Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
ELSEVIER
Tetrahedron Letters 46 (2005) 3843–3846

Avoiding the classical resolution during the synthesis of MeO-BIPHEP and 3,3′-disubstituted derivatives

Evgueni Gorobets,[a] Bronwen M. M. Wheatley,[a] J. Matthew Hopkins,[a] Robert McDonald[b] and Brian A. Keay[a,*]

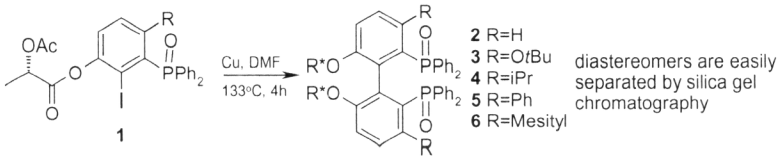
[a]*Department of Chemistry, University of Calgary, Calgary, AB, Canada T2N 1N4*
[b]*Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2*

Received 7 March 2005; revised 28 March 2005; accepted 28 March 2005
Available online 12 April 2005

Abstract—The Ullmann coupling of 1 (R = H) gives a 2:1 mixture of diastereomers 2 (R = H) in 81% yield that are easily separated by silica gel chromatography. This procedure avoids the generally cumbersome and sometimes difficult resolution step with DBTA. Similar Ullmann couplings and separation of the corresponding diastereomers are employed with other derivatives of 1 (R = O*t*Bu, *i*Pr, Ph, and mesityl) ultimately affording a new series of 3,3′-disubsituted-MeO-BIPHEP derivatives. The use of these new derivatives in palladium-catalyzed asymmetric Heck reaction, Pd-catalyzed polyene cyclizations and rhodium-catalyzed hydrogenations is also reported.

We recently reported the synthesis, resolution, and applications of a variety of 3,3′-disubstituted BIPHEP derivatives (3,3′ groups = OMe, O*i*Pr, OPiv, and OTolyl).[1] In order to compare their efficacy in asymmetric reactions with that of MeO-BIPHEP **11** (Scheme 2), we embarked on preparing **11** according to the procedure reported by Schmid et al.[2,3] but quickly found the resolution step with dibenzoyl-L-tartaric acid ((−)-DBTA) or di-*p*-toluoyl-L-tartaric acid ((−)-DTTA) to be cumbersome. Since then, we have experienced similar resolution problems with some of our newer 3,3′-disubstituted MeO-BIPHEP derivatives **3–6** (3,3′ groups = O*t*Bu, *i*Pr, Ph,[4] and mesityl) and thus embarked on designing a new synthesis of MeO-BIPHEP **11** that would alleviate the need for a classical resolution step. Herein we report our new synthetic strategy toward the preparation of phosphine oxides **2–6** that involved the attachment of a substrate bound chiral auxiliary to a suitable Ullmann precursor (i.e., **1**) (Scheme 1), so that upon affecting an Ullmann coupling diastereomers would be formed that could be easily separated by column chromatography.[5] In addition, the corresponding phosphines of **3–6** are used in some asymmetric transformations.

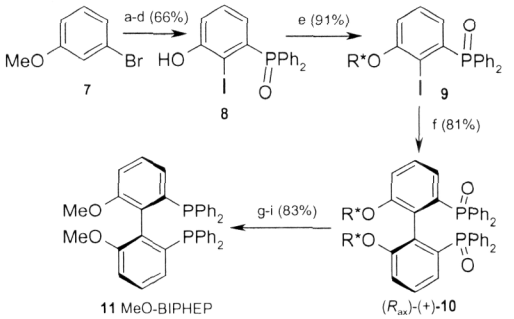
We started by redesigning the synthesis toward MeO-BIPHEP (Scheme 2) to allow for the incorporation of a chiral auxiliary prior to the Ullmann coupling.



Scheme 1.

