Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6279–6283
Tetrahedron Letters

Palladium-catalyzed asymmetric synthesis of allylic alcohols from unsymmetrical and symmetrical racemic allylic carbonates featuring C–O-bond formation and dynamic kinetic resolution

Hans-Joachim Gais,* Oleg Bondarev and Ralf Hetzer

Institut für Organische Chemie der Rheinisch-Westfälischen, Technischen Hochschule (RWTH) Aachen, Landoltweg 1, 52056 Aachen, Germany

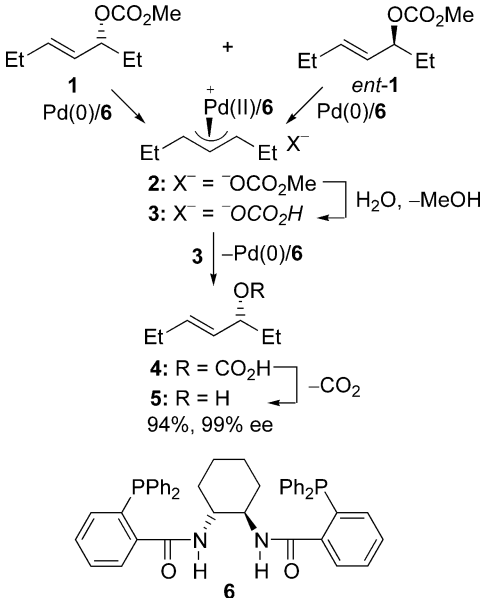
Received 30 June 2005; accepted 12 July 2005

Abstract—Described is the asymmetric synthesis of the allylic alcohols **11** (85% ee), **15** (99% ee), **17** (93% ee), **19** (61% ee), and **21** (69% ee) through a Pd-catalyzed reaction of the unsymmetrical carbonates *rac*-**10**, *rac*-**12**, *rac*-**14**, *rac*-**16**, *rac*-**18**, and *rac*-**20**, respectively, with $KHCO_3$ and H_2O in the presence of bisphosphane **6**. Similarly the allylic alcohols **23** (99% ee) and **25** (97% ee) have been obtained from the symmetrical carbonates *rac*-**22** and *rac*-**24**, respectively. Reaction of the *meso*-biscarbonate **26** with H_2O and Pd(0)/**6** afforded alcohol **27** (96% ee), which was converted to the PG building block **32**. The unsaturated bisphosphane **33** showed in the synthesis of alcohols **36**, **37**, and **39** a similar high selectivity as **6**. The formation of alcohols **11**, **15**, and **17** involves an efficient dynamic kinetic resolution.

1. Introduction

Chiral allylic alcohols are important intermediates in the synthesis of natural and non-natural compounds.[1] Several methods have been developed for their asymmetric synthesis including kinetic resolution[2] and those based on C–H-[1c,3] and C–C-bond[4] formation. Particularly interesting are alternative approaches featuring C–O bond formation.[5] We have recently described a Pd-catalyzed asymmetric synthesis of allylic alcohols, **5**, through reaction of the corresponding symmetrical racemic carbonates, *rac*-**1**, with the chiral catalyst Pd(0)/**6**[6] and water[7a] (Scheme 1[7b]).

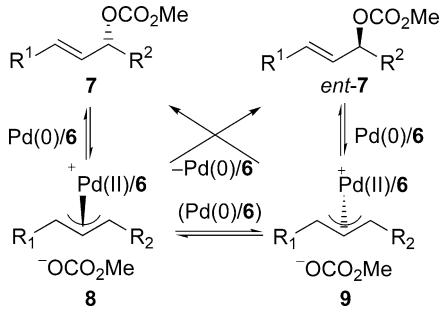
The important steps of this synthesis are (1) the in situ anion exchange of the π-allyl-Pd complex through hydrolysis, **2**→**3**, and (2) the enantioselective substitution of the latter complex by the hydrogen carbonate ion with formation of an allylic hydrogen carbonate, **4**, the decomposition of which gives the allylic alcohol, **5**. Key to the attainment of a high efficiency is the conversion of both enantiomers of the allylic carbonate, **1**



Scheme 1.

