Asymmetric Catalysis

DOI: 10.1002/ange.201000577

Copper-Free Asymmetric Allylic Alkylation with Grignard Reagents**

*Olivier Jackowski and Alexandre Alexakis**

During the past decade, the copper-catalyzed enantioselective allylic alkylation reaction has been extensively studied owing to its powerful potential to deliver a variety of enantiopure compounds. By using Grignard, diorganozinc, or triorganoaluminum reagents, the regio- and enantioselectivity of the C–C bond-formation step is controlled using different types of ligands, such as phosphites, phosphoramidites, ferrocenes, and peptides.[1] The use of ligands that are based on an N-heterocyclic carbene (NHC) framework, first used in the asymmetric copper-catalyzed conjugate addition reaction,[2] was more recently introduced for the asymmetric allylic alkylation (AAA) reaction with great success. The groups of Okamoto,[3] Hong,[4] and Tomioka[5] used Grignard reagents as their organometallic reagent, whereas Hoveyda and coworkers[6] reported the use of diorganozinc and triorganoaluminum reagents. Most NHC ligands that have been reported thus far are C_2 symmetric; the Hoveyda group has developed a series of bidentate ligands wherein a free hydroxy group forms an intermediate alkoxy copper species (Figure 1).

Since our first report on the copper-catalyzed AAA reaction,[7] we have focused on Grignard reagents. In contrast to diorganozinc reagents, Grignard reagents are commercially available, or very easily prepared, and a variety of alkyl groups can be added using these reagents. Another advantage of Grignard reagents is their ability to deprotonate the imidazolium salt,[8] without requiring a preformed copper or silver carbene. Our NHC ligands kept the diphenyl imidazoline core, with a mesityl group on one nitrogen atom, and a more flexible benzylic group, rather than a directly linked aromatic group, on the second nitrogen atom. Thus, several NHC ligands were synthesized based on this design (Figure 2). During our work, Uchida and Katsuki went on the same design with ligand **L3**, which appeared to be very good for the copper-catalyzed asymmetric conjugate addition.[9]

During the course of these studies on copper-catalyzed AAA reactions with Grignard reagents and the alkoxy NHC ligands, we observed that the same result was obtained with or without the copper catalyst (Scheme 1).

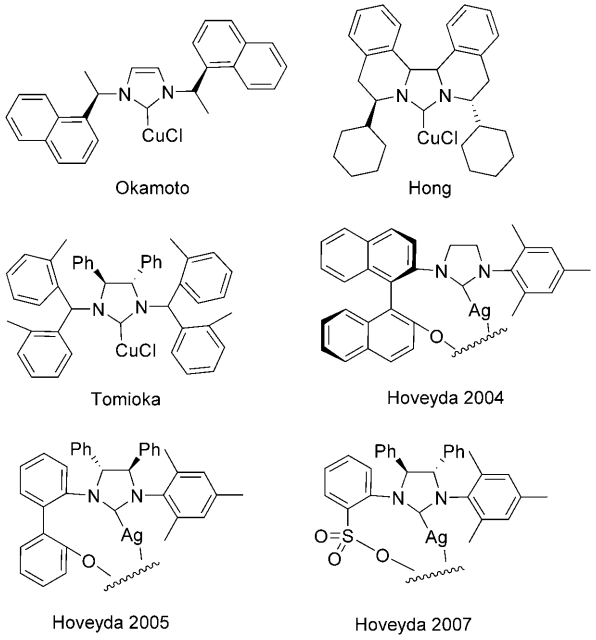


Figure 1. NHC ligands used in Asymmetric Allylic Alkylation (AAA) reactions.

