Organic Process Research & Development **2007**, *11*, 592–597

Solvent-Free Asymmetric Anhydride Opening in a Ball Mill

Toni Rantanen, Ingo Schiffers, and Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Landoltweg 1, D-52074 Aachen, Germany

Abstract:

The mechanochemical technique of ball milling has been applied to the asymmetric opening of *meso*-anhydrides, mediated by the *cinchona* alkaloid quinidine. A simple workup procedure affords the products, optically active dicarboxylic acid monoesters, in high yields, with up to 64% ee. With most substrates no column chromatography was needed. A range of various alcohols, as well as anhydrides, reacted well thus demonstrating the scope of this methodology. Even mixtures of purely solid components react, and no solvent is required (except during the workup). The possible use of almost equimolar amounts of starting materials significantly simplifies the product isolation compared to the standard solution reaction.

Introduction

The successful development of enantioselective catalysts, which are applicable in the synthesis of complex molecules, increases the demand for environmentally benign transformations[1] to improve the sustainability of chemical processes. On one hand, the scope of catalytic methods based on nontoxic, small organic molecules has been expanded,[2] and on the other hand, the effective use of alternative reaction media such as supercritical CO_2,[3] ionic liquids,[4] or simply water,[5] which circumvent the problems associated with many of the traditionally used volatile organic solvents, has been demonstrated.[6] However, by far the best "green" alternative is, of course, to avoid the use of any solvent.[7]

With the vision that organocatalytic processes would benefit from solvent-free reaction conditions, we initiated an investigation of mechanochemical approaches for solvent-free, asymmetric reactions catalyzed by small organic molecules. The technique of ball milling has often been used for grinding minerals into fine particles and for the preparation and modification of inorganic solids.[8] In contrast, in the field of synthetic organic chemistry it has only found few applications, which include oxidative 2-naphthol dimerizations,[9] Heck-type cross-couplings,[10] the protection of diamines,[11] the preparation of phosphorus ylides,[12] the metal-free reductive benzylization of malononitrile,[13] and the functionalization of fullerenes.[14] Our ball milling studies were focused on the asymmetric proline-catalyzed aldol reaction and the *cinchona* alkaloid-mediated asymmetric opening of *meso* anhydrides.[15] Herein, we describe details of the latter transformation and demonstrate the scope of this methodology.

Results and Discussion

The asymmetric opening of *meso*-anhydrides mediated by the pseudoenantiomeric *cinchona* alkaloids quinine and quinidine presents a versatile strategy for establishing multiple stereogenic centers in a target molecule. Furthermore, the resulting functional groups of the products (dicarboxylic acid monoesters) can selectively be manipulated in subsequent transformations.[16] As a consequence of detailed optimization studies,[17,18] products with up to 99% enantiomeric excess (ee) can now be obtained in almost quantitative yield (Scheme 1). Large-scale reactions have been reported by various companies.[16h,i, k,m]

The mechanochemical solvent-free variant of the asymmetric *meso*-anhydride opening presented here was per-

* To whom the correspondence should be addressed. Telephone: +49 241-8094 675. Fax: +49 241-8092 391. E-mail: Carsten.Bolm@oc.rwth-aachen.de.

(1) Anastas, P. T., Warner, J. C., Eds. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

(2) For some recent reviews on enantioselective organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248−5286. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (d) Pihko, P. M. *Angew. Chem.* **2006**, *118*, 558−561. *Angew. Chem., Int. Ed.* **2006**, *45*, 544−547. (e) List, B. *Chem. Commun.* **2006**, 819−824.

(3) For recent reviews on the use of supercritical carbon dioxide as solvent in catalysis, see: (a) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746−756. (b) Leitner, W. *Pure Appl. Chem.* **2004**, *76*, 635−644.

(4) For a recent overview on catalysis performed in ionic liquids, see: Zhang, Z. C. In *Advances in Catalysis*; Gates, B. C., Knözinger, H., Eds.; Elsevier: New York, 2006; Vol. 49, pp 153−237.

(5) For recent reviews on organic reactions in aqueous media, see: (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095−3165. (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68−82.

(6) For some recent reviews on the use of green solvents in organic synthesis, see: (a) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195−218. (b) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267−278. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Angew. Chem.* **2006**, *118*, 4008−4012. *Angew. Chem., Int. Ed.* **2006**, *45*, 3904−3908.

(7) For an overview on solvent-free organic reactions, see: (a) Cave, G. W.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159−2169. (b) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, 2003. For organic solid-state reactions, see: (c) Kaupp, G.; Schmeyers, J.; Boy, J. *J. Prakt. Chem.* **2000**, *342*, 269−280. (d) Kaupp, G. *Top. Curr. Chem.* **2005**, *254*, 945−183. (e) Kaupp, G. *Cryst. Eng. Commun.* **2006**, *8*, 794−804.