Keywords: Asymmetric synthesis; Palladium catalysis; Allylic alcohols.
* Corresponding author. Tel.: +49 241 8094686; fax: +49 241 8092665; e-mail: Gais@RWTH-Aachen.de

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.044



Scheme 2.

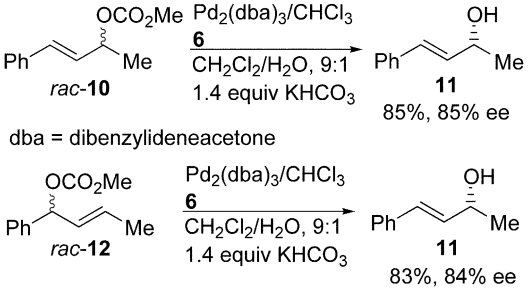
and *ent*-**1**, to one π-allyl-Pd complex, **2**, by the catalyst because of the symmetrical carbon skeleton of the substrate and the C_2-symmetry of the ligand **6**.

It was now of interest to see whether racemic unsymmetrical allylic carbonates are also capable to undergo a highly efficient catalytic transformation to the corresponding allylic alcohols with Pd(0)/**6** and water. Here the situation is much more complex since both enantiomers of the substrate, **7** and *ent*-**7**, react with the catalyst with formation of two diastereomeric π-allyl-Pd complexes, **8** and **9**, respectively (Scheme 2).[8] Only if there is (1) a different reactivity of the complexes, (2) a fast interconversion of both complexes or racemization of the substrate, (3) a high stereoselectivity induced by the ligand, and (4) a high regioselectivity caused by the substituents can the racemic substrate be completely converted to the chiral alcohol with high enantio- and regioselectivity. An interconversion and racemization could in principle be caused either by an *anti* substitution of the allyl complexes by the Pd(0) catalyst (e.g., **8**→**9**) and/or by a Pd-centered *syn* substitution of the allyl complex by the anion (e.g., **8**→*ent*-**7**), respectively.[2f,8–10] However, examples for a Pd-catalyzed allylic substitution of unsymmetrical racemic substrates of type *rac*-**7** that proceed with high yield and enantioselectivity (dynamic kinetic resolution[2h]) are very rare.[11]

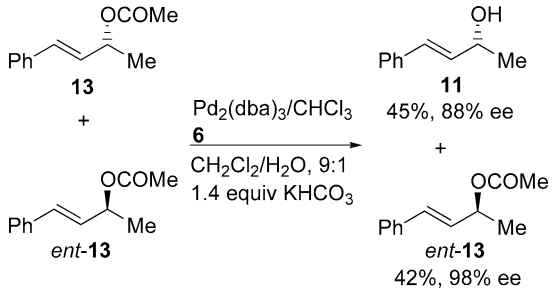
2. Results and discussion

2.1. Unsymmetrical substrates

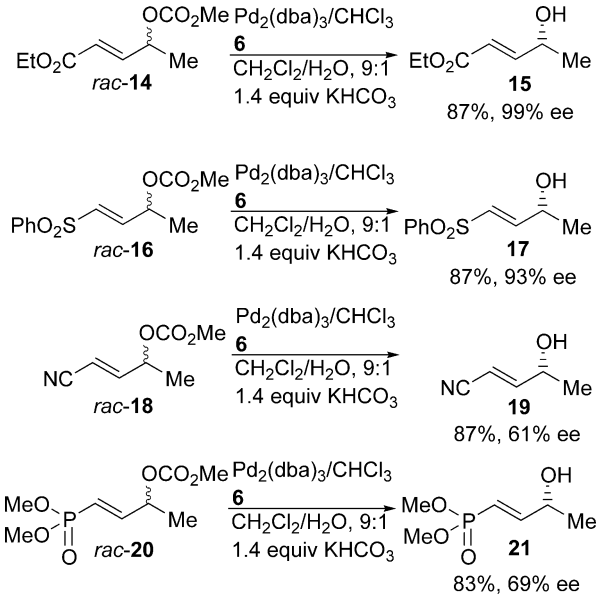
We selected the racemic allylic carbonates shown in Schemes 3–5 because of their electronically and sterically different substituents, which are expected to provide for a high regioselectivity of the substitution[2f,g,12] and the importance of the corresponding allylic alcohols as starting material for the synthesis of chiral compounds.



