Chiral N,P Ligands

Synthesis of Versatile Chiral N,P Ligands Derived from Pyridine and Quinoline**

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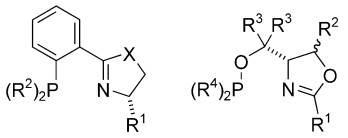
Chiral phosphanyl oxazolines **1** (PHOX)[1] and related compounds such as **2**[2] and **3**[3] have established themselves as highly versatile, readily accessible ligands for controlling the stereochemistry of metal-catalyzed reactions. The success of



1 X = O
2 X = NR

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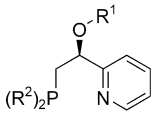

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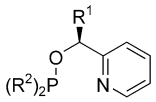

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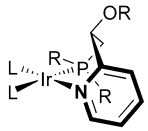

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these ligands in the Ir-catalyzed hydrogenation of olefins[2–4] and imines,[5] and the intention to mimic the coordination sphere of Crabtree's catalyst ($[(Cy_3P)(pyridine)Ir(cod)]PF_6$)[6] (Cy = cyclohexyl, cod = 1,5-cyclooctadiene) with a chiral bidentate ligand, motivated us to prepare chiral pyridyl phosphanes having the general structure **4**.[7] On the basis of simple force-field calculations carried out with a fixed standard geometry for the P-Ir-N core and the known propensity of 2-(oxymethyl)pyridines to adopt an antiperiplanar conformation of the N-C-C-O fragment,[8] we anticipated that these ligands would form a rigid chelate ring in a

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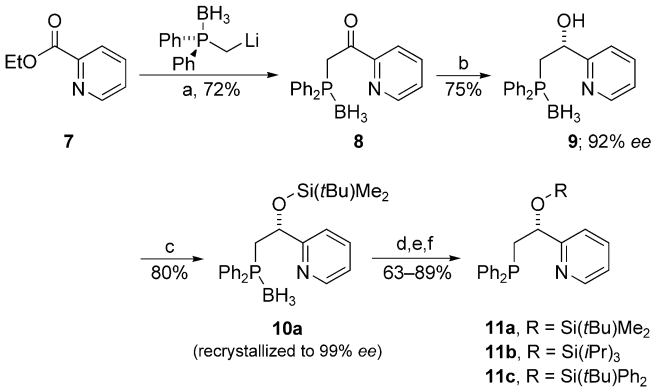
[**] Financial support for this work from the American and Swiss National Science Foundations is gratefully acknowledged. N.Z. thanks the Fonds der Chemischen Industrie for a Kekulé fellowship. The authors kindly thank Dr. Thomas Lectka (The Johns Hopkins University) for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200352755

boat conformation (**6**), thus generating a similar steric environment around the Ir atom as the PHOX ligands. However, as oxazoline and pyridine ligands are expected to have different electronic effects on a coordinated metal, we thought that pyridine-derived ligands, such as **4**, could induce new patterns of reactivity and selectivity. We report here the synthesis and application of a series of pyridyl phosphanes **4** along with the analogous quinoline derivatives and pyridyl phosphinites **5**.

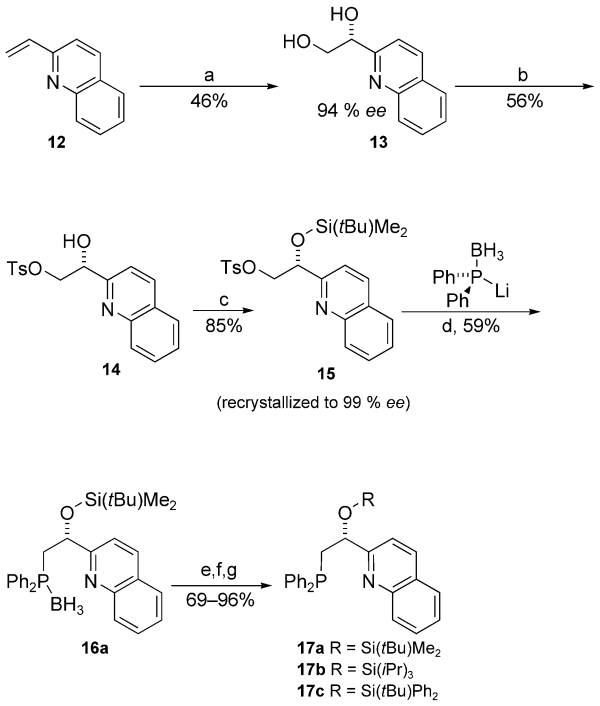
We felt that the ready availability of all starting materials was of utmost importance. With this in mind, we chose ethyl picolinate (**7**) as an appropriate entry point (Scheme 1). This