(8) (a) Kaupp, G.; Naimi-Jamal, M. R.; Ren, H.; Zoz H. In *Advanced Technologies Based on Self-Propagating and Mechanochemical Reactions for Environmental Protection*; Cao, G., Delogu, F., Orrú, R., Eds.; Research Signpost: Kerala, 2003; pp 83−100. (b) Kipp, S.; Sepelák, V.; Becker, K. D. *Chem. Unserer Zeit* **2005**, *39*, 384−392.

(9) Rasmussen, M. O.; Axelsson, O.; Tanner, D. *Synth. Commun.* **1997**, *27*, 4027−4030.

(10) (a) Tullberg, E.; Peters, D.; Frejd, T. *J. Organomet. Chem.* **2004**, *689*, 3778−3781. (b) Tullberg, E.; Schacher, F.; Peters, D.; Frejd, T. *Synthesis* **2006**, 1183−1189.

(11) Kaupp, G.; Naimi-Jamal, M. R.; Stepanenko, V. *Chem. Eur. J.* **2003**, *9*, 4156−4160.

(12) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. *J. Am. Chem. Soc.* **2002**, *124*, 6244−6245.

(13) Zhang, Z.; Gao, J.; Xia, J.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2005**, *3*, 1617−1619.

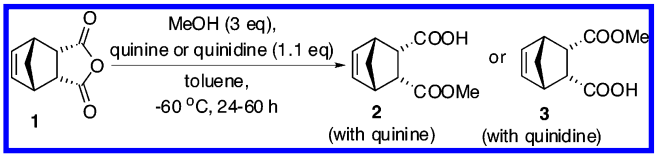
(14) Wang, G.-W.; Zhang, T.-H.; Li, Y.-J.; Lu, P.; Zhan, H.; Liu, Y.-C.; Murata, Y.; Komatsu, K. *Tetrahedron Lett.* **2003**, *44*, 4407−4409.

(15) Rodriguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem.* **2006**, *118*, 7078−7080. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924−6926.

Published on Web 02/10/2007

10.1021/op6002743 CCC: $37.00

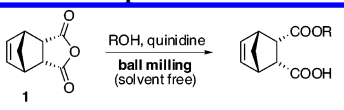
Scheme 1. **Alkaloid-mediated asymmetric opening of a *meso*-anhydride under standard conditions using toluene as solvent and methanol as nucleophile**

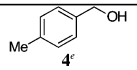
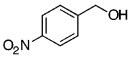
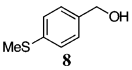
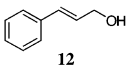


formed in a commercially available micromill (Fritsch GmbH) with two 45-mL grinding bowls containing 5-mm diameter balls, both composed of chemically inert and nonabrasive zirconium oxide. Due to the friction between the reaction components, milling balls, and reaction vessels a slight temperature increase (above ambient temperature) was observed. Consequently, a milling cycle involving a rotational speed of 250 rpm for 25 min followed by a 5-min cooling pause was selected, since the asymmetric *meso*-anhydride opening is known to be temperature sensitive.[19] This milling cycle was then repeated until the reaction was complete.[20] Initially, the reaction time was 36 h. Later, for most substrates ball milling for 24 h was found to be sufficient for complete conversion. In many cases all reactants were solids.

First, reactions between anhydride **1** and various alcohols were investigated. The results are summarized in Table 1.

Table 1. **Mechanochemical asymmetric anhydride opening with various alcohols as nucleophiles in a ball-mill[a]**



Entry	Alcohol	Yield (%)[b]	ee (%)[c]	Product[d]
1	 **4**[e]	91	61	**5**
2	**4**	91	60	**5**
3[f]	**4**	91	45	**5**
4	 **6**	88	40	**7**
5	 **8**	85	55	**9**
6	 **10**	92	64	**11**
7	 **12**	75	50	**13**
8	MeOH	77	51	**3**
9	*i*-PrOH	59	13	**14**
10	*t*-BuOH	n.d.	n.d.	n.d.

[a] Reaction conditions: quinidine (1.1 mmol), anhydride **1** (1.0 mmol), alcohol (1.0 mmol), ball milling, 250 rpm, milling cycle: 25 min milling/5 min break, reaction time 24−36 h. [b] After column chromatography, if required; see text. [c] Determined by chiral GC (Lipodex E) of the corresponding lactone. [d] In all cases the products had (2*R*,3*S*) configuration. Comp. ref 17b. [e] Here, 3.0 equiv of **4** were used. [f] Performed on a 5 mmol scale.