Scheme 3.



Scheme 4.



Scheme 5.

Treatment of the carbonate *rac*-**10** with 4 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in the two-phase solvent system composed of CH_2Cl_2 and H_2O at room temperature for 36 h gave alcohol **11**[13] with 85% ee in 85% yield (Scheme 3). Formation of the isomeric alcohol was not observed (⩾98%). A reduction of the amount of the catalyst to 2 mol % saw a decrease of the ee-value of **11** to 78%. Interestingly, at the same catalyst concentration but in the single-phase solvent system THF/H_2O the ee-value of **11** dropped to 35%. Similarly, the omission of $KHCO_3$ in the reaction of *rac*-**10** with the catalyst in CH_2Cl_2/H_2O resulted in the isolation of **11** with only 41% ee. Finally the isomeric carbonate *rac*-**12** was submitted to the reaction with 4 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature for 36 h, which afforded exclusively alcohol **11** (⩾98%) with 84% ee in 83% yield.

With the less reactive acetate *rac*-**13** a highly selective kinetic resolution took place (Scheme 4).[10] Treatment

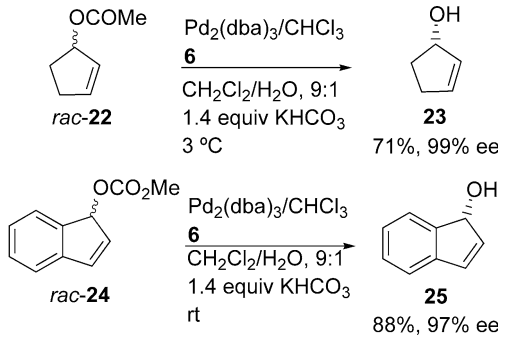
of *rac*-**13** with 4 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O gave alcohol **11** with 88% ee in 45% yield and acetate *ent*-**13**[13] with 98% ee in 42% yield. A non-linear regression of a series of ee- and conversion-values gave a selectivity factor of $S = 73 \pm 32$.

Next the synthetically more attractive functionalized racemic carbonates *rac*-**14**, *rac*-**16**, *rac*-**18**, and *rac*-**20** were investigated (Scheme 5). Treatment of the ester *rac*-**14** with 8 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature for 96 h gave alcohol **15**[14a,b] with 99% ee in 87% yield. The sulfone *rac*-**16** afforded under similar conditions with half amount of the catalyst alcohol **17**[14b,15] with 93% ee in 87% yield. The utilization of THF/H_2O instead of CH_2Cl_2/H_2O resulted also in this case in a decrease of the ee-value of **17** to 60% (89% yield). The substitutions of the nitrile *rac*-**18** and the phosphonate *rac*-**20** proceeded less selectively. Reaction of *rac*-**18** and *rac*-**20** with 4 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature for 96 h furnished alcohol **19**[16] with 61% ee in 87% yield and alcohol **21**[17] with 69% ee in 83% yield, respectively. All of the substitutions of *rac*-**14**, *rac*-**16**, *rac*-**18**, and *rac*-**20** were highly regioselective (⩾98%).

2.2. Symmetrical substrates

The cyclic allylic alcohols **23**[18] and **25**[19] (Scheme 6) are valuable starting materials for the synthesis of chiral ligands and biologically active compounds. Therefore the substitutions of the acetate *rac*-**22** and carbonate *rac*-**24** were studied.

