Asymmetric Cyanophosphorylation

Enantioselective Synthesis of Cyanohydrin *O*-Phosphates Mediated by the Bifunctional Catalyst Binolam–AlCl**

Alejandro Baeza, Jesús Casas, Carmen Nájera, José M. Sansano, and José M. Saá**

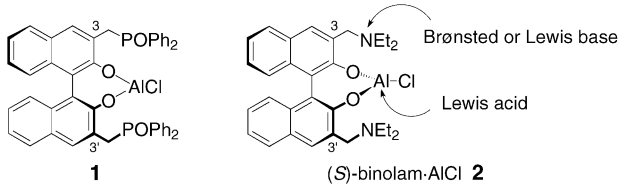
Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

Modern organic chemistry is committed to a number of social demands, including the pressure to develop catalytic, highly efficient processes (in terms of both chemical yield and stereochemical purity), which are not aggressive toward the environment. With this in mind, we carried out a study on the enantioselective synthesis of cyanohydrins and derivatives thereof.

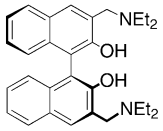
[*] Prof. Dr. C. Nájera, Dipl.-Chem. A. Baeza, Dipl.-Chem. J. Casas, Dr. J. M. Sansano
Departamento de Química Orgánica, Universidad de Alicante
Apartado 99, 03080 Alicante (Spain)
Fax: (+34) 96-590-3549
E-mail: cnajera@ua.es
Prof. Dr. J. M. Saá
Departament de Química, Universitat de les Illes Balears
07071 Palma de Mallorca (Spain)
Fax: (+34) 971-173-426
E-mail: jmsaa@uib.es

[**] This work was supported by the DGES of the Spanish Ministerio de Ciencia y Tecnología (PB97–0123 and BQU2001–0724-C02-) and by Generalitat Valenciana (CTIOIB/2002/320). A.B. also thanks Generalitat Valenciana for a predoctoral fellowship.

Owing to the fact that optically active α-hydroxynitriles (cyanohydrins) are versatile building blocks for the synthesis of biologically active compounds,[1] the search for simple processes for the enantioselective hydrocyanation of carbonyl compounds has occupied organic chemists for a number of years. Enzymatic methods aside,[1b] until recently most of the chiral catalysts designed and developed by chemists for these endeavors have been monofunctional catalysts, such as standard Lewis acids[2] or organocatalysts.[3] For reasons of efficacy, organic chemists are interested in the design of bifunctional and multifunctional catalysts. Recently, C_2-symmetric bifunctional catalysts[4] based on a 2,2′-dihydroxy-1,1′-binaphthalene–aluminum complex with either phosphinoyl or amino arms at C3 and C3′ (**1**[5] and **2**,[6] respectively) were



1 (*S*)-binolam·AlCl **2**



(*S*)-binolam **3**

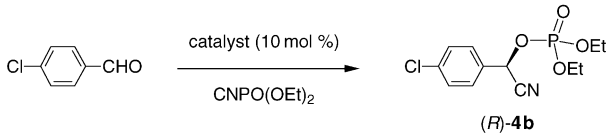
shown to promote the highly enantioselective silylcyanation of aldehydes. The asymmetric cyanation of ketones with trimethylsilyl cyanide in the presence of a peptidic chiral ligand is also promoted by an aluminum complex that acts as a bifunctional catalyst.[7] However, the intrinsic instability of cyanohydrins (and their silyl ethers) has moved researchers to look for new routes to directly access robust, multipurpose *O*-protected cyanohydrins. The asymmetric cyanoformylation of ketones catalyzed by a chiral tertiary amine[8] and of aldehydes by an yttrium–lithium–binol heterobimetallic complex,[9] or by the monometallic aluminum complex **2**,[10] are just recent examples of the upsurge of activity in this area, focused on the enantioselective synthesis of cyanohydrin *O*-carbonates.