At the beginning of the investigation, 3 equiv of alcohol were used since reactions in toluene with equimolar amounts of anhydride and nucleophile were known to be slow. To our surprise, however, we found that in the ball mill 1 equiv of nucleophile was sufficient for affording products in high yields with essentially unchanged enantioselectivities (Table 1, entries 1 and 2). As a consequence of the reduced reagent amount the workup procedure was simplified from a tedious extraction sequence to a simple acidic wash yielding the desired hemiesters in high purity.[21] Scaling up the reaction (Table 1, entry 3), afforded the product in high yield with a slightly lower enantioselectivity, presumably due to increased friction caused by the larger amount of solids in the reaction vessel. Various alcohols proved applicable, and only in few cases (Table 1, entries 7−9) was flash chromatography necessary in order to remove unreacted alcohol and/or anhydride. Generally, the conversion was higher than 95%, and no side-products could be detected by GC or NMR spectroscopy. The best results were achieved in reaction of anhydride **1** with *p*-methyl and *o*-bromobenzyl alcohol (**4** and **10**) yielding the corresponding products **5** and **11** in yields ≥91% with enantioselectivities of 60 and 64% ee, respectively (Table 1, entries 2 and 6). Compared to the results obtained in solution, the ee of product **3** stemming

(16) For some reviews on the topic, see: (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. I* **1999**, 1765−1784. (b) Spivey, A. C.; Andrews, B. I. *Angew. Chem.* **2001**, *113*, 3227−3230. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131−3134. (c) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965−2984. For some examples in total synthesis utilizing this concept, see: (d) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793−8794. (e) Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. *Tetrahedron: Asymmetry* **1999**, *10*, 3403−3407. (f) Bernardi, A.; Arosio, D.; Manzoni, L.; Micheli, F.; Pasquarello, A.; Seneci, P. *J. Org. Chem.* **2001**, *66*, 6209−6216. (g) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737−1741. (h) Mittendorf, J.; Buchholz, J.-B.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, 136−140. (i) Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433−436. (j) Basso, A.; Banfi, L.; R. Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575−579. (k) Keen, S. P.; Cowden, C. J.; Bishop, B. C.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H.; Lieberman, D. R.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771−1779. (l) Archambaud, S.; Aphecetche-Julienne, K.; Guingant, A. *Synlett* **2005**, 139−143. (m) Yue, T.-Y.; McLeod, D. D.; Albertson, K. B.; Beck, S. R.; Deerberg, J.; Fortunak, J. M.; Nugent, W. A.; Radesca, L. A.; Tang, L.; Xiang, C. D. *Org. Process Res. Dev.* **2006**, *10*, 262−271.

(17) (a) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195−196. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984−6991. (c) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455−3467. (d) Bolm, C.; Atodiresei, I.; Schiffers, I. *Org. Synth.* **2005**, *82*, 120−125.

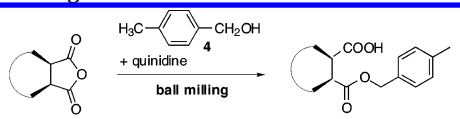
(18) (a) Shintani, R.; Fu, G. C. *Angew. Chem.* **2002**, *114*, 1099−1101. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057−1059. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174−175. (c) Johnson, J. B.; Yu, R. T.; Fink, P. Bercot, E. A.; Rovis, T. *Org. Lett.* **2006**, *8*, 4307−4310. For a substoichiometric version of this desymmetrization reaction based on the use of Sharpless' bis-cinchona alkaloid derivatives, see: (d) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542−9543. (e) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302−11303.

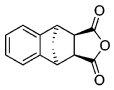
(19) Since the alkaloid-mediated asymmetric anhydride opening is known to be temperature sensitive, a control experiment with anhydride **1** and alcohol **4** in toluene at room temperature was performed. After 24 h the corresponding product was obtained with 83% ee in 71% yield. An analogous experiment performed at 60 °C led (quantitatively) to a racemate. A racemic product was also obtained by reacting **1** and **4** in the absence of a solvent at 60 °C (with a stirring bar).

(20) Performing the catalysis at a lower rotational speed resulted in an ineffective mixing of the reactants and lower yields were observed. Milling without the cooling pause of 5 min or using a higher rotational speed led to a decrease in enantioselectivity presumably due to heating of the reaction vessel through friction.

(21) For the workup of the small-scale reactions reported here, a relatively large amount of solvent was used. Further optimization studies shall reveal the minimal solvent quantity required for full product isolation. At the present stage, the term "solvent-free" can only relate to the reaction itself.