Scheme 1. Synthesis of pyridyl phosphanes **11a–c**. a) $Ph_2PCH_3{\cdot}BH_3$ (1 equiv), TMEDA (1.1 equiv), *s*BuLi (1.1 equiv), −78 °C, 2 h, then **7** (1.1 equiv), −78 °C to RT, 18 h; b) (−)-Ipc_2BCl (2.5 equiv), THF, 0 °C, 19 h; c) *t*$BuMe_2SiOTf$ (1.4 equiv), 2,6-lutidine, CH_2Cl_2, RT, 2 h, (after recrystallization, 59%); d) $(Bu_4N)F$ (2 equiv), THF, RT, 4 h, 99%; e) $(iPr)_3SiOTf$ (1.4 equiv), 2,6-lutidine, CH_2Cl_2, RT, 18 h, 94%; or *t*$BuPh_2SiCl$ (1.25 equiv), imidazole (4.3 equiv), CH_2Cl_2, 80%; f) diethylamine, RT, 12 h, **11a** (63%), **11b** (81%), **11c** (89%). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Tf = trifluoromethanesulfonyl.

was readily alkylated by lithiated BH_3-protected methyldiphenylphosphane to yield ketone **8**.[9] This material could be reduced to **9** by (−)-chlorodiisopinocampheyl borane [(−)-Ipc_2BCl],[10] in good yield and high enantioselectivity. As this product is an oil, we directly carried it forward in hopes of recrystallizing a later intermediate. We capped the benzyl alcohol by straightforward protection with *t*$BuMe_2SiOTf$ to provide **10a**, in which the ethereal oxygen atom has been rendered noncoordinating. As this material could be obtained enantiomerically pure after recrystallization, it was chosen as the common intermediate for the construction of all other analogues. At this point, it was unclear what role the silane might play during catalysis. To gain insight, we cleaved the silyl group and reprotected the alcohol with either $(iPr)_3SiOTf$ (**10b**) or *t*$BuPh_2SiCl$ (**10c**). Finally, the free phosphanes **11a–c** were obtained by stirring the corresponding boranes in diethylamine overnight, and filtering the reaction mixture through silica gel.[11]

To increase the steric bulk of the coordinating N-heterocycle, we wanted to replace the pyridine ring by a quinoline unit. However, the enantioselective reduction of the quinoline analogue of **8** with Ipc_2BCl was sluggish and gave only 70% *ee*. Therefore, an alternative route based on the Sharpless dihydroxylation[12] of 2-vinylquinoline[13] (**12**) was devised (Scheme 2).



Scheme 2. Synthesis of quinolyl phosphanes **17a–c**. a) $K_2OsO_4{\cdot}H_2O$ (1 mol%), $(DHQD)_2PHAL$ (1 mol%), $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (3 equiv), *t*$BuOH/H_2O$ (1:1), 0 °C to RT; b) TsCl (1 equiv), pyridine, −10 °C, 4 h; c) *t*$BuMe_2SiCl$ (1.3 equiv), imidazole (2.5 equiv), CH_2Cl_2, RT, 5 h, (after recrystallization, 74%); d) $Ph_2PH{\cdot}BH_3$ (1.2 equiv), *n*BuLi (1.2 equiv), THF, −78 °C to 0 °C, 1 h, then **15**, THF/DMF (3:2), RT, 24 h; e) $(Bu_4N)F$ (2 equiv), THF, RT, 4 h, 99%; f) $(iPr)_3SiOTf$ (1.4 equiv), 2,6-lutidine, CH_2Cl_2, RT, 18 h, 99%; or *t*$BuPh_2SiCl$ (1.25 equiv), imidazole (4.3 equiv), CH_2Cl_2, 79%; g) diethylamine, RT, 12 h, **17a** (69%), **17b** (86%), **17c** (96%). $(DHQD)_2PHAL$ = hydroquinidine-1,4-phthalazinediyl diether, Ts = toluene-4-sulfonyl.

