry 13). Further reduction of the AcOH amount (to 1 equiv.) resulted in lower enantioselectivity (entry 14). Importantly, the reaction is scalable under the optimal conditions and the *ee* value of raw product **21a** (80% *ee*) can be improved up to 96% *ee* by a single crystallization from an acetone/ water mixture (entry 15).

Hydroxycoumarin **19a** and sulfur-containing analogue **19b** reacted with benzylideneacetone derivatives **20a–c** bearing donor or acceptor groups in the aromatic ring under the proposed conditions to afford the corresponding Michael adducts **21b–d** in moderate to high yields and with reasonable *ee* values (Table 2, entries 1–3). Cyclohexenone **20d** could also be used as acceptor component, however, the enantiomeric enrichment of product **21e** was lower (entry 4).

The catalyst 7 could be easily recovered and reused. After the reaction was completed, the solvent and AcOH were evaporated under vacuum (20 Torr), adduct 21a was extracted with Et<sub>2</sub>O and a fresh solution of starting compounds and AcOH in THF was added to the residue (Table 3, columns 3, 4). Once or twice recovered catalyst 7 exhibited nearly the same catalytic performance as the freshly prepared one (cycles 1–3). However, after the third recovery, yield of product and to some extent enantioselectivity of the reaction progressively reduced (cycles 4-6). Presumably, the deactivation may be caused by gradual "leaching" of the catalyst during the extraction of product. The assumption is in agreement with catalyst mass loss after the recovery by 10-12 wt% per cycle. However, it does not explain the reduction of the *ee* values of adduct 21a, which most likely indicates the formation of undesirable by-products from the catalyst.

To identify these by-products, we studied freshly prepared catalyst **7** and recovered samples of the catalyst by electrospray ionization mass spectrometry (ESI-MS). We supposed that the ESI-MS(+) would contain mainly peaks of the catalyst and of ionic com-

| Cycle            | Time [h] | Reactions in THF/<br>AcOH system <sup>[a]</sup> |        | Reactions in<br>THF <sup>[b]</sup> |        |
|------------------|----------|---|--------|------------------------------------|--------|
|                  |          | Yield [%]                                       | ee [%] | Yield [%]                          | ee [%] |
| 1                | 45       | 97  | 78     | 73                                 | 68     |
| 2                | 45       | 94  | 78     | 95                                 | 60     |
| 3                | 45       | 93  | 77     | 90                                 | 60     |
| 4                | 45       | 61  | 76     | 86                                 | 59     |
| 5                | 45       | 42  | 76     | 75                                 | 57     |
| 6                | 100      | 51  | 73     | 63                                 | 53     |
| 7 <sup>[c]</sup> | 45       | _   | -      | 87                                 | 58     |

**Table 3.** Recycling of catalyst 7 in reactions of 19a with 20ain AcOH/THF system and in THF.

<sup>[a]</sup> The reactions were carried out as described above (see footnote<sup>[a]</sup> to Table 2). After extraction of product **21a** (Et<sub>2</sub>O) the residue was dried at 20–30 Torr for 30 min, fresh portions of reagents, THF and AcOH were added and the reaction was re-performed.

<sup>[b]</sup> The reactions and the recovery of the catalyst were carried out without AcOH additive.

<sup>[c]</sup> The reaction was carried out in the presence of reactivated by the treatment with AcOH catalyst, which was recovered from the 6th cycle.

pounds formed from the catalyst whereas the molecules that do not contain ionic groups would give much lower peaks.<sup>[14]</sup> In this case, the AcOH was not added to the reaction mixture in order to simplify the recovery of the catalyst and the ESI-MS(+) analysis of recovered samples. Recycling experiments in "pure" THF (Table 3, columns 5, 6) gave somewhat different results than that obtained in the THF/AcOH system (Table 3, columns 3, 4). In the second cycle, the yield of 21a became 22% higher and the ee 8% lower than in the first cycle. Then, both figures were gradually diminishing in each further cycle to attain minimum magnitudes in the sixth cycle. We recorded the ESI-MS(+) of freshly prepared catalyst 7 and of other three samples of the catalyst, one of which was taken from the reaction stopped after 8 h from the beginning and another two operated in the reaction over one (45 h) and six (325 h) catalytic cycles, respectively (Figure 3).