Table 2. **Asymmetric anhydride opening with various anhydrides using the ball-mill[a]**



Entry	Anhydride	Yield (%)[b]	ee (%)[c]	Product[d]
1	 **1**	91	60	(2*R*,3*S*)-**5**
2	 **15**	78	32[e]	(2*R*,3*S*)-**16**
3	 **17**	89	57	(2*R*,3*S*)-**18**
5	 **19**	91	26	(1*R*,2*S*)-**20**
6	 **21**	90	55	(1*R*,2*S*)-**22**
7	 **23**	84	46	(1*S*,2*R*)-**24**
8	 **25**	–[f]	–	–

[a] Reaction conditions: quinidine (1.1 mmol), anhydride (1.0 mmol), alcohol **4** (1.0 mmol), ball milling at 250 rpm, milling cycle: 25 min milling/5 min break, reaction time 24−36 h. [b] After column chromatography, if required, see text. [c] Determined after conversion into the corresponding lactone by GC using a chiral column (Lipodex E). [d] For the determination of the absolute configuration, see ref 17a. The one given for **16** is based on assuming an analogous pathway of the anhydride opening as for the other substrates. [e] The ee was determined from the methyl(*p*-methyl-benzyl)diester by HPLC using a chiral column (see Experimental Section for details). [f] No conversion after 24 h.

from the anhydride opening of **1** with methanol was only moderate (51%; entry 8), which was attributed to the phase behavior and to the higher reaction temperature during the catalysis in the ball mill. The attempted anhydride opening with *tert*-butanol remained unsuccessful (entry 10), and only traces of the product were observed.

On the basis of these results and taking into account that other reactions with ortho-bromo-substituted benzyl alcohol **10** could potentially be hampered by steric interactions with the substrates, para-substituted benzyl alcohol **4** was selected as nucleophile for the subsequent studies. Table 2 summarizes the data obtained from reactions of **4** with other anhydrides.

As shown in Table 2, the asymmetric anhydride opening with (1 equiv of) *p*-methylbenzyl alcohol (**4**) in the presence of (1.1 equiv of) quinidine also proceeded well with substrates other than **1**. Generally, the yields were high (up to 91%) and the enantioselectivities moderate (26−57% ee). A simple acidic wash gave pure products, and only in reactions starting from anhydrides **15**, **17**, and **23** was flash chromatography necessary in order to remove unreacted alcohol and/or anhydride. A few more results are noteworthy. For example, in solution studies anhydride **15** proved unreactive, whereas under ball-milling conditions the asymmetric anhydride opening with alcohol **4** as nucleophile proceeded well, affording the corresponding hemiester **16** with 32% ee in 78% yield. No conversion of 3-methyl glutaric acid anhydride (**27**) was observed after 24 h under ball-milling conditions.

The attempt to increase the enantioselectivity by using greater than stoichiometric amounts of quinidine (2.0 equiv) in the asymmetric anhydride opening of **1** with **4** led to no improvement and afforded **5** with 60% ee in 90% yield. Performing the reaction between **1** and **4** in a round-bottomed flask under mixing with a simple stir bar gave results that were difficult to reproduce.[22] Generally, the yield of product **5** was lower, whereas the ee was higher than under ball-milling conditions. These observations were, on one hand, attributed to non-effective mixing of the solid components and, on the other, to better temperature control, which avoided warming of the reaction mixture. Trying to effect a catalytic ball-milling reaction with **10** mol % of Sharpless' bis(cinchona) alkaloid $(DHQ)_2AQN$[23] according to Deng's protocol[18c,d] led to products **3** and **5** in good yields (57 and 90%), but with significantly lower enantioselectivities (5 and 15%, respectively).

Conclusion

In summary, we have expanded the scope of the solvent-free ball-milling methodology. The mechanically induced, solid-state desymmetrization of *meso*-anhydrides mediated by the *cinchona* alkaloid quinidine leads to optically active hemiesters in high yields and moderate enantioselectivities. Except for the workup, no solvent is required,[21] and even mixtures of purely solid components react. Compared to the standard reaction performed in solution the possible use of almost equimolar amounts of starting materials significantly simplifies the product isolation.

Experimental Section

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Anhydride **15** was synthesized according to a known procedure.[24] The ball-milling experiments were performed using a Fritsch Planetary Micro Mill model "Pulverisette 7" with two 45-mL grinding bowls and 5-mm diameter grinding balls made of zirconium oxide. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 300 or Inova 400 spectrometer and were recorded relative to $CHCl_3$ as internal standard. Mass spectra were measured on a Finnigan SSQ

(22) Interestingly, after stirring for some time, the solid reactants formed a sticky paste in the reaction flask. This in turn hindered the efficient movement of the stirring bar. An analogous behavior is observed in the ball mill. There, however, the mixing is more efficient at this stage.
(23) $(DHQ)_2AQN$: 1,4-bis(dihydroquinyl)anthraquinone.
(24) Fotins, J.; Smithrud, D. B. *J. Org. Chem.* **2005**, *70*, 4452−4459.