The oxidation of **12** reproduciblity provided diol **13** in acceptable yield and high *ee* value on a multigram scale (46%, 94% *ee*).[14] Selective tosylation of the primary alcohol, followed by silylation provided enantiomerically pure **15** after recrystallization from ethyl acetate/hexanes. Sulfonate displacement by $LiPPh_2{\cdot}BH_3$ gave the protected ligand **16a**. At this point, the overall diversity of the ligand set can be expanded by judicious choice of nucleophile, and we have obtained similar results with di-*o*-tolyl, di-*m*-xylyl, and dicyclohexylphosphane–borane complexes.[15] As outlined for the pyridyl phosphanes, the free ligands **17a–c** were obtained by exchange of the silyl group and deborination.

Cationic Ir complexes were made from *N*-heteroaryl phosphanes **11a–c** and **17a–c**. Heating a dichloromethane solution of the appropriate ligand in the presence of 0.5 equivalent of $[Ir(cod)Cl]_2$ for 2 h followed by counterion exchange with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$)[16] (1.6 equiv), in the presence of water,

provided the complexes as orange solids. These are generally air and moisture stable, as well as being amenable to chromatography on silica gel (dichloromethane/pentanes).[17]

We were able to obtain crystals of (*S*)-**19a** suitable for X-ray analysis.[18] The crystal structure confirmed the absolute configuration originally assigned to ligands **17a–c** and **11a–c**, based on heuristic rules for Ipc_2BCl reduction[10] and asymmetric dihydroxylation.[12] It also showed the expected boat conformation of the chelate ring (see structure **6**). We also determined the crystal structures of racemic PF_6^- analogues of **19b** and **19c**,[18] which show a much higher tendency to crystallize than the corresponding enantiomerically pure BAr_F salts. The chelate ring and the silyloxy groups in these two complexes, and in complex (*S*)-**19a**, adopt virtually the same geometry. The chiral equatorial/axial arrangement of the two *P*-phenyl groups is very similar to that found in Ir–PHOX complexes (see Figure 1).[5] Moreover, space-filling models show that the quinoline and the isopropyloxazoline moieties occupy similar regions in space. The striking similarity between the chiral coordination spheres in the quinolyl phosphane and PHOX complexes suggests that, although the ligand structures are distinctly different, they should allow comparable levels of enantiocontrol.

In the three crystal structures mentioned above, the silyl groups are bent toward the coordination sphere. As shown in Figure 1, one of the Si-phenyl groups is located above the Ir atom (distance between the essentially parallel Ph and P-Ir-N planes ca. 3.7 Å), close enough to interact with the active

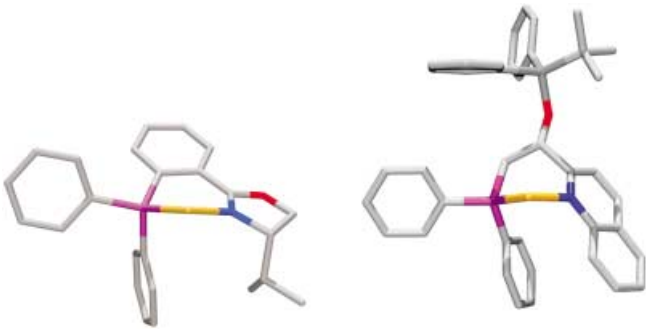
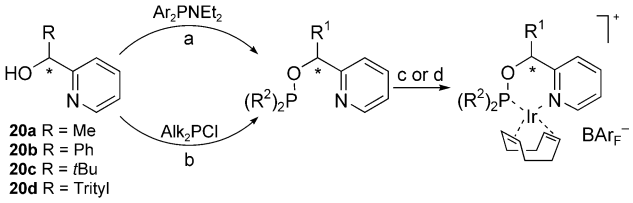