In continuation of our search for highly efficient catalytic systems (perfect catalysts, as described by Noyori),[11] we now report the first enantioselective cyanophosphorylation of aldehydes catalyzed by the monometallic bifunctional system **2**. We also describe herein a number of useful applications of the resulting enantiomerically enriched cyanohydrin *O*-phosphates as valuable, previously unknown chiral building blocks in standard modern organic synthesis.[12,13]

In our search for the best catalytic system for the cyanophosphorylation of aldehydes, we examined the reaction of *p*-chlorobenzaldehyde with commercially available diethyl cyanophosphonate in the presence of a series of Lewis acids under a variety of reaction conditions, as shown in Table 1. All catalytic systems were freshly prepared by stirring

 DOI: 10.1002/anie.200351552

Table 1: Cyanophosphorylation of *p*-chlorobenzaldehyde catalyzed by preformed Lewis acid–(*S*)-**3** complexes.[a]

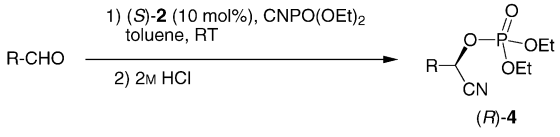


(*R*)-**4b**

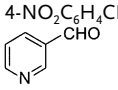
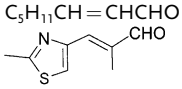
Entry	Lewis acid	Solvent	*t* [h]	Conversion [%][b]	*ee* [%][c]
1	Me_2AlCl	CH_2Cl_2	19	>98	70
2	Me_2AlCl	THF	24	96	98
3	Me_2AlCl	$PhCH_3$	20	>98	96
4	Me_2AlCl[d]	$PhCH_3$	48	<15	–
5	Me_2AlCl[e]	$PhCH_3$	48	–	–
6	Et_2AlCN	$PhCH_3$	7	>98	56
7	Me_2AlOMe	$PhCH_3$	0.6	>98	62
8	$Ti(OiPr)_4$	$PhCH_3$	1	>98	24

[a] Reagents and conditions: catalyst (10 mol%) preformed from (*S*)-**3** and the Lewis acid (1:1), $CNPO(OEt)_2$, solvent, room temperature, then workup with 2 M HCl. [b] Determined by ^{1}H NMR spectroscopic analysis after acidic workup. [c] Determined by HPLC analysis on a chiral phase (Daicel Chiralpak AD). [d] Molecular sieves (4 Å) were added (7.5% water, 50 mg/0.25 mmol; see reference [6]). [e] Triphenylphosphane oxide (20 mol%) was added.

Table 2: Enantioselective synthesis of (*R*)-cyanohydrin *O*-phosphates **4** catalyzed by complex (*S*)-**2**.



(*R*)-**4**

Entry	Aldehyde	*t* [h]	**4**	Yield [%][a]	*ee* [%][b]
1	PhCHO	4	**a**	89	98
2	$4\text{-}ClC_6H_4CHO$	20	**b**	88	96
3	$4\text{-}(MeO)C_6H_4CHO$	10	**c**	87	98
4	$4\text{-}NO_2C_6H_4CHO$	50	**d**	87	26
5		24	**e**	90	4
6	$CH_3CH=CHCHO$	2	**f**	89	88
7	$C_5H_{11}CH=CHCHO$	6	**g**	90	94
8		4	**h**	89	90
9	$C_6H_{13}CHO$	3	**i**	90	98[c]
10	$PhCH_2CH_2CHO$	2	**j**	90	92

[a] Yields of the cyanohydrin *O*-phosphates after acidic hydrolysis and column chromatography. [b] Enantiomeric excesses were determined by HPLC analysis on a chiral phase (Daicel Chiralcel OD-H, and Daicel Chiralpak AD and AS). [c] Determined by GC on a chiral phase (γ-cyclodextrin).

a 1:1 mixture of the ligand (*S*)-binolam (**3**) and the desired Lewis acid at room temperature in the appropriate solvent for 1 h. *p*-Chlorobenzaldehyde and diethyl cyanophosphonate (3 equiv relative to aldehyde) were then added in one portion at room temperature under an argon atmosphere, and the resulting mixture was stirred for the time stated.