Keywords: Ullmann coupling; BIPHEP derivatives.
* Corresponding author. Tel.: +1 403 220 5340; fax: +1 403 284 1372; e-mail: keay@ucalgary.ca

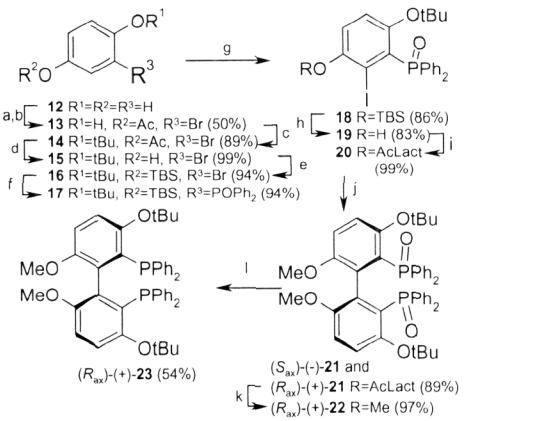
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.183



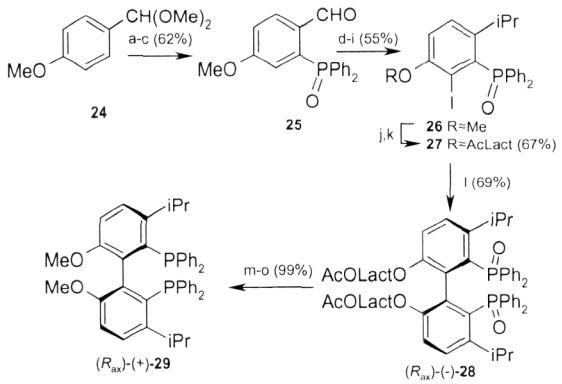
Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 1 h, then Ph_2PCl, −78 °C to rt, 2 h; (b) H_2O_2, MeOH, rt, 0.5 h (93% two steps); (c) LDA, THF, −78 °C, 1.5 h; then I_2, THF, −78 °C to rt, 1 h (76%); (d) BBr_3, DCM, rt, 12 h (93%); (e) (*S*)-2-acetoxypropanoyl chloride, TEA, DCM, rt, 1 h (91%); (f) Cu powder, DMF, 150 °C, 3 h; separation of diastereomers by silica gel chromatography (76% both diastereomers); (g) KOH, EtOH, rt, 0.5 h; (h) MeI, DCM, H_2O, Adogen, rt, 24 h (94% two steps); (i) Cl_3SiH, *n*-Bu_3N, xylene, 145 °C, 24 h (89%).

Halogen–metal exchange of bromide **7** with *n*-BuLi followed by the addition of $ClPPh_2$[6] and H_2O_2[7] gave a phosphine oxide that when treated with LDA at −78 °C in THF followed by iodine gave **8** after removal of the methyl group with BBr_3. Reaction of **8** with (*S*)-2-acetoxypropanoyl chloride[8] gave **9**, which was subjected to an Ullmann coupling[9] to give a 33% de in favor of diastereomer (R_{ax})-(+)-**10**. The diastereomers were easily separated by silica gel chromatography, with the diastereomer with the S_{ax} configuration always having the larger R_f. Removal of the chiral auxiliary (KOH, EtOH), methylation (MeI, Adogen), and trichlorosilane reduction[10] of the phosphine oxides provided MeO-BIPHEP **11**. Although the sequence is two steps longer than the original, a resolution step was not necessary and the diastereomers from the Ullmann coupling were easily separated.