We had previously observed that the Pd-catalyzed reaction of the carbonate derived from alcohol *rac*-**23** with water in CH_2Cl_2 afforded **23** with only 43% ee in 91% yield.[7a] The carbonate of *rac*-**23** shows a strong memory effect in Pd-catalyzed allylic substitution in the presence of **6**, that is, both enantiomers not only react with a different rate with the chiral catalyst but also with a different enantioselectivity with the nucleophile.[12,20] Most importantly, the catalyst Pd(0)/**6** also causes a partial racemication of the slower reacting enantiomer of the carbonate. This suggested the use of the less reactive acetate *rac*-**22**. Treatment of *rac*-**22** with 4 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature for 18 h afforded alcohol **23** with 88% ee in 89% yield. Gratifyingly, lowering the temperature to 3 °C allowed the isolation of alcohol **23** with 99% ee in 83% yield after a reaction time of 72 h under otherwise identical reaction conditions. Similarly, reaction of the racemic carbonate *rac*-**24** with 2 mol % of Pd(0)/**6** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature for 24 h gave indenol **25** with 97% ee in 88% yield.



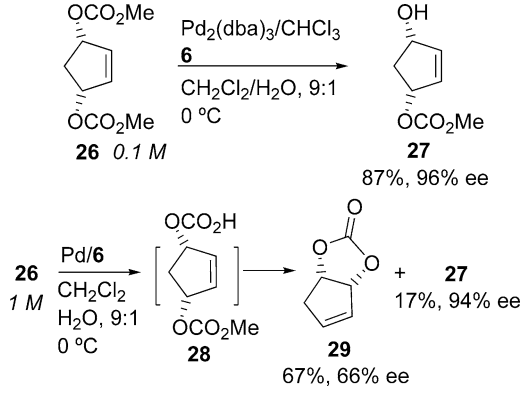
Scheme 6.

2.3. Synthesis of a prostaglandin building block

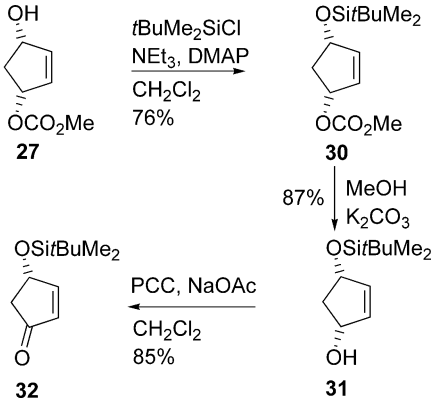
As a final example, the substitution of the *meso*-configured biscarbonate **26** was studied (Scheme 7).

Treatment of **26** with 4 mol % of Pd(0)/**6** in CH_2Cl_2/H_2O at 0 °C and a concentration of 0.1 M of the substrate for 48 h afforded alcohol **27** with 96% ee in 87% yield. At room temperature, the ee-value of **27** fell to 53%. Interestingly, the same reaction of **26** at a concentration of 1 M gave **27** with 94% ee in 17% yield and carbonate **29**[21] with 66% ee in 67% yield. Carbonate **29** is most likely formed by a competing Pd/**6**-catalyzed intra-molecular substitution of the hydrogen carbonate **28**.

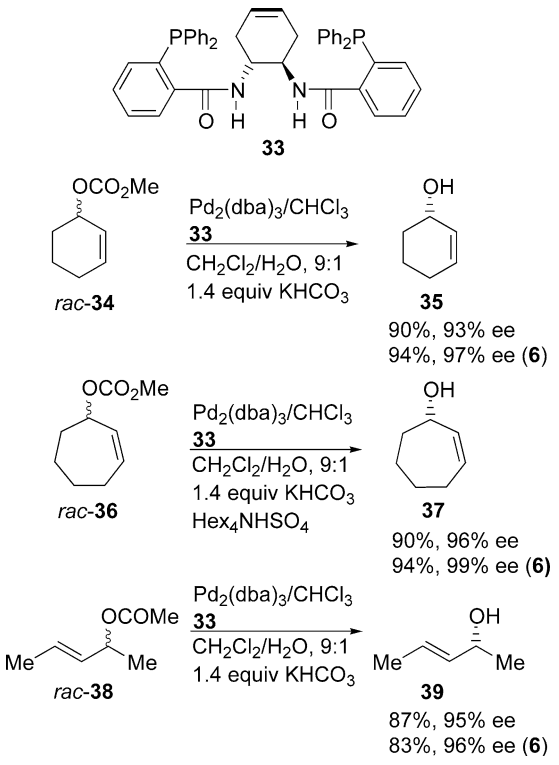
The synthetic utility of alcohol **27** is demonstrated by its conversion to ketone **32** (Scheme 8), the enantiomer of which is a key starting material in the asymmetric synthesis of prostaglandins.[22] Silyl protection of the