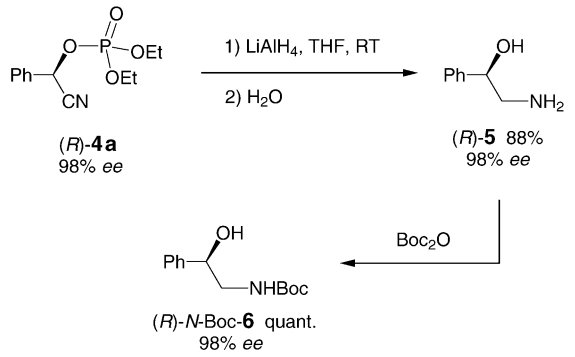
As shown (Table 1, entries 2 and 3), the best results were obtained with (*S*)-binolam–AlCl **2** (10 mol%), generated in situ by mixing (*S*)-binolam **3** and commercial diethylaluminum chloride in anhydrous toluene or THF. Although a very high enantiomeric excess was observed when the reaction was performed in THF (Table 1, entry 2), toluene was selected as the solvent for further studies, as its use led to a cleaner reaction (Table 1, entry 3). The reaction became impractically slow at lower temperatures. No important effects analogous to those observed with 4-Å molecular sieves and triphenylphosphane oxide in the cyanosilylation of aldehydes in the presence of complex **2**[6] were observed in this cyanophosphorylation reaction (Table 1, entries 4 and 5). The reaction was accelerated by using the corresponding chiral aluminum methoxide complex, but a lower enantiomeric excess was observed (Table 1, entry 7), even at lower temperatures. Catalytic titanium aggregates also accelerated the addition reaction but did not improve the enantioselectivity of the cyanophosphorylation relative to the aluminum complexes (Table 1, entry 8). A number of aldehydes were subjected to the optimized reaction conditions to assess the scope and limitations of the preparation of (*R*)-cyanohydrin *O*-phosphates **4** (Table 2).

Aromatic, aliphatic, and α,β-unsaturated aldehydes were found to undergo highly efficient enantioselective cyanophosphorylation under these reaction conditions in high yields (Table 2). Aromatic aldehydes with electron-withdrawing substituents reacted somewhat slowly (Table 2, entries 2 and 4). Furthermore, in the case of *p*-nitrobenzaldehyde, enantioselectivity was found to be poor (Table 2, entry 4), which suggests the existence of a competing achiral route as a result of coordination of the nitro group to the aluminum center. It was thought that heteroaromatic aldehydes, or other aldehydes with a basic site to compete with the amino-armed catalyst, would be a challenging substrates. In fact, pyridine-3-carboxaldehyde afforded almost racemic material (Table 2, entry 5). However, the reaction of an aldehyde that bears a thiazole moiety[14] led to **4h** (a possible key intermediate in the synthesis of epothilone A[14,15]) in excellent chemical yield and stereochemical purity (Table 2, entry 8), in accordance with the lower basicity of the thiazole nitrogen atom (pK_a 2.4). As expected, when the aluminum complex (*R*)-**2** was used with the aldehydes in entries 1 and 2 of Table 2, the enantiomeric products (*S*)-**4** were obtained in reliable and reproducible chemical yields and enantiomeric excesses. Most importantly, the valuable chiral ligand **3** was readily extracted from the reaction mixture (93% recovery) after acidic workup, and could be reused without any significant loss of activity. Thus, compound **4a** was again obtained in 98% *ee* (see Table 2, entry 1) with recovered ligand **3**, as reported previously.[6,11]