The diastereomeric Ullmann coupling strategy was applied to the synthesis of ligands **23**, **29**, and **34**. Compound (+)-**23** was prepared in twelve steps from hydroquinone **12** as outlined in Scheme 3. The Ullmann coupling of **20** provided a 24% de in favor of (R_{ax})-(+)-**21**. The diastereomers of **21** were separated and the R_{ax}-isomer carried on to compound (R_{ax})-(+)-**23**.[11] Compound (+)-**29** was prepared in 15 steps from **24** (Scheme 4). Ullmann coupling of **27** again gave a 3:2 mixture of (R_{ax})-**28** and (S_{ax})-**28** that were easily separated by column chromatography. Finally, Ullmann coupling of **32** gave a 1:1.3 mixture of diastereomers **33** (Scheme 5) that was eventually converted into compound (R_{ax})-**34** in 12 steps from 2-bromo-4-methoxyaniline (**30**).[12] The same sequence outlined in Scheme 5 was used to prepare the 3,3′-dimesitylene compound **35**. Removal of the chiral auxiliary from (+)-**35** and methylation gave (−)-**36**. Reduction of (−)-**36** with Cl_3SiH resulted in the reduction of only one of the two phosphine oxides in 25% yield (75% unreacted (−)-**36**). Changing the reaction conditions never afforded the desired bis-phosphine. Interestingly, treatment of (−)-**36** with alane unexpectedly gave compound **37**.

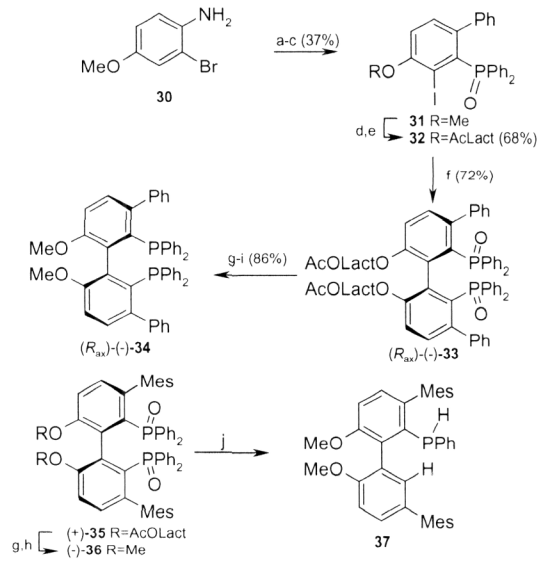


Scheme 3. Reagents and conditions: (a) Ac_2O, AcOH, rt, 1 h; (b) Br_2, $CHCl_3$, 0 °C, 1 h; (c) 2-methyl-propene, DCM, TfOH, −78 °C, 4 h; (d) KOH, EtOH, rt, 15 min; (e) TBSCl, imid, DMC, rt, 1 h; (f) *n*-BuLi, THF, −78 °C, 1 h; then Ph_2PCl, 2 h; then H_2O_2, MeOH, 0 °C, 20 min; (g) LDA, THF, −78 °C, 1.5 h; then I_2, −78 °C to rt, 1.5 h; (h) TBAF, THF, rt, 15 min; (i) (*R*)-2-acetoxypropanoyl chloride, DCM, TEA, DMAP, 0 °C, 30 min; (j) Cu, DMF, 150 °C, 6 h; separation of diastereomers by silica gel chromatography (89% for both diastereomers); (k) KOH, EtOH, rt, 30 min; then MeI, DCM, Adogen, rt, 12 h; (l) $HSiCl_3$, xylene, 105 °C, 24 h.