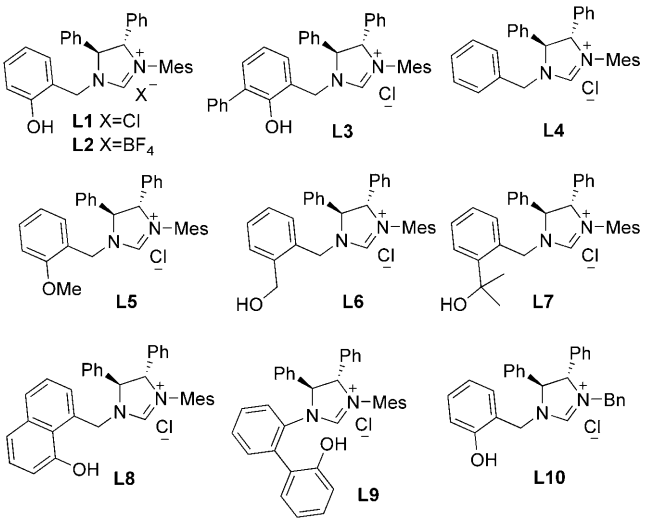


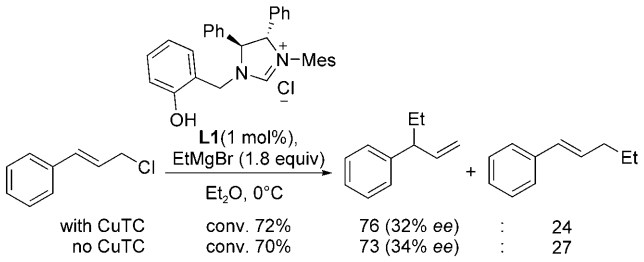
Figure 2. NHCs used in this study. Bn = benzyl, Mes = mesityl.

A preliminary investigation was performed using an ethyl Grignard reagent on cinnamyl bromide, with and without copper (Scheme 1). Surprisingly, the results were identical for the two reactions. Such an observation had already been reported by Lee and Hoveyda on a specific substrate and specific Grignard reagents.[10] Very recently, they also

[*] Dr. O. Jackowski, Prof. Dr. A. Alexakis
Department of Organic Chemistry
University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva (Switzerland)
Fax: (+41) 22-379-32-15
E-mail: alexandre.alexakis@unige.ch

[**] We thank the Swiss National Research Foundation (Grant No. 200020-126663) and COST action D40 (SER contract No. C07.0097) for financial support.

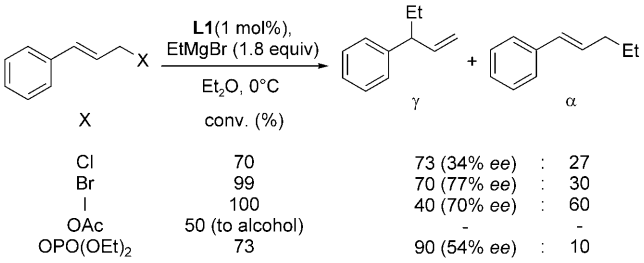
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000577.



Scheme 1. The NHC-catalyzed AAA reaction of a Grignard reagent. CuTC = copper thiophene carboxylate.

reported the AAA reactions of cinnamyl phosphate derivatives without copper using organozinc and organoaluminum reagents.[11] However, they insisted that Grignard reagents did not work well for this reaction, even on cinnamyl halides. In view of our results, we decided to explore this new reactivity of NHC–Grignard-reagent complexes for the copper-free AAA reaction.

First, the substrate scope, and particularly the leaving group, was explored (Scheme 2). The highest enantioselectivities were obtained with a good leaving group, but the

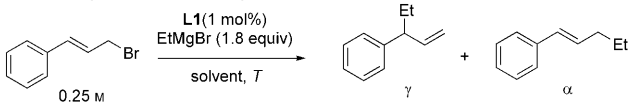


Scheme 2. Leaving group effect on the AAA reaction.

regioselectivity followed the opposite trend, the best result was obtained with cinnamyl phosphate. The acetate was not a successful leaving group, since direct attack on the carbonyl group occurred. Therefore, the conditions were optimized with cinnamyl bromide as the best compromise. The solvents, the temperature, the catalyst loading, and concentration of the reaction mixture were also evaluated (Table 1). The reaction time was kept to one hour to better investigate the reactivity.