The ESI-MS(+) spectra of the starting catalyst **7** contained mainly a peak of the corresponding cation **22** (m/z = 377.2335). However, the relative abundance of other peaks presented in the spectra of the recovered samples along with (or instead of) the peak of cation **22** depended on the operation period of the catalyst. These peaks were assigned to corresponding cations **23** (m/z = 505.2948) and **24** (m/z = 667.3269) in accordance with their m/z values. Notably, Lai and Xu with co-authors<sup>[35]</sup> recorded similar intermediates, which were reversibly generated in the reaction mixture composed of compounds **19a**, **20a** and (R, R)-1,2-diamino-1,2-diphenylethane/LiClO<sub>4</sub>/AcOH catalytic system under homogeneous conditions, by ESI-MS.

The ESI-MS(+) of the catalyst **7**, that was taken from the reaction after 8 h from the beginning, contained peaks of cations **22**, **23** and **24** in a 4:3:1 ratio and in the ESI-MS(+) of samples of the catalyst that had operated in the reaction over one (45 h) or six (325 h) catalytic cycles the peak of cation **24** was the major one (Figure 3).

Along with reported literature data, these results allowed us to monitor transformations of catalyst 7 in the studied reaction. The main catalytic cycle can be described by the conventional scheme,<sup>[36]</sup> which includes the condensation of the cation 22 with benzylideneacetone 20a, the protonation of enimine 23 (for example, by carbon acid 19a), followed by the reaction of the iminium dication  $23 + H^+$  with hydroxycoumarin 19a to afford adduct 24, which may exist as an equilibrium mixture of enamine 24a and imine 24b isomers. The catalytic cycle was completed by the hydrolysis of imine 24b, followed by the elimination of the Michael adduct 21a and release of the active cation 22 (Scheme 2).

The ESI-MS data indicated that cations 24a and/or 24b accumulated in recovered samples of catalyst 7. The cation 24b evidently served as a source of active cation 22 for each successive cycle. Along with the main catalytic cycle, a side catalytic process promoted by secondary amine isomer  $24a^{[37]}$  may also take place. Apparently, this process is responsible for reduction of the ee value of adduct 21a in the second and subsequent cycles performed in the presence of recovered catalyst samples, which did not contain cation 22 according to ESI-MS(+) (Table 3, columns 5, 6). Further reduction of both activity and selectivity in the fifth and especially in the sixth cycles along with the presence of the major peak (m/z = 667.3269)in ESI-MS(+) of the 5-fold recovered catalyst indicated that a catalytically inactive isomer, possibly, a special hindered hemi-aminal 25, was generated from the imine-enamine pair 24. Intramolecular formation of stable hemi-aminals from corresponding open-chained compounds containing amino and hydroxy groups has been reported.<sup>[38]</sup>.

Basing on these mechanistic considerations, we reactivated the 5-fold recovered catalyst sample by treating it with a solution of AcOH in THF (1/5). It was found that the ESI-MS(+) of the obtained material differed considerably from that of the catalyst before acidic treatment. Unlike the latter, it contained the major peak of active cation 22 (m/z = 377.2335), which presumably is derived from regeneration by the action of acid imine 24b, along with a low peak (~ 6%) of isomeric cations 24, 25 (m/z = 667.3269). The rate and enantioselectivity of the reaction between compounds 19a and 20a in THF solution containing the reactivated catalyst (Table 3, cycle 7) were considerably higher than that in the two preceding cycles, being somewhat poorer, though, than the correspond-



Figure 3. ESI-MS(+) monitoring of the composition of catalyst 7 in the Michael reaction between 19a and 20a.

ing characteristics of the reaction catalyzed by freshly prepared or just once recovered catalyst **7**. The obtained results explain a favourable impact of acidic co-catalyst (AcOH) on the studied reaction.