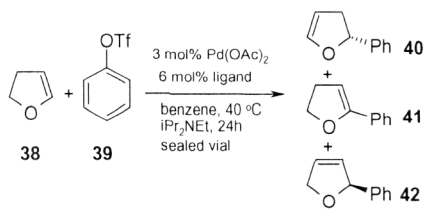
Scheme 4. Reagents and conditions: (a) *t*-BuLi, Et_2O, −25 °C, 3 h, then Ph_2PCl, −78 °C to rt, 12 h; (b) H_2O_2, MeOH, rt, 1 h (68% two steps); (c) *p*TsOH, acetone, rt, 1.5 h (91%); (d) MeMgBr, THF, 5 °C, 1 h; (e) MnO_2, acetone, rt, 36 h; (f) MeMgBr, THF, rt, 1 h; (g) Ac_2O, 120 °C, 24 h; (h) H_2, Pt_2O, 1 atm, rt, 6 h; (i) LDA, THF, −78 °C, 1.5 h; then I_2, THF, −78 °C to rt, 2 h (55% six steps); (j) BBr_3, DCM, rt, 20 h (93%); (k) (*S*)-2-acetoxypropanoyl chloride, TEA, DCM, rt, 1 h (67% two steps); (l) Cu powder, DMF, 133 °C, 4 h; separation of diastereomers by silica gel chromatography (69% both diastereomers); (m) KOH, EtOH, rt, 1 h; (n) MeI, DCM, H_2O, Adogen, rt, 48 h; (o) Cl_3SiH, *n*-Bu_3N, xylene, 135 °C, 48 h (99% three steps).

With (+)-(*R*)-**23**, (+)-(*R*)-**29**, and (−)-(*R*)-**34** in hand, we compared the efficacy of these ligands in the asymmetric Heck arylation of 2,3-dihydrofuran and compared the results to those obtained with (+)-MeO-BIPHEP (**11**, Table 1). (+)-MeO-BIPHEP **11** provided 65% conversion to products and gave 92% ee of **40**, 63% ee of **42** along with a small amount of the conjugated product **41** (Table 1, entry 1). The ratio of **40**:**41**:**42** was 83:7:10. The best result was with the 3,3′-di-O*t*Bu



Scheme 5. Reagents and conditions: (a) n-$C_5H_{11}ONO$, benzene (or mesitylene), reflux, 1.5 h (52%); (b) n-BuLi, THF, −78 °C, 3 h, then Ph_2PCl, −78 °C to rt, 12 h; then H_2O_2, MeOH, rt, 1 h (91%); (c) LDA, THF, −78 °C, 1.5 h; then I_2, THF, −78 °C to rt, 2 h (78%); (d) BBr_3, DCM, rt, 20 h (93%); (e) (*S*)-2-acetoxypropanoyl chloride, TEA, DCM, rt, 1 h (72%); (f) Cu powder, DMF, 145 °C, 4 h; separation of diastereomers by silica gel chromatography (72% both diastereomers); (g) KOH, EtOH, rt, 1 h; (h) MeI, DCM, H_2O, Adogen, rt, 48 h; (i) Cl_3SiH, n-Bu_3N, xylene, 135 °C, 48 h (93% three steps); (j) alane, THF, reflux, 3 h (78%).

Table 1. Asymmetric Heck results with ligands **11**, **23**, **29**, and **34**



	Ligand	% Conversion	Ratio of products		
			40 (% ee)	**41**	**42** (% ee)
1	(+)-(*R*)-**11**	65	83 (92)	7	10 (63)
2	(+)-(*R*)-**23**	100	96 (89)	0	4 (11)[a]
3	(+)-(*R*)-**29**	12	66 (51)	0	34 (25)
4	(−)-(*R*)-**34**	14	99 (>99)	0	1 (>99)[a]
5	(−)-(*R*)-**34**	60	99 (>99)	0	1 (>99)[a,b]
6	(*R*)-BINAP	41	91 (81)	0	9 (61)[c]

[a] The major enantiomer of **42** had the *R*-configuration.
[b] 10 mol % $Pd(OAc)_2$, 20 mol % (−)-(*R*)-**34**.
[c] Results reported by Hayashi and co-workers.[13]