First, lowering the temperature to −15 °C improved the enantioselectivity without affecting the regioselectivity (Table 1, entries 1 and 7). However, at −30 °C, a small erosion of the regioselectivity was observed (Table 1, entry 8). The solvent played an important role: a moderately coordinating solvent was required (Table 1, entries 1 and 2), but both THF (Table 1, entry 3) and a noncoordinating solvent (Table 1, entries 4 and 5) afforded poor regio- and enantioselectivities. The effect of concentration was also addressed: dilution slowed down the reaction without any noticeable change in selectivity (Table 1, entry 9), whereas increased concentration decreased the regioselectivity (Table 1, entry 10). Higher catalyst loading (4%, instead of 1%) was clearly not important (Table 1, entry 12), but the absence of an NHC

Table 1: Optimization of experimental conditions.[a]



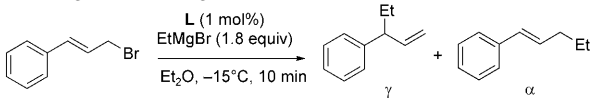
Entry	Solvent	*T* [°C]	Conversion [%][b]	γ/α[b]	*ee* [%][c]
1	Et_2O	−15	>99	76:24	85
2	MTBE	−15	53	75:25	72
3	THF	−15	40	50:50	42
4	CH_2Cl_2	−15	47	10:90	40
5	toluene	−15	40	50:50	67
6	Et_2O[d]	−15	>99	77:23	84
7	Et_2O	0	>99	70:30	77
8	Et_2O	−30	98	67:33	86
9	Et_2O[e]	−15	76	70:30	83
10	Et_2O[f]	−15	94	50:50	84
11	Et_2O[g]	−15	≤1	–	–
12	Et_2O[h]	−15	>99	76:24	82

[a] Reaction time was 1 hour in all cases. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by SFC on a chiral stationary phase. [d] With CuTC (1 mol%). [e] 0.125 M. [f] 0.5 M. [g] No ligand. [h] 4 mol% ligand. SFC = supercritical fluid chromatography, MTBE = methyl *tert*-butyl ether.

stopped the reaction (Table 1, entry 11). We also checked that the regio- and enantioselectivities were the same at the beginning and at the end of the reaction. In conclusion, the reaction works well in diethyl ether at −15 °C with 1 mol% of ligand **L1** and the reaction times can even be decreased to 10 minutes.

With these optimal conditions in hand, several ligands were tested to improve the regio- and enantioselectivities (Table 2).

Table 2: Ligand screening.



Entry	L	Conversion [%][a]	γ/α[a]	*ee* [%][b]
1	**L1**	≥99	76:24	85
2	**L2**	≥99	70:30	80
3	**L3**	70	70:30	57
4	**L4**	80	75:25	53
5	**L5**	98	70:30	51
6	**L6**	98	72:28	61
7	**L7**	≥99	67:33	63
8	**L8**	≥99	67:33	53
9	**L9**	99	69:31	36
10	**L10**	≥99	9:91	34

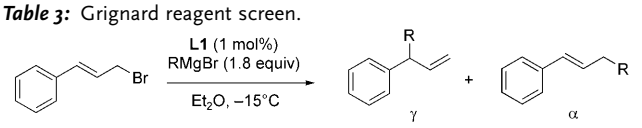
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by SFC on a chiral stationary phase.

The counter ion (Cl versus BF_4) had no significant effect on the reaction (Table 2, entries 1 and 2). However, the regiochemistry (around 7:3) seems to be directed by the mesityl group on the ligand. Ligand **L10**, which contained a benzyl group instead of a mesityl group, gave a reversal of the regioselectivity in favor of the α product (Table 2, entry 10).