Figure 1. Comparison of [Ir(**1**)(cod)]PF_6 (R^1 = *i*Pr, R^2 = Ph) and the PF_6^- analogue of *rac*-**19c**. Hydrogen atoms, cod, and PF_6^- ions in both structures have been omitted for clarity.

site of the catalyst. Therefore, it is not surprising that in catalytic studies the enantioselectivity was found to depend on the structure of the silyl group (see below).

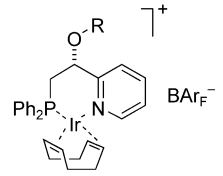
The success with phosphinite ligands **3**[3] prompted us to replace the R_2PCH_2 fragment in ligands **4** by a R_2PO group (Scheme 3). The requisite alcohols were readily prepared by reduction of commercially available ketones (**20a**, **b**) with sodium borohydride or alkylating the appropriate aldehyde with 2-lithiopyridine (**20c**, **d**). By this route, a diverse set of ligands with many different R groups, ranging from simple methyl to colossal trityl, could be readily prepared. The racemic alcohols were then resolved into their component enantiomers by chiral HPLC (see Supporting Information).[19] To our surprise, all attempts to react chlorodiarylphosphanes with pyridyl alkoxides were unsuccessful. However, *N*,*N*-diethylaminodiaryl phosphanes in the presence of acidic heterocycle salts[20] led to the desired phosphinites in all but



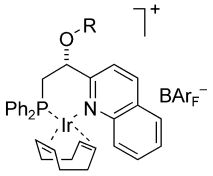
21a R^1 = Me, R^2 = Ph, (*S*), 71%
21b R^1 = Me, R^2 = *o*Tol, (*S*), 65%
21c R^1 = Ph, R^2 = Ph, (*R*), 67%
21d R^1 = Ph, R^2 = *o*Tol, (*S*), 70%
21e R^1 = Ph, R^2 = Cy, (*S*), 65%
21f R^1 = Ph, R^2 = *t*Bu, (*R*), 58%
21g R^1 = *t*Bu, R^2 = Ph, (*S*), 78%
21h R^1 = *t*Bu, R^2 = *o*Tol, (*R*), 90%
21i R^1 = *t*Bu, R^2 = Cy, (*S*), 86%
21j R^1 = *t*Bu, R^2 = *t*Bu, (*S*), 79%
21k R^1 = Trityl, R^2 = Ph, (*R*), 95%

Scheme 3. Synthesis of pyridyl phosphinite complexes **21a–k**. a) Ar_2PNEt_2/4,5-dichloroimidazole/triethylamine (1:1:1; 1.5—3.0 equiv), CH_2Cl_2, RT, 1–3 d; b) Alk_2PCl (1 equiv), KH (1.1 equiv), Et_2O/DMF (9:1), 0 °C to RT, 18 h; c) $[Ir(cod)Cl]_2$ (0.5 equiv), CH_2Cl_2, 50 °C, 2 h, then $NaBAr_F$ (1.5 equiv), 50 °C, 30 min; d) $[Ir(cod)Cl]_2$ (0.5 equiv), CH_2Cl_2, 0–50 °C, 2 h, then $NaBAr_F$ (1.5 equiv), 50 °C, 30 min.

the most congested systems.[21] The products were then isolated by column chromatography, under argon, in greater than 97% purity (^{31}P NMR). In contrast to their aryl conjoiners, dialkyl chlorophosphanes readily react with pyridyl alkoxides. The instability of the resultant phosphinites meant that it was imperative to carefully control reagent stoichiometry, and when this was done simple filtration of the reaction mixture through degassed silica provided >90% pure material. The corresponding Ir complexes were made by a slightly modified procedure, because of the higher ligand sensitivity. Again, the resultant complexes are stable red to orange solids that can be purified by chromatography or crystallization.