#### Conclusions

In summary, we have synthesized for the first time a simple recoverable organocatalyst for asymmetric Michael reactions between C-nucleophiles and  $\alpha,\beta$ unsaturated ketones containing the *trans*-1(*S*),2(*S*)-diaminodiphenylethane unit modified with the 1-methylimidazolium cation. In the presence of this catalyst and an acidic co-catalyst (AcOH), hydroxycoumarin and its S-analogue reacted with benzylideneacetone derivatives or cyclohexenone to afford the corresponding Michael adducts in good yields (up to 97%) and with reasonable enantioselectivity (up to 80%). The catalyst could be easily separated from products and efficiently reused three times, then, in subsequent runs, its activity and enantioselectivity of reactions became lower. The analysis of recovered catalyst samples by ESI-MS allowed us to detect plausible origins of the deactivation and the obtained information may be useful for developing robust immobilized organo-



Scheme 2. Transformations of catalyst 7 in the asymmetric Michael reaction between 19a and 20a according to ESI-MS(+).

catalysts for asymmetric Michael reactions, involving an iminium ion formation step.

## **Experimental Section**

#### **Typical Procedure for the Michael Reaction**

The reactions were carried out using **19a** (0.10 mmol), **20a** (0.12 mmol), catalyst **7** (10.4 mg, 0.02 mmol) and AcOH (30  $\mu$ L, if necessary) in THF (0.15 mL) at room temperature. After the reaction was completed, the solvent and AcOH were evaporated, the product and remaining starting compounds were extracted with Et<sub>2</sub>O (5×10 mL). The ether solution was evaporated under reduced pressure (20 torr) and the residue was purified by column chromatography (hexane/ethylacetate from 3/1 to 2/1) to afford compounds **21a** as colorless crystals. <sup>1</sup>H and <sup>13</sup>C NMR spectra of products **21** were in accordance with reported data.<sup>[30-33]</sup> The catalyst remaining after extraction with Et<sub>2</sub>O was dried under reduced pressure (20 Torr), fresh portions of **19a**, **20a**, THF and AcOH (if necessary) were added to the catalysts and the reaction was re-performed.

Syntheses of and analytical data (NMR, IR,  $[\alpha]_D^{20}$  and HR-MS) for new compounds are given in the Supporting Information.

#### Acknowledgements

Financial support by the President of the Russian Federation (grant for young Ph.D. No. 3551.2012.3), by the Russian Academy of Sciences (Basic Research Program No. 1 of the Department of Chemistry and Material Sciences) and by the Russian Foundation of Basic Research (project 12-03-00420) are gratefully acknowledged.

#### References

- a) A. Dondoni, A. Massi, Angew. Chem. 2008, 120, 4716–4739; Angew. Chem. Int. Ed. 2008, 47, 4638–4660;
   b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, Angew. Chem. 2008, 120, 6232–6265; Angew. Chem. Int. Ed. 2008, 47, 6138–6171; c) H. Pellissier, Recent Developments in Asymmetric Organocatalysis, Royal Society of Chemistry: Cambridge. 2010, ISBN 978-1-84973-054-9.
- [2] P. I. Dalko, Enantioselective Organocatalysis: Reactions and Experimental Procedures, Wiley-VCH, Weinheim, 2007.
- [3] a) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* 2007, 2575–2600; b) M. López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* 2010, 27, 1138–1167.