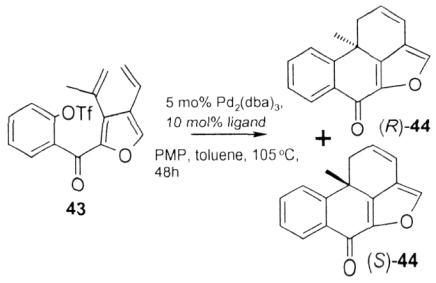
bisphosphine **23** (entry 2). The conversion to products was 100% with **40** formed in 96% yield with 89% ee. Ligand **23** well outperformed (+)-(*R*)-BINAP in % conversion, ratio of **40**:**42** and in % ee of **40**.[13] Both the 3,3′-di-*i*Pr derivative **29** (entry 29) and 3,3′-di-Ph derivative **34** (entry 4) gave poor conversions at 3 mol % Pd loading (12% and 14%, respectively);[14] however, when the Pd loading was increased to 10 mol % with ligand **34**, the conversion increased to 60% in a 24 h period. It is noteworthy that **34** gave **40** not only with a 99% ee but also with an excellent **40**:**42** ratio of 99:1 (entries 4 and 5). This is the highest % ee and product ratio observed to date in our laboratory using a variety of chiral catalysts.[1,15] Work is continuing to improve the % conversion with (−)-(*R*)-**34**.

Ligands (+)-(*R*)-**23**, (+)-(*R*)-**29**, and (−)-(*R*)-**34** were then used in the palladium catalyzed polyene cyclization (**43** → **44**) and compared to the results obtained with (+)-(*R*)-MeO-BIPHEP (**11**, Table 2). (+)-(*R*)-MeO-BIPHEP (**11**) afforded (*R*)-**44** in 72% ee (53% yield). The use of the 3,3′-di-O-*t*Bu ligand (+)-(*R*)-**23** gave a comparable yield and slightly lower % ee than with **11**; however, the absolute stereochemistry of the major enantiomer was opposite of that obtained with (+)-(*R*)-**11**. This result is in line with the results obtained with other 3,3′-diOR BIPHEP derivatives reported previously.[1]

3,3′-Di-Ph-BIPHEP derivative (−)-(*R*)-**34** gave a low 53% yield and disappointing 24% ee. In this case, the major enantiomer had the *R*-configuration, which was in line with that obtained using (+)-(*R*)-**11**. Finally, (+)-(*R*)-**29** gave (*R*)-**44** in excellent yield (83%) and with an 80% ee. This is the highest % ee we have observed in this reaction to date.[1,16]

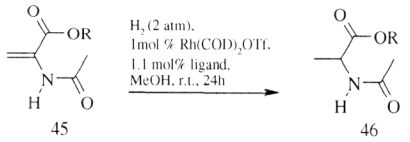
Ligands (+)-(*R*)-**23**, (+)-(*R*)-**29**, and (−)-(*R*)-**34** were then used in catalytic hydrogenations of acid **45** (R = H) and ester **45** (R = Me) and compared to results obtained with MeO-BIPHEP **11** (Table 3).[17] While (+)-(*R*)-MeO-BIPHEP **11** performed poorly in the hydrogenation of **45** (entry 1) an improvement was observed with ligand (+)-(*R*)-**29**. A lower % ee upon using (+)-(*R*)-**29** with acid **45** (R = H) was surprising given the excellent results with other ligands; repeating the reaction did not change the % ee. The best results were seen with ligands (+)-(*R*)-**23** and (−)-(*R*)-**34** with the latter giving the best results on hydrogenation with both the acid and ester of **45**.