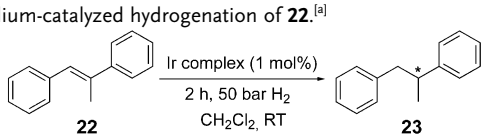
18a R = Si(*t*Bu)Me_2
18b R = Si(*i*Pr)$_3$
18c R = Si(*t*Bu)Ph_2



19a R = Si(*t*Bu)Me_2
19b R = Si(*i*Pr)$_3$
19c R = Si(*t*Bu)Ph_2

The iridium complexes synthesized above were used to hydrogenate several representative alkenes. The efficacy of the complexes in the hydrogenation of *trans*-α-methylstilbene (**22**) are summarized in Table 1. In general, the phosphinites are superior in terms of both enantioselectivity and conversion. In the case of the pyridyl phosphanes (**18a–c**) the nature of the silane seems to play a disproportionately large role. This can be rationalized in light of the crystal structures discussed above. High enantioselectivity was also obtained with other substrates such as monoaryl alkenes **24** and **25**,

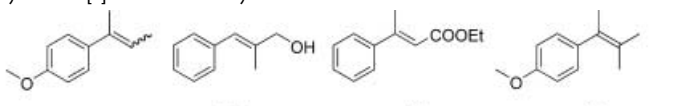
Table 1: Iridium-catalyzed hydrogenation of **22**.[a]



(1)

Catalyst	Configuration	Conv. (%)[b]	*ee* (%)[c]
18a	*R*	93	88 (*R*)
18b	*R*	>99	57 (*R*)
18c	*R*	>99	4 (*R*)
19a	*R*	80	45 (*R*)
19b	*R*	92	45 (*R*)
19c	*R*	69	56 (*R*)
21a	*S*	>99	90 (*S*)
21b	*S*	>99	93 (*S*)
21c	*R*	>99	94 (*R*)
21d	*S*	>99	95 (*S*)
21e	*S*	>99	87 (*S*)
21f	*R*	>99	96 (*R*)
21g	*S*	>99	90 (*S*)
21h	*R*	>99	96 (*R*)
21i	*S*	>99	96 (*S*)
21j	*S*	>99	97 (*S*)
21k	*R*	44	38 (*R*)

[a] Conditions: see Equation (1); experimental procedures: see Ref. [3]. [b] Determined by GC.[3] [c] Determined by HPLC.[3]

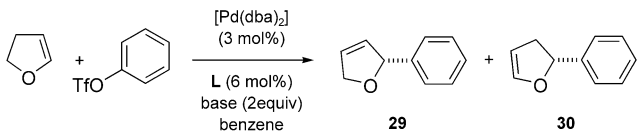


(*E*)-**24**; (*Z*)-**25** **26** **27** **28**

24: **21c**; 87% *ee*, >99% **21h**; 96% *ee*, >99% **21f**; 95% *ee*, >99% **21j**; 81% *ee*, >99%
25: **21c**; 90% *ee*, >99%

allylic alcohol **26**, and ethyl 2-methylcinnamate **27**. Of particular note is the tetrasubstituted alkene **28**, a substrate that gives low conversion and poor enantioselectivity with most catalysts. Overall, the complexes rival the best catalysts developed so far, and in some cases match the highest reported *ee* values.

To further demonstrate the generality and utility of N-heteroaryl phosphanes and phosphinites we tested the ligands as catalyst precursors for several palladium-catalyzed processes. While the phosphinites formed rather unselective complexes in this regard, the phosphanes proved to be far superior, especially in the enantioselective Heck reaction (Scheme 4). While the product mixtures contain slightly more of isomer **30** than when PHOX complexes are used, the enantiomeric excess equaled the highest reported values.[22]



L = **11a** (proton sponge, 60 °C, 3 days): 87% *ee* (**29**), **29/30** = 97:3, 97% conv.
L = **11b** (EtN*i*Pr$_2$, 60 °C, 3 days): 92% *ee* (**29**), **29/30** = 98:2, 83% conv.
L = **17a** (EtN*i*Pr$_2$, 50 °C, 2 days): 97% *ee* (**29**), **29/30** = 83:17, 100% conv.
L = **17b** (proton sponge, 50 °C, 2 days): 99% *ee* (**29**), **29/30** = 95:5, 48% conv.