7000 instrument or on a Hewlett-Packard GC/MS apparatus-system (column HP-5 MS, 30 m × 0.25 mm × 0.25 μm; mass selective detector 5973). HPLC analysis was performed using a Chiralpak OD-H column, 4.6 × 250 mm, $\lambda = 254$ nm. For the determination of the enantiomeric ratios, the hemiesters were reduced with $LiBEt_3H$ and cyclized to lactones, which were then analyzed by GC.[17b] GC analysis was performed using the chiral column Lipodex E (2,6-*O*-dipentyl-3-*O*-butyryl-γ-CD) and the following conditions: column head pressure: 1.0 bar N_2; 100 °C (50 min), heating rate 3.0 °C/min up to 180 °C (60 min); injector temperature 200 °C, detector temperature 250 °C. Melting points were measured in open glass capillaries with a Büchi-apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer P241 instrument at rt (ca. 20 °C) using solvents of Merck UVASOL-quality. Infrared spectra were recorded on a Perkin-Elmer 1760 FT apparatus either as KBr pellets or neat. All microanalyses were conducted on a Heraeus CHN RAPID instrument at the Institut für Organische Chemie der RWTH Aachen. Preparative column chromatography: Merck silica gel 60, particle size 0.063−0.200 (230−400 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates, Merck, Darmstadt. All experiments were conducted at least twice to ensure reproducibility.

General Procedure for the Anhydride Opening in the Ball Mill (GPR 1). In a clean, dry, ball-milling vessel 60 zirconium oxide balls, the anhydride (1 mmol), quinidine [1.1 equiv or 0.1 equiv of $(DHQ)_2AQN$], and the alcohol (1.0 equiv) were sequentially added. The vessel was closed and the milling started (ball-milling cycle: 250 rpm, 25-min milling time, 5-min pause). This milling cycle was repeated until the reaction was complete. The mixture was then carefully transferred into a separation funnel using first 2 N HCl (2 × 15 mL) and then EtOAc (3 × 20 mL). The organic phase was separated and washed with 2 N HCl (3 × 15 mL). The combined aqueous fractions were extracted with EtOAc (1 × 20 mL). After drying of the combined organic fractions ($MgSO_4$), the solvent was evaporated. If required, the product was purified by flash chromatography.

(2*R*,3*S*)-3-*endo*-Methoxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (3). The compound was isolated as a colorless solid according to **GPR 1** using anhydride **1** and methanol with quinidine as mediator. The analytical data is in accordance with the ones already published.[17b]

(2*R*,3*S*)-3-*endo*-*p*-Methylbenzyloxycarbonyl-bicyclo-[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (5). The compound was isolated as a colorless oil according to **GPR 1** using the anhydride **1**, *p*-methylbenzyl alcohol (**4**), and quinidine: $[\alpha]^{25}_D = +5.3$ (*c* 2.68, $CDCl_3$); ee = 61% as determined by GC analysis of the corresponding lactone: Lipodex E, $t_1 = 84.4$ min, $t_2 = 84.9$ min (major); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (d, $J = 8.5$ Hz, 1H), 1.49 (dt, $J = 1.8$, 8.5 Hz, 1H), 2.35 (s, 3H), 3.19 (d, $J = 8.8$ Hz, 2H), 3.30−3.36 (m, 2H), 4.98 (AB-system, $J = 12.4$ Hz, 2H), 6.23 (dd, $J = 3.0$, 5.5 Hz, 1H), 6.30 (dd, $J = 3.0$, 5.5 Hz, 1H), 7.12−7.24 (m, 4H), 9.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 46.1, 46.6, 48.1, 48.3, 48.7, 66.3, 128.3, 129.0, 132.7, 134.2, 135.4, 137.7, 172.1, 178.3; IR (KBr): 2974, 1730, 1676, 1519, 1330, 1294, 1191, 1043, 797 cm^{-1}; EI-MS: $m/z = 286$ (M^+, 4), 268 (4), 240 (3), 170 (4), 121 (3), 105 (100), 91 (4), 77 (4), 66 (4). Anal. calcd for $C_{17}H_{18}O_4$ (286.32): C, 71.31; H, 6.34. Found: C, 71.19; H, 6.29.