- [4] a) C. J. Borths, D. E. Carrera, D. W. C. MacMillan, *Tetrahedron* 2009, 65, 6746–6753; b) H. Pellissier, *Tetrahedron* 2007, 63, 9267–9331.
- [5] a) N. K. Rana, R. Unhale, V. K. Singh, *Tetrahedron Lett.* 2012, 53, 2121–2124; b) F. Li, Y. Z. Li, Z. S. Jia, M. H. Xu, P. Tian, G.-Q. Lin, *Tetrahedron* 2011, 67, 10186–10194.
- [6] a) B. List, R. A Lerner, C. F. Barbas III, J. Am. Chem. Soc. 2000, 122, 2395-2396; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, J. Am. Chem. Soc. 2001, 123, 5260-5267; c) M. Amedjkouh, Tetrahedron: Asymmetry 2005, 16, 1411-11414; d) A. Cordova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, Chem. Commun. 2005, 3586-3588; e) Z. Jiang, Z. Liang, X. Wu, Y. Lu, Chem. Commun. 2006, 2801-2803; f) A. Cordova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, Chem. Eur. J. 2006, 12, 5383-5397; g) M. Amedjkouh, Tetrahedron: Asymmetry 2007, 18, 390-395; h) A. M. Bernard, A. Frongia, R. Guillot, P. P. Piras, F. Secci, M. Spiga, Org. Lett. 2007, 9, 541-544; i) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, Chem. Commun. 2007, 957–959; j) I. Kumar, S. R. Bhide, C. V. Rode, Tetrahedron: Asymmetry 2007, 18, 1210-1216; k) D. Zhang, C. Yuan, Tetrahedron 2008, 64, 2480-2488.
- [7] a) B. Zhang, L. Cai, H. Song, Z. Wang, Z. He, Adv. Synth. Catal. 2010, 352, 97–102; b) S. Luo, J. Li, P. Zhou, J. P. Cheng, Chem. Eur. J. 2010, 16, 4457–4461; c) D. Ding, C. G. Zhao, Eur. J. Org. Chem. 2010, 20, 3802–3805.
- [8] a) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* 2007, 18, 2249–2293; b) F. Giacalone, M. Gruttadauria, P. Agrigento, V. Campisciano, R. Noto, *Catal. Commun.* 2011, 16, 75–80; c) A. Massi, A. Cavazzini, L. del Zoppo, O. Pandoli, V. Costa, L. Pasti, P. P. Giovannini, *Tetrahedron Lett.* 2011, 52, 619–622.
- [9] D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron:* Asymmetry **2007**, 18, 299–365.
- [10] a) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* 2007, 107, 5471–5569; b) S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.* 2009, 78, 737–784; c) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* 2010, 39, 1600–1632.
- [11] O. V Maltsev, I. P Beletskaya, S. G Zlotin, Russ. Chem. Rev. 2011, 80, 1067–1113.
- [12] a) M. C. Varela, S. M. Dixon, K. S. Lam, N. E. Schore, *Tetrahedron* 2008, 64, 10087–10090; b) T. E. Kristensen, K. Vestli, M. G. Jakobsen, F. K. Hansen, T. Hansen, J. Org. Chem. 2010, 75, 1620–1629; c) I. Mager, K. Zeitler, Org. Lett. 2010, 12, 1480–1483; d) E. Alza, S. Sayalero, P. Kasaplar, D. Almaşi, M. A. Pericás, Chem. Eur. J. 2011, 17, 11585–11595.
- [13] a) O. V. Maltsev, A. S. Kucherenko, S. G. Zlotin, *Eur. J. Org. Chem.* 2009, 5134–5137; b) O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky, S. G. Zlotin, *Eur. J. Org. Chem.* 2010, 2927–2933; c) S. K. Ghosh, Z. Zheng, B. Ni, *Adv. Synth. Catal.* 2010, *352*, 2378–2382; d) O. V. Maltsev, A. S. Kucherenko, S. G. Zlotin, *Mendeleev Commun.* 2011, *21*, 146–148.
- [14] O. V. Maltsev, A. O. Chizhov, S. G. Zlotin, *Chem. Eur. J.* 2011, 17, 6109–6117.