Scheme 4. Enantioselective Heck reaction. dba = *trans*,*trans*-dibenzylideneacetone, proton sponge = 1,8-bis(dimethylamino)naphthalene.

The results presented indicate considerable potential for these structurally simple and readily available heteroaryl phosphanes and phosphinites. Their modular nature, which enables easy tuning of steric and electronic properties, suggests that these ligands should be widely applicable in asymmetric catalysis.

Received: September 1, 2003 [Z52755]

Keywords: asymmetric catalysis · Heck reaction · hydrogenation · ligand design · N,P ligands

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[17] For long-term storage (> 2 weeks), complexes were kept under argon at −25 °C.

[18] CCDC-217683 (**19a**), CCDC-218218 (*rac*-**19b**), CCDC-218219 (*rac*-**19c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). *rac*-**19c**: crystallized from CH_2Cl_2/Et_2O, $C_{47}H_{50}F_6Ir_1N_1O_1P_2Si_1$, $M_r = 1041.16$, orange block $0.20 \times 0.22 \times 0.24$ mm, triclinic, space group $P\bar{1}11$, $a = 10.9930(8)$, $b = 12.8619(7)$, $c = 15.8814(12)$ Å, $\alpha = 98.936(9)$, $\beta = 104.955(6)$, $\gamma = 95.555(7)°$, $V = 2120.9(3)$ Å^3, $\rho_{calcd} = 1.630$ g cm^{-3}, $\mu = 3.316$ mm^{-1}, $F(000) = 1044.000$, $Z = 2$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, graphite monochromator), $T = 173$ K, Θ scan range $3.168 < \Theta < 33.000°$. 108123 reflections collected ($\pm h$, $\pm k$, $\pm l$), 15971 independent reflections, 12910 observed reflections [$I > 3\sigma(I)$], 532 refined parameters. $R = 0.0345$, $Rw = 0.0242$, max. residual electron density −2.55(3.06) e$^-$ Å^{-3}, located near the metal center. There were no restraints applied. Hydrogen atoms were calculated and refined as riding atoms. Data collection was performed with a Kappa CCD diffractometer. Programs used: structure solution: SIR79 (A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. Grazia, G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115), structure refinement: CRYSTALS (D. J. Watkin, *Crystals*, *Issue 11*, Chemical Crystallography Laboratory, Oxford, **2001**), weighting scheme: Chebychev polynomial (J. R. Carruthers, D. J. Watkin, *Acta Crystallogr. Sect. A* **1979**, *35*, 698). We thank Markus Neuburger for assistance in solving the crystal structures of *rac*-**19b** and *rac*-**19c**.

[19] While we have chosen to separate the enantiomers on expediency grounds, this is by no means necessary as enantioselective routes to all but one are known. **20a**: a) B. Lipshutz, L. Asher, K. Noson, *Org. Lett.* **2002**, *4*, 4045; b) R. Seemayer, M. P. Schneider, *Tetrahedron: Asymmetry* **1992**, *3*, 827; c) M. D. Garret, R. Scott, G. N. Sheldrake, *Tetrahedron: Asymmetry* **2002**, *13*, 2201; **20b**: d) A. G. Davies, J. Kenyon, K. Thaker, *J. Chem. Soc.* **1956**, 3394; e) N. A. Salvi, S. Chattopadhyay, *Tetrahedron* **2001**, *57*, 2833; **20c**: f) C. Bolm, M. Zehnder, D. Bur, *Angew. Chem.* **1990**, *102*, 206; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 205; g) C. Bolm, M. Ewald, M. Felder, G. Schlingloff, *Chem. Ber.* **1992**, *125*, 1169; g) G. Cheulucci, F. Soccolini, *Tetrahedron: Asymmetry* **1992**, *3*, 1235.

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