When we tried to synthesize compounds **4** from the corresponding enantiomerically pure cyanohydrins, to determine the absolute configuration of our cyanophosphorylation products, we observed that partial racemization occurred in the presence of organic bases (triethylamine, pyridine, and *N*-methylimidazole) and with both diethyl chlorophosphate[16] and diethyl cyanophosphonate as phosphorylating agents. Partial racemization was also observed when cyanophosphates **4a** and **4j** were synthesized by treating optically pure cyanohydrins with diethyl chlorophosphite in pyridine, followed by iodine-mediated oxidation.[17] In this reaction the

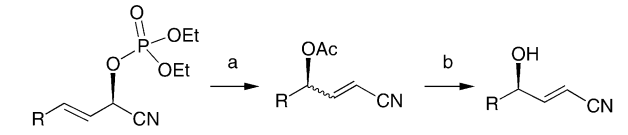
enantiomeric excess is lost in the first step as revealed by the chiral HPLC data of the intermediate cyanohydrin *O*-phosphite. These results clearly enhance the value of this catalytic cyanophosphorylation of aldehydes, which ensures access to enantiomerically enriched compounds **4**.

To demonstrate interesting applications of the chiral cyanohydrin *O*-phosphates **4** obtained, we investigated their reduction to the corresponding aminoalcohols, as well as stereospecific [3,3] sigmatropic chirality transfer. No loss of enantiomeric excess was observed in the reduction of compound (*R*)-**4a** with lithium aluminum hydride to give enantiomerically enriched β-aminoalcohol (*R*)-**5**[18] and, after protection of the amino group, its *N*-Boc derivative **6**,[19] in good chemical yields (Scheme 1). These transformations also served to confirm the absolute configuration already assigned to **4**.



Scheme 1. Reduction of chiral cyanohydrin *O*-phosphate **4a**. Boc = *tert*-butoxycarbonyl.

Palladium-catalyzed allylic displacement of allylic phosphates (*R*)-**4f** and (*R*)-**4g** with sodium acetate as the nucleophile gave the expected γ-acetates **7f** and **7g** as 0.25:1 and 0.2:1 *Z*/*E* mixtures, respectively. Basic hydrolysis of the crude acetates **7**, according to the reported procedure,[20] led to the *R*-configured *E* cyanoallylic alcohols **8f** and **8g** in 75 and 83% yield, respectively. No loss of enantiomeric excess was observed (Scheme 2). These cyanoallylic alcohols are important building blocks for organic synthesis.[20–24] The



(*R*)-**4f** (R = Me) 88% *ee*
(*R*)-**4g** (R = C_5H_{11}) 94% *ee*
(*R*)-**8f** 75%, 88% *ee*
(*R*)-**8g** 83%, 94% *ee*

Scheme 2. Asymmetric palladium-catalyzed allylic substitution of cyanophosphorylation products **4f** and **4g**: a) $Pd(OAc)_2$, PPh_3, NaOAc; b) K_2CO_3, MeOH.

absolute configuration of allylic alcohols **8f**[21] and **8g**,[20] assigned on the basis of the reported $[\alpha]_D$ values, is in accordance with the well-known double inversion described for palladium-catalyzed allylic nucleophilic substitution of chiral allylic phosphates.[25]

A strong nonlinear effect (NLE)[26] was apparent for the enantioselective cyanophosphorylation of aldehydes.[27] This unexpected behavior (to the best of our knowledge it is the first example described in the literature for an aluminum-based catalytic complex) can be assigned to the different stability of dimeric species relative to monomers, according to HF/6-31G* ab initio calculations.[28] Thus, whereas the combinations *R,R* or *S,S* can form unstable dimeric species (relative to monomers) with tetravalent aluminum atoms and nonligating aminomethyl arms, the corresponding *R,S* dimer cannot form a similar species, and this combination gives rise instead to much more stable, weakly bound monomers with internal coordination by one aminomethyl arm.[29]