- [15] E. Alza, S. Sayalero, X. C. Cambeiro, R. Martín-Rapún, P. O. Miranda, M. A. Pericàs, *Synlett* 2011, 464– 468.
- [16] A. Erkkilä, I. Majander, P. M. Pihko, Chem. Rev. 2007, 107, 5416–5470.
- [17] a) H. Kim, C. Yen, P. Preston, J. Chin, Org. Lett. 2006, 8, 5239–5242; b) J. W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J. G. Deng, Y. C. Chen, Org. Lett. 2007, 9, 413– 415.
- [18] T. E. Kristensen, K. Vestli, F. K. Hansen, T. Hansen, *Eur. J. Org. Chem.* 2009, 5185–5191.
- [19] a) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, Y. D. Wu, J. Am. Chem. Soc. 2003, 125, 5262–5263; b) Z. Tang, F. Jiang, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, Y. D. Wu, Proc. Natl. Acad. Sci. USA 2004, 101, 5755–5760; c) X. Liu, L. Lin, X. Feng, Chem. Commun. 2009, 6145–6158; d) X. H. Chen, J. Yu, L. Z. Gong, Chem. Commun. 2010, 46, 6437–6448.
- [20] L. Tuchman-Shukrona, M. Portnoy, Adv. Synth. Catal. 2009, 351, 541–546.
- [21] T. Miura, S. Nishida, A. Masuda, N. Tada, A. Itoh, *Tet-rahedron Lett.* 2011, 52, 4158–4160.
- [22] S. Luo, J. Li, L. Zhang, H. Xu, J.-P. Cheng, *Chem. Eur. J.* 2008, 14, 1273–1281.
- [23] a) J. F. Larrow, E. N. Jacobsen, J. Org. Chem. 1994, 59, 1939–1942; b) M. A. Lapitskaya, K. K. Pivnitskii, Russ. Chem. Bull. 1997, 46, 96–99.
- [24] A. L. Fuent De Arriba, D. G. Seisdedos, L. Simon, J. R. Moran, V. Alcazar, C. Raposo . J. Org. Chem. 2010, 75, 8303–8306.
- [25] a) C. Wu, H. Kobayashi, B. Sun, T. M. Yoo, C. H. Paik, O. A. Gansow, J. A. Carrasquillo, I. Pastan, M. W. Brechbiel, *Bioorg. Med. Chem.* 1997, *5*, 1925–1934;
  b) F. Xue, S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* 2008, *350*, 2194–2198;
  c) A. Minarini, G. Marucci, C. Bellucci, G. Giorgi, V. Tumiatti, M. L. Bolognesi, R. Matera, M. Rosini, C. Melchiorre, *Bioorg. Med. Chem.* 2008, *16*, 7311–7320.
- [26] Q. Zhu, Y. Lu, Org. Lett. 2010, 12, 4156–4159.
- [27] M. Pittelkov, R. Lewinsky, J. B. Christensen, *Synthesis* 2002, 2195–2202.
- [28] T. Meinertz, W. Kasper, C. Kahl, E. Jähnchen, J. Clin. *Pharmacol.* **1978**, *5*, 187–188.
- [29] a) H.-M. Yang, Y.-H. Gao, L. Li, Z.-Y. Jiang, G.-Q. Lai, C.-G. Xia, L.-W. Xu, *Tetrahedron Lett.* **2010**, *51*, 3836– 3839; b) H.-M. Yang, L. Li, K.-Z. Jiang, J.-X. Jiang, G.-Q. Lai, L.-W. Xu, *Tetrahedron* **2010**, *66*, 9708–9713.
- [30] N. Halland, T. Hansen, K. A. Jørgensen, Angew. Chem. 2003, 115, 5105–5107; Angew. Chem. Int. Ed. 2003, 42, 4955–4957.
- [31] H. Kim, C. Yen, P. Preston, J. Chin. Org. Lett. 2006, 8, 5239–5242.
- [32] T. E. Kristensen, K. Vestli, F. K. Hansen, T. Hansen, *Eur. J. Org. Chem.* 2009, 5185–5191.
- [33] Z. Dong, L. Wang, X. Chen, X. Liu, L. Lin, X. Feng, *Eur. J. Org. Chem.* 2009, 5192–5197.
- [34] J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen Org. Lett. 2007, 9, 413–415.
- [35] H.-M. Yang, L. Li, K.-Z. Jiang, J.-X. Jiang, G.-Q. Lai, L.-W. Xu, *Tetrahedron* 2010, 66, 9708–9713.

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- [36] a) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
- [37] a) V. G Granik, Russ. Chem. Rev. 1984, 53, 383–400;
  b) B. Jeso, J. C. Pommier, J. Chem. Soc. Chem. Commun. 1977, 565–566.
- [38] a) D. Y. Yang, Y. S. Chen, P. Y. Kuo, J. T. Lai, C. M. Jiang, C. H. Lai, Y. H. Liao, P. T. Chou, Org. Lett. 2007, 9, 5287–5290; b) C. H. Lin, J. F. Jhang, D. Y. Yang, Org. Lett. 2009, 11, 4064–4067; c) G. Zigeuner, G. Duesberg, E. Fuchs, F. Paltauf, Monatsh. Chem. 1970, 101, 1794–1796.