Scheme 7.



Scheme 8.



Scheme 9.

hydr- oxy group of **27** afforded the silyl ether **30** in 76% yield. Transesterification of carbonate **30** gave alcohol **31** in 87% yield. Finally, oxidation of **31** afforded ketone **32** in 85% yield.[23,24]

2.4. Investigation of the unsaturated ligand 33

The bisphosphane **33**[25] (Scheme 9) is an unsaturated analog of **6**, the potential of which for catalysis has not yet been explored. We were interested to apply **33** as a ligand in Pd-catalyzed allylic substitution in order to see whether the double bond interferes with the catalytic cycle perhaps leading to a different activity and selectivity of Pd(0)/**33** as compared to Pd(0)/**6**.

Treatment of the six-membered cyclic carbonate *rac*-**34** with 4 mol % of Pd(0)/**33** and 1.4 equiv of $KHCO_3$ in CH_2Cl_2/H_2O at room temperature furnished the alcohol **35** with 93% ee in 90% yield. The use of saturated ligand **6** in this transformation had given **35** with 97% ee.[7a] Similarly, reaction of the seven-membered cyclic carbonate *rac*-**36** afforded alcohol **37** with 96% ee in 90% yield: The analogous reaction in the presence of **6** had furnished **37** with 99% ee in 94% yield.[7a] Finally, the acyclic carbonate *rac*-**38** was tested. Its substitution afforded under similar conditions alcohol **39** with 95% ee in 87% yield, which in the case of **6** had been obtained with 96% ee in 83% yield.[7a,26,27]

3. Conclusion

The reaction of racemic allylic carbonates with HCO_3^-, water, and Pd(0)/**6** or Pd(0)/**33** allows a simple catalytic asymmetric synthesis of a number of synthetically interesting unsymmetrical and symmetrical allylic alcohols. The high enantioselectivity observed with some of the unsymmetrical racemic carbonates points to the operation of an efficient dynamic kinetic resolution featuring either an interconversion of the intermediate diastereomeric π-allyl-Pd complexes and/or a racemization of the substrate, which are faster than the highly selective substitution of the more reactive π-allyl-Pd complex.[28] Experiments with the unsaturated bisphosphane **33** showed it to have a similar selectivity and activity in Pd-catalyzed allylic substitution as its saturated analog **6**.

Acknowledgments

Financial support of this work by the Deutsche Forschungsgemeinschaft (SFB 380) is gratefully acknowledged.

References and notes

1. (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631; (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012; (c) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1–415; (d) Hanson, R. M. *Org. React.* **2002**, *60*, 1–156.
2. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000, pp 231–285; (b) Gais, H.-J.; Theil, F. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 2, pp 335–578; (c) Kim, M.-J.; Ahn, Y.; Park, J. *Cur. Opin. Biotechnol.* **2002**, *13*, 578–587; (d) Pámies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261; (e) Williams, M. J.; Allen, J. V. *Tetrahedron Lett.* **1996**, *37*, 1859; (f) Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8423–8424; (g) Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377–2379; (h) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.
3. (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73; (b) Itsuno, M. *Org. React.* **1998**, *52*, 395–576.
4. (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539.
5. (a) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320–10321; (b) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. *Chem. Soc. Rev.* **2002**, *31*, 223–229; (c) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Mehani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727–4742; (d) Faller, J. W.; Wilt, J. C. *Tetrahedron Lett.* **2004**, *45*, 7613–7616; (e) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867.
6. (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000, pp 593–649; (b) Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Martorell, A.; Dominguez, B.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure Appl. Chem.* **2004**, *76*, 589–601.
7. (a) Lüssem, B. J.; Gais, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6066–6067; (b) While formation of **5** should be irreversible that of **2** and **4** could be reversible.

8. Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobson, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 833–884.
9. (a) Grennberg, H.; Langer, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190–1192; (b) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863.
10. (a) Gais, H.-J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem. Eur. J.* **2003**, *9*, 4202–4221; (b) Lüssem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041–4052.
11. For one special example, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.
12. (a) Rowe, G. J.; Spilling, C. D. *J. Org. Chem.* **2003**, *68*, 9502–9505; (b) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406–9413; (c) Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, 4067–4076.
13. (a) Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *Chem. Eur. J.* **2003**, *9*, 2963–2968; (b) Onaran, M. B.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 8136–8141; (c) Ghanem, A.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 57–62.
14. (a) Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050–2058; (b) Enders, D.; Jandeleit, B.; von Berg, S.; Raabe, G.; Runsink, J. *Organometallics* **2001**, *20*, 4312–4332.
15. Carretero, J. C.; Dominguez, E. *J. Org. Chem.* **1992**, *57*, 3867–3873.
16. Tiecco, M.; Testaferri, L.; Marini, F.; Santi, C.; Bagnoli, L.; Temperine, A. *Tetrahedron: Asymmetry* **1999**, *10*, 747–757.
17. Attolini, M.; Iacazio, G.; Peiffer, G.; Maffei, M. *Tetrahedron Lett.* **2002**, *43*, 8547–8549.
18. (a) Fukazawa, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2323–2326; (b) Bertilsson, S. K.; Soedergren, M. J.; Andersson, P. G. *J. Org. Chem.* **2002**, *67*, 1567–1573; (c) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984–5986.
19. Takahashi, M.; Koike, R.; Ogasawara, K. *Chem. Pharm. Bull.* **1995**, *43*, 1585–1587.
20. Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539–2549.
21. Hydrolsis of **29** afforded the corresponding (3*R*,4*S*)-configured diol: Wang, Z. M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 6895–6897.
22. Noyori, R.; Suziki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876.
23. Myers, A. G.; Hammond, M.; Wu, Y. *Tetrahedron Lett.* **1996**, *37*, 3083–3086.
24. Access to *ent*-**32** is also provided because of the availability of *ent*-**6**.
25. Oppolzer, W.; Kuo, D. L.; Hutzinger, M. W.; Léger, R.; Durand, J.-O.; Leslie, C. *Tetrahedron Lett.* **1997**, *38*, 6213–6216.
26. Representative experimental procedure. A Schlenk flask was successively charged with argon, $Pd_2dba_3/CHCl_3$ (104 mg, 0.10 mmol), **6** (138 mg, 0.20 mmol) and degassed CH_2Cl_2 (45 mL). The solution was stirred at room temperature for 15 min and then degassed water (5 mL) and carbonate **26** (1.08 g, 5 mmol) were added. After the mixture was stirred at 4 °C for 48 h, it was poured in hexane/EtOAc, 1:1 (100 mL). The mixture was filtered through silica gel and the filtrate was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexane/EtOAc, 4:1) afforded alcohol **27** (687 mg, 87%) with 96% ee (GC, Hydrodex-β-6-TBDM), $[\alpha]_D^{21}$ −64.3 (*c* 5.0, CH_2Cl_2).
27. The ee-values and absolute configurations of the allylic alcohols were determined by GC on chiral columns and comparison of their optical rotations with the literature data, respectively.
28. Interestingly, treatment of *rac*-**16** with Pd(0)/(*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-oxazole afforded **17** (91%) with only 5% ee.