From a mechanistic viewpoint, we postulate that the enantioselective cyanophosphorylation reaction described above involves the intervention of a bifunctional catalyst (either Lewis acid–Lewis base or Lewis acid–Brønsted base). This is supported by the following observations. First, the reaction promoted by the aluminum derivative of (*S*)-binol, rather than that derived from (*S*)-binolam, led to the racemic cyanohydrin *O*-phosphate in very low conversion (10%) after 48 h. Second, the addition of an external base (triethylamine, 20 mol%) under otherwise standard conditions led to the acceleration of the reaction and induced a dramatic drop in the enantiomeric excess of the product (38% *ee*).

Experimental Section

Dimethylaluminum chloride (1M solution in hexanes, 0.025 mmol, 25 μL) was added to a solution of enantiopure (*S*)-binolam **3**[30] (0.025 mmol, 11.4 mg) in dry toluene (1 mL) under argon, and the resulting suspension was stirred at room temperature for 1 h. The freshly distilled aldehyde (0.25 mmol) and diethyl cyanophosphonate (0.75 mmol, 125 μL) were then added in one portion. The reaction was monitored by ^{1}H NMR spectroscopy and when it was judged complete, aqueous hydrochloric acid (2M, 2 mL) and ethyl acetate (2 mL) were added. The resulting mixture was stirred vigorously for 10 min, then the emulsion was filtered and the organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography to give the pure cyanohydrin *O*-phosphate **4**.

Received: April 2, 2003 [Z51552]

Keywords: aluminum · asymmetric catalysis · homogeneous catalysis · binaphthols · cyanohydrins

[1] a) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; b) H. Gröger, *Adv. Synth. Catal.* **2001**, *343*, 547–558; c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682; d) F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609–1619; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564; e) M. North, *Synlett* **1993**, 807–820; f) C. G. Kruse in *Chirality in Industry* (Eds.: A. N. Collins, G. N. Schedrake, J. Crosby), Wiley, Chichester, **1992**, pp. 279–299.

[2] For recent examples, see: a) T. Ooi, T. Miura, K. Takaya, H. Ichikawa, K. Maruoka, *Tetrahedron* **2001**, *57*, 867–873; b) Y. N. Belokon, B. Green, N. S. Ikonnikov, M. North, T. Parsons, V. I. Tararov, *Tetrahedron* **2001**, *57*, 771–779; c) C. Baleizao, B. Gigante, H. García, A. Corma, *Green Chem.* **2002**, *4*, 272–274; d) Z. Yang, Z. Zhou, C. Tang, *Synth. Commun.* **2001**, *31*, 3031–3036.

[3] For reviews, see: a) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481 – 2495; b) P. L. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840 – 3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726 – 3748.

[4] For reviews, see: a) M. Shibasaki, M. Kanai, *Chem. Pharm. Bull.* **2001**, *49*, 511 – 524; b) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865 – 1882; c) H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5246 – 5251; d) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989 – 1999.

[5] a) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641 – 2642; b) Y. Yamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805 – 814.

[6] J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Org. Lett.* **2002**, *4*, 2589 – 2592.

[7] H. Deng, M. P. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2002**, *114*, 1051 – 1054; *Angew. Chem. Int. Ed.* **2002**, *41*, 1009 – 1012.

[8] S. K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195 – 6196.

[9] J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2002**, *114*, 3788 – 3790; *Angew. Chem. Int. Ed.* **2002**, *41*, 3636 – 3638.

[10] J. Casas, A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá, *Tetrahedron: Asymmetry* **2003**, *14*, 197 – 200.

[11] R. Noyori, *Angew. Chem.* **2002**, *114*, 2108 – 2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 – 2022.

[12] I. Micó, C. Nájera, *Tetrahedron* **1993**, *49*, 4327 – 4332, and references therein.