On the other hand, the enantioselectivity seems to be controlled by the substituent on the other nitrogen atom of the NHC. The simple benzyl motif in ligand **L4** afforded lower enantiomeric excess values, which showed the necessity of the phenolic hydroxy group (Table 2, entry 4). The homologated naphthol moiety **L8** did not improve the enantioselectivity (Table 2, entry 8). The number of carbon atoms between the nitrogen and the oxygen atoms seems important, as the carbene reported by Hoveyda et al. (**L9**), which contained a phenylphenol moiety, gave the lowest asymmetric induction (Table 2, entry 9). Similarly low enantioselectivities were observed with **L6** and **L7**, which both had four carbon atoms between the substituents (Table 2, entries 6 and 7). The steric hindrance around the hydroxy group also had an important effect on the enantiomeric excess (Table 2, entry 3), as the carbene reported by Uchida and Katsuki (**L3**) gave lower *ee* values. Finally, the best result (85% *ee*) was obtained with ligand **L1** (Table 2, entry 1), which contained three carbon atoms between the nitrogen and the hydroxyl groups; this chain length seems to be essential for the enantioselectivity.

Next, the scope of the reaction was screened with different Grignard reagents on cinnamyl bromide (Table 3). The selectivities observed seemed to be independent of the Grignard reagent used. Apart from the methyl Grignard reagent (Table 3, entry 1), which is known for its low reactivity and selectivity, all of the primary Grignard reagents (Table 3, entries 2–7) offered quite good regioselectivities (76:24 to 88:12) and good enantioselectivities (up to 86% *ee*). The most remarkable result was the reaction with *t*BuMgBr (Table 3, entry 9). The analogous copper-catalyzed reaction gave a lower *ee* value,[1] thus showing that the copper-free reaction may be complementary to the copper-catalyzed established procedures.

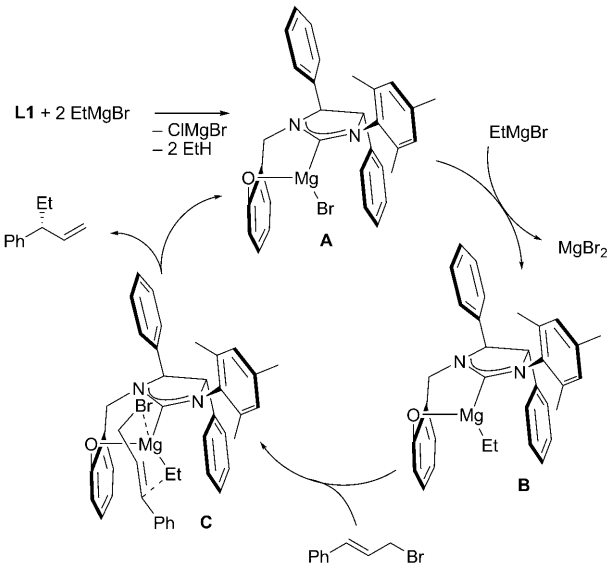
Table 3: Grignard reagent screen.



Entry	R	Yield [%]	γ/α[a]	*ee* [%][b]
1	Me	88	83:17	70 (*R*)
2	Et	82	76:24	85 (*R*)
3	*n*Bu	83	77:23	85 (*R*)
4	*i*Bu	86	84:16	82 (*R*)
5	*t*BuO$(CH_2)_4$	97	79:21	80 (*R*)
6	Ph$(CH_2)_2$	97	88:12	86 (*R*)
7	$Me_2C{=}CH(CH_2)_2$	90	82:18	86 (*R*)
8	*i*Pr	93	69:31	82 (*R*)
9	Cy	88	68:32	84 (*R*)
10	*t*Bu	58	73:27	68 (*S*)

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by SFC or GC on a chiral stationary phase. Cy = cyclohexyl.