(2*R*,3*S*)-3-*endo*-*p*-Nitrobenzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (7). The compound was isolated as a slightly yellow solid according to **GPR 1** using anhydride **1**, *p*-nitrobenzyl alcohol (**6**), and quinidine: mp dec; $[\alpha]^{25}_D = -11.4$ (*c* 3.70, $CDCl_3$); ee = 40% as determined by GC analysis of the corresponding lactone; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (d, $J = 8.5$ Hz, 1H), 1.52 (dt, $J = 1.7$, 8.8 Hz, 1H), 3.20 (br s, 2H), 3.31−3.39 (m, 2H), 5.10 (AB-system, $J = 13.3$ Hz, 2H), 6.19 (dd, $J = 2.7$, 5.7 Hz, 1H), 6.28 (dd, $J = 3.0$, 5.7 Hz, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 46.3$, 46.6, 48.1, 48.2, 48.9, 64.9, 123.6, 128.5, 134.4, 135.4, 143.0, 147.5, 171.8, 177.9; IR (KBr): 3076, 2983, 1703, 1602, 1515, 1430, 1338, 1192, 842 cm^{-1}; EI-MS: $m/z = 317$ (M^+, 4), 284 (6), 256 (8), 252 (54), 137 (26), 136 (29), 119 (10), 91 (13), 66 (100). Anal. calcd for $C_{16}H_{15}NO_6$ (317.29): C, 60.57; H, 4.77; N, 4.41. Found: C, 60.55; H, 4.42; N, 4.24.

(2*R*,3*S*)-3-*endo*-*p*-Thiomethoxybenzyloxycarbonyl-bicyclo-[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (9). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **1**, *p*-thiomethoxybenzylalcohol (**8**), and quinidine: $[\alpha]^{25}_D = +1.6$ (*c* 4.18, $CDCl_3$); ee = 55% as determined by GC analysis of the corresponding lactone; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 8.7$ Hz, 1H), 1.47 (dt, $J = 1.7$, 8.7 Hz, 1H), 2.45 (s, 3H), 3.17 (br s, 2H), 3.30−3.34 (m, 2H), 4.95 (AB-system, $J = 12.2$ Hz, 2H), 6.21 (dd, $J = 2.8$, 5.6 Hz, 1H), 6.28 (dd, $J = 2.9$, 5.6 Hz, 1H), 7.21 (s, 4H), 10.73 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.5$, 46.0, 46.4, 48.0, 48.2, 48.6, 65.9, 126.3, 128.8, 132.4, 134.2, 135.3, 138.4, 172.1, 178.5; IR (KBr): 2976, 1718, 1177, 804 cm^{-1}; EI-MS: $m/z = 318$ (M^+, 17), 153 (4), 137 (100), 122 (6), 99 (2), 91 (3). Anal. calcd for $C_{17}H_{18}O_4S$ (318.38): C, 64.13; H, 5.70. Found: C, 63.84; H, 6.08.

(2*R*,3*S*)-3-*endo*-*o*-Bromobenzyloxycarbonyl-bicyclo-[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (11). The compound was isolated as a colorless solid according to **GPR 1** using anhydride **1**, *o*-bromobenzyl alcohol (**10**), and quinidine: mp 112 °C (en); $[\alpha]^{25}_D = +0.4$ (*c* 1.99, $CDCl_3$); ee = 64% as determined by GC analysis of the corresponding lactone; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (d, $J = 8.6$ Hz, 1H), 1.49 (dt, $J = 1.6$, 8.5 Hz, 1H), 3.20 (br s, 2H), 3.35 (dq, $J = 3.0$, 8.1 Hz, 2H), 5.10 (AB-system, $J = 12.9$ Hz, 2H), 6.23 (dd, $J = 2.8$, 5.5 Hz, 1H), 6.29 (dd, $J = 3.0$, 5.5 Hz, 1H), 7.13−7.20 (m, 1H), 7.26−7.32 (m, 1H), 7.35−7.40 (m, 1H), 7.52−7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 46.3$, 46.6, 48.1, 48.2, 48.8, 66.0, 123.4, 127.4, 129.5, 130.0, 132.6, 134.5, 135.3, 171.8, 177.8; IR (KBr): 3400, 2980, 1744, 1436, 1341, 1257, 1171, 1077, 1025, 754, 669 cm^{-1}; EI-MS: $m/z = 352/350$ (M^+, 5), 287/285 (21), 181 (18), 171/169 (100), 137 (24), 107 (13), 90 (24), 66

(97). Anal. calcd for $C_{16}H_{15}BrO_4$ (351.18): C, 54.72; H, 4.31. Found: C, 54.89; H, 4.46.

(2*R*,3*S*)-3-*endo*-Cinnamoyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (13). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **1**, cinnamyl alcohol (**12**), and quinidine: $[\alpha]^{25}_D = +2.6$ (*c* 1.66, $CDCl_3$); ee = 50% as determined by GC analysis of the corresponding lactone; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (d, $J = 8.7$ Hz, 1H), 1.41 (dt, $J = 1.7$, 8.6 Hz, 1H), 3.03−3.15 (m, 2H), 3.15−3.29 (m, 2H), 4.47−4.67 (m, 2H), 6.10−6.29 (m, 3H), 6.47−6.59 (m, 1H), 7.13−7.38 (m, 5H), 10.19 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.1$, 46.4, 48.0, 48.3, 48.7, 65.1, 123.2, 126.6, 127.8, 128.4, 133.8, 134.4, 135.4, 136.2, 172.1, 178.6; IR (KBr): 3852, 3743, 2361, 2339, 1696, 1550, 672 cm^{-1}; EI-MS: *m*/*z* = 298 (M^+, 3), 280 (2), 182 (3), 117 (100), 115 (14), 91 (8). Anal. calcd for $C_{18}H_{18}O_4$ (298.32): C, 72.47; H, 6.08. Found: C, 72.70; H, 5.96.