[13] a) T. Schrader, *Chem. Eur. J.* **1997**, *3*, 1273 – 1282; b) T. Schrader, *Angew. Chem.* **1995**, *107*, 1001 – 1002; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 917 – 919.

[14] a) D. Sawada, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 215 – 219; *Angew. Chem. Int. Ed.* **2000**, *39*, 209 – 213; b) D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 10521 – 10532.

[15] a) K. C. Nicolaou, D. Hepworth, N. P. King, M. R. V. Finlay, R. Scarpelli, M. M. A. Pereira, B. Bollbuck, A. Bigot, B. Werschkun, N. Winssinger, *Chem. Eur. J.* **2000**, *6*, 2783 – 2800; b) J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410 – 6424.

[16] R. L. Letsinger, W. B. Lunsford, *J. Am. Chem. Soc.* **1976**, *98*, 3655 – 3661.

[17] J. W. Perich, P. F. Alewood, R. B. Johns, *Synthesis* **1986**, 572 – 573.

[18] $[\alpha]_D = -48.0$ ($c = 2$, EtOH). For the *S* form $[\alpha]_D = +48.6$ ($c = 2.01$, EtOH). B. T. Cho, S. K. Kang, S. H. Shin, *Tetrahedron: Asymmetry* **2002**, *13*, 1209 – 1217.

[19] $[\alpha]_D = -3.4$ ($c = 1$, EtOH); for the *S* form $[\alpha]_D = +3.5$ ($c = 1$, EtOH); A. Kawamoto, M. Wills, *Tetrahedron: Asymmetry* **2000**, *11*, 3257 – 3261.

[20] D. V. Johnson, H. Griengl, *Tetrahedron* **1997**, *53*, 617 – 624.

[21] M. Tiecco, L. Testaferri, F. Marini, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **1999**, *10*, 747 – 757.

[22] I. Yamakawa, H. Urabe, Y. Kobayashi, F. Sato, *Tetrahedron Lett.* **1991**, *32*, 2045 – 2048.

[23] H. Abe, H. Nitta, A. Mori, S. Inoue, *Chem. Lett.* **1992**, 2443 – 2446.

[24] Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, *Tetrahedron Lett.* **1987**, *28*, 6351 – 6354.

[25] J. Tsuji in *Palladium Reagents and Catalysts, Innovation in Organic Synthesis*, Wiley, Chichester, **1995**.

[26] For some recent reviews of the NLE, see: a) H. B. Kagan, *Synlett* **2001**, 888 – 899; b) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382 – 390; c) D. Heller, H.-J. Drexler, C. Fischer, H. Buschmann, W. Baumann, B. Heller, *Angew. Chem.* **2000**, *112*, 505 – 509; *Angew. Chem. Int. Ed.* **2000**, *39*, 495 – 499.

[27] A weaker, positive NLE was observed in the enantioselective cyanoformylation reaction of aldehydes; J. Casas, unpublished results.

[28] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.

[29] a) J. A. Francis, C. N. McMahon, S. G. Bott, A. R. Barron, *Organometallics* **1999**, *18*, 4399 – 4416; b) J. Lewinski, J. Zachara, I. Justyniak, *Organometallics* **1997**, *16*, 4597 – 4605; c) J. Lewinski, J. Zachara, I. Justyniak, *Chem. Commun.* **1997**, 1519 – 1520; d) D. A. Atwood, F. P. Gabbai, J. Lu, M. P. Remington, D. Rutherford, M. P. Sibi, *Organometallics* **1996**, *15*, 2308 – 2313; e) R. Kumar, M. L Sierra, J. P. Oliver, *Organometallics* **1994**, *13*, 4285 – 4293; f) M. L. Sierra, V. Srini, J. de Mel, J. P. Oliver, *Organometallics* **1989**, *8*, 2486 – 2488.

[30] (*S*)- and (*R*)-binolam are commercially available from MEDALCHEMY, S. L.