Table 2. Asymmetric Pd-catalyzed polyene cyclization results with ligands **11**, **23**, **29**, and **34**



	Catalyst	% Yield	Ratio of enantiomers		% ee
			(*R*)-**44**	(*S*)-**44**	
1	(+)-(*R*)-**11**	53	**86**	14	72
2	(+)-(*R*)-**23**	56	19	**81**	62
3	(+)-(*R*)-**29**	83	**90**	10	80
4	(−)-(*R*)-**34**	53	**62**	38	24

Table 3. Asymmetric hydrogenation results with ligands **11**, **23**, **29**, and **34**



45 46

	Catalyst	R	% Conversion	% ee (config)
1	(+)-(*R*)-**11**	Me	100	25.6 (*R*)
		H	100	19.5 (*R*)
2	(+)-(*R*)-**23**	Me	100	94.6 (*R*)
		H	100	97.7 (*R*)
3	(+)-(*R*)-**29**	Me	100	80.6 (*R*)
		H	100	37.1 (*R*[a])
4	(−)-(*R*)-**34**	Me	100	98.5 (*R*)
		H	77	96.8 (*R*)

[a] Reaction attempted twice.

We have shown that a diastereoselective Ullmann coupling using a (+)-2-acetoxypropanoyl group as the chiral auxiliary provides biaryl systems that are easily separated by silica gel chromatography, thereby avoiding the generally cumbersome and sometimes difficult resolution step with (L)-DBTA. Interestingly, ligands (+)-(*R*)-**23**, (+)-(*R*)-**29**, and (−)-(*R*)-**34** each gave the best % ee's in the Hayashi Heck reaction, palladium-catalyzed polyene cyclization and catalytic hydrogenation of **45**, respectively, indicating that one specific 3,3-disubstituted BIPHEP ligand is not ideal for all asymmetric transformations. Work is continuing to shorten the synthetic routes to 3,3′-disubsituted BIPHEP derivatives and applying these ligands in other asymmetric reactions.

Acknowledgements

We thank Merck Frosst (Pointe Claire, PQ), NSERC CRD program, and the University of Calgary for financial support. In addition NSERC and the Alberta Ingenuity Fund are thanked for postgraduate scholarships (for B.M.M.W. and J.M.H.).

Supplementary data

Experimental procedures for the diastereoselective Ullmann coupling of **9**, **20**, **27**, and **32** are provided. The X-ray crystal structure of **37** is also provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.183.

References and notes

1. Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597–3601.
2. (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schonholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897; (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370–389.
3. Another reason for preparing **11** is its high cost from Aldrich Chemical Co. 2005–06 price = $0.86/mg ($Cdn).
4. (a) The synthesis of 3,3′-diphenyl MeO-BIPHEP was recently reported by Zhang and co-workers and involved a resolution step with (L)-DTTA: Wu, S.; He, Minsheng; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2177–2180; (b) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695; (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069.
5. We were not concerned about achieving high diastereoselectivity in the Ullmann coupling as both enantiomers of the various BIPHEP derivatives were required for application purposes.
6. Hall, T. J.; Hargis, J. H. *J. Org. Chem.* **1986**, *51*, 4185–4189.
7. Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694.
8. (*S*)-2-Acetoxypropanoyl chloride is available from Aldrich.
9. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
10. Takaya, H.; Mashima, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629–635.
11. The lower yield of 54% was due to loss of some of the *t*-butyl group in the presence of Cl_3SiH at 105 °C.
12. Ishibashi, H.; Kobayashi, T.; Machida, N.; Tamura, O. *Tetrahedron* **2000**, *56*, 1469–1473.
13. (a) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188; (b) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
14. Stirring the reaction longer did not increase the % conversion. We are continuing to investigate why the reaction appears to stall with ligands **29** and **34**.
15. Andersen, N. G. Ph.D. Dissertation, University of Calgary, 2000.
16. (a) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605–607; (b) Lau, S. Y. W.; Andersen, N. G.; Keay, B. A. *Org. Lett.* **2001**, *3*, 181–184; (c) Che, D.; Andersen, N. G.; Lau, S. Y. W.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1919–1925; (d) Andersen, N. G.; McDonald, R.; Keay, B. A. *Tetrahedron: Asymmetry* **2001**, *12*, 263–269; (e) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766–10773; (f) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S.; Nieman, J. A. *Can. J. Chem.* **1997**, *75*, 1163–1171.
17. Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489–3496.