(2*R*,3*S*)-3-*endo*-Isopropoxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic Acid (14). The compound was isolated as a colorless solid according to **GPR 1** using anhydride **1**, isopropyl alcohol, and quinidine: mp 87 °C (en); $[\alpha]^{25}_D = -0.4$ (*c* 2.24, $CDCl_3$); ee = 13% as determined by GC analysis of the corresponding lactone; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (d, $J = 6.4$ Hz, 3H), 1.17 (d, $J = 6.2$ Hz, 3H), 1.29 (d, $J = 8.7$ Hz, 1H), 1.44 (dt, $J = 1.8$, 8.6 Hz, 1H), 3.10−3.18 (m, 2H), 3.18−3.32 (m, 2H), 4.89 (sept, $J = 6.3$ Hz, 1H), 6.19 (dd, $J = 3.0$, 5.4 Hz, 1H), 6.26 (dd, $J = 3.0$, 5.4 Hz, 1H), 11.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 21.7, 46.2, 46.5, 48.0, 48.6, 48.7, 67.8, 134.3, 135.3, 171.7, 178.7; IR (KBr): 2976, 2360, 1709, 1339, 1209, 1101, 909, 717 cm^{-1}; EI-MS: *m*/*z* = 224 (M^+, 1), 206 (1), 182 (2), 164 (15), 137 (12), 117 (33), 99 (20), 66 (100). Anal. calcd for $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19. Found: C, 64.23; H, 7.20.

(2*R*,3*S*)-3-*endo*-*p*-Methylbenzyloxycarbonyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2-carboxylic Acid (16). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **15**, *p*-methylbenzyl alcohol (**4**), and quinidine. In order to determine the ee, the initial product was converted into the corresponding methyl(*p*-methylbenzyl)diester by DCC-coupling. This compound was then analyzed by HPLC using a chiral column (Chiralcel OD-H column, 90:10 heptane/2-propanol, 0.5 mL/min, 15.0 min major, 17.9 min minor). The absolute configuration of **16** is based on assuming an analogous pathway of the anhydride opening as for the other substrates: $[\alpha]^{25}_D = +14.8$ (c 2.22, $CDCl_3$); ee = 32%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ (d, $J = 9.1$ Hz, 1H), 1.86 (dt, $J = 1.5$, 9.1 Hz, 1H), 2.35 (s, 3H), 3.44−3.49 (m, 2H), 3.62 (br s, 2H), 4.82 (AB-system, $J = 12.1$ Hz, 2H), 7.04−7.26 (m, 8H), 9.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 47.46, 47.52, 47.65, 47.77, 49.8, 66.2, 123.1, 123.3, 126.0, 126.1, 128.5, 129.0, 132.7, 137.7, 143.4, 143.7, 171.0, 176.6; IR (KBr): 3742, 3017, 2975, 2355, 1720, 1520, 1175, 757 cm^{-1}; EI-MS: *m*/*z* = 336 (M^+, 36), 318 (5), 220 (11), 215 (17), 141 (19), 122 (22), 116 (49), 105 (100), 91 (5). Anal. calcd for $C_{21}H_{20}O_4$ (336.38): C, 74.98; H, 5.99. Found: C, 74.64; H, 6.33.

(2*R*,3*S*)-3-*exo*-*p*-Methylbenzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic Acid (18). The compound was isolated as a colorless solid according to **GPR 1** using anhydride **17**, *p*-methylbenzyl alcohol (**4**), and quinidine: mp 97−98 °C (en); $[\alpha]^{25}_D = -10.7$ (*c* 1.88, $CDCl_3$); ee = 57% as determined by GC analysis of the corresponding lactone: Lipodex E, $t_1 = 79.1$ min, $t_2 = 80.1$ min (major); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (dt, $J = 1.5$, 9.1 Hz, 1H), 2.16 (d, $J = 8.9$ Hz, 1H), 2.35 (s, 3H), 2.62−2.73 (m, 2H), 3.09−3.19 (m, 2H), 5.05 (AB-system, $J = 12.1$ Hz, 2H), 6.18−6.27 (m, 2H), 7.16 (d, $J = 7.9$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 10.62 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 45.3, 45.4, 45.7, 47.3, 47.4, 66.6, 128.4, 129.1, 132.6, 137.8, 137.9, 138.0, 173.2, 179.8; IR (KBr): 2977, 1730, 1436, 1334, 1258, 1173, 1023, 803, 716 cm^{-1}; EI-MS: *m*/*z* = 286 (M^+, 7), 268 (3), 240 (1), 165 (5), 122 (52), 105 (100), 91 (13), 77 (11), 66 (20). Anal. calcd for $C_{17}H_{18}O_4$ (286.32): C, 71.31; H, 6.34. Found: C, 71.29; H, 6.22.

(1*R*,2*S*)-*cis*-2-*p*-Methylbenzyloxycarbonyl-cyclohexane-1-carboxylic Acid (20). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **19**, *p*-methylbenzyl alcohol (**4**), and quinidine: $[\alpha]^{25}_D = +0.7$ (*c* 1.65, $CDCl_3$); ee = 26% as determined by GC analysis of the corresponding lactone: Lipodex E, $t_1 = 75.9$ min (major), $t_2 = 76.9$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34-1.62$ (m, 4H), 1.72−1.84 (m, 2H), 1.98−2.12 (m, 2H), 2.34 (s, 3H), 2.82−2.91 (m, 2H), 5.19 (AB-system, $J = 12.2$ Hz, 2H), 7.15 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 23.7, 23.8, 26.1, 26.3, 42.48, 42.51, 66.3, 128.1, 129.0, 132.9, 137.7, 173.2, 179.8; IR (KBr): 2938, 2863, 1710, 1217, 1177, 733 cm^{-1}; EI-MS: *m*/*z* = 276 (M^+, 21), 248 (12), 230 (6), 186 (5), 155 (16), 122 (75), 121 (100), 105 (76). Anal. calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.54; H, 7.30. Found: C, 69.28; H, 7.52.

(1*R*,2*S*)-*cis*-2-*p*-Methylbenzyloxycarbonyl-cyclohex-4-ene-1-carboxylic Acid (22). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **21**, *p*-methylbenzyl alcohol (**4**), and quinidine: $[\alpha]^{25}_D = -0.7$ (*c* 3.21, $CDCl_3$); ee = 55% as determined by GC analysis of the corresponding lactone: Lipodex E, $t_1 = 78.4$ min (major), $t_2 = 79.0$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31-2.46$ (m, 5H), 2.52−2.68 (m, 2H), 3.05−3.14 (m, 2H), 5.10 (AB-system, $J = 12.1$ Hz, 2H), 5.64−5.73 (m, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 25.6, 25.8, 39.60, 39.62, 66.5, 124.9, 125.1, 128.1, 129.0, 132.7, 137.8, 172.8, 179.4; IR (KBr): 3850, 3748, 3681, 3428, 2949, 2364, 2343, 2224, 1700, 1548, 1181, 662 cm^{-1}; EI-MS: *m*/*z* = 274 (M^+, 4), 256 (3), 228 (3), 121 (5), 105 (100), 79 (7). Anal. calcd for $C_{16}H_{18}O_4$ (274.31): C, 70.06; H, 6.61. Found: C, 70.03; H, 6.71.

(1*S*,2*R*)-*cis*-2-*p*-Methylbenzyloxycarbonyl-3,3-dimethylcyclopropane-1-carboxylic Acid (24). The compound was isolated as a colorless oil according to **GPR 1** using anhydride **23**, *p*-methylbenzyl alcohol (**4**), and quinidine: $[\alpha]^{25}_D = +0.3$ (*c* 2.16, $CDCl_3$); ee = 46% as determined by

GC analysis of the corresponding lactone: Lipodex E, t_1 = 71.6 min, t_2 = 72.7 min (major); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.41 (s, 3H), 1.97 (s, 2H), 2.35 (s, 3H), 5.11 (AB-system, J = 12.1 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 9.79 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 21.1, 27.3, 28.0, 32.8, 32.9, 67.0, 128.5, 129.2, 132.3, 138.1, 170.4, 173.7; IR (KBr): 2954, 2355, 1729, 1446, 1176, 1109, 808 cm^{-1}; EI-MS: m/z = 262 (M^+, 8), 162 (1), 141 (2), 121 (17), 113 (13), 105 (100), 77 (7). Anal. calcd for $C_{15}H_{18}O_4$ (262.30): C, 68.68; H, 6.92. Found: C, 68.70; H, 6.64.

Acknowledgment

We are grateful to the *Fonds der Chemischen Industrie* and to the *Deutsche Forschungsgemeinschaft (DFG*) within the SPP 1179 ('Organocatalysis') for financial support.

Received for review December 18, 2006.

OP6002743