The observed reactivity can be tentatively explained by the following proposed mechanism (Scheme 3): First, the imidazolidinium salt **L1** is doubly deprotonated by two molecules of the Grignard reagent to form intermediate **A**; Complex **B** is then generated from the reaction of **A** with the Grignard reagent. Interaction with the substrate leads to complex **C**, which adopts a pseudo-chair conformation that offers an explanation for the observed regio- and enantioselectivities. The product is then released and intermediate **A** is regenerated to begin another cycle.



Scheme 3. Tentative catalytic cycle.

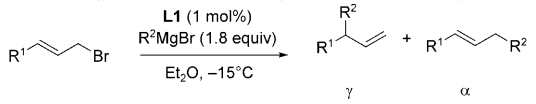
It should be kept in mind that, in the absence of an NHC, the reaction afforded < 5% of substitution product. The electron donation by the carbene to the Lewis acidic magnesium atom should enhance the nucleophilicity of the R group of the Grignard, which explain its higher reactivity.[12] On the other hand, the hydroxy group could maintain a tighter transition state that allows a better enantioselectivity than **L4**, which lacks this hydroxy group.

With these encouraging results in hand, EtMgBr and Ph$(CH_2)_2$MgBr were tested on different cinnamyl bromide derivatives and on aliphatic substrates (Table 4).

With cinnamyl derivatives, the regioselectivities obtained were independent of the aryl substituent. However, the enantiomeric excess values increased (up to 91% *ee*) with increasing steric hindrance (Table 4, entry 5) or with a more electron-withdrawing 4-$CF_3C_6H_4$ group (Table 4, entry 4). In contrast, an electron-donating group, such as 4-$MeOC_6H_4$, decreased the enantiomeric excess (Table 4, entry 3). The reaction of an aryl Grignard reagent (Table 4, entry 7) only afforded moderate results with lower reactivity, no regioselectivity, and only 50% *ee*. In all cases involving aliphatic substrates, the γ product was obtained with high selectivities, ranging from 86:14 to 95:5. Both the regioselectivity and enantioselectivity followed a counter-intuitive trend, being better with the bulkiest substituent (*t*Bu group; Table 4, entry 14). This is a reversal of the trend followed by copper-catalyzed reactions, thus showing again the complementarities of the two methods.

The procedure was extended to the formation of stereogenic quaternary carbon centers from their corresponding trisubstituted allylic substrates, as a mixture of *E* and *Z* compounds (Table 5). The reaction proceeded much faster

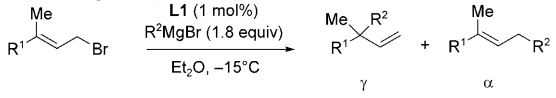
Table 4: Cinnamyl derivatives and aliphatic substrate scope.



Entry	R^1	R^2	Yield [%]	γ/α[a]	*ee* [%][b]
1	Ph	Et	82	76:24	85 (*R*)
2	4-MeC_6H_4	Et	87	77:23	88 (*R*)
3	4-MeOC_6H_4	Et	59	81:19	73 (*R*)
4	4-$CF_3C_6H_4$	Et	80	76:24	90 (*R*)
5	1-Naphthyl	Et	88	71:29	91 (*R*)
6	2-Naphthyl	Et	84	74:26	87 (*R*)
7	4-$CF_3C_6H_4$	Ph	66[c]	50:50	50 (*S*)
8	Me	$Ph(CH_2)_2$	94	86:14	33 (*R*)
9	$Ph(CH_2)_2$	Et	94	87:13	54 (*S*)
11	$BrCH_2$	$Ph(CH_2)_2$	98	>98:2	61 (*R*)
12	Cy	Et	72	88:12	78 (*R*)
13	*t*Bu	Et	99[c]	88:12	84 (*R*)
14	*t*Bu	$Ph(CH_2)_2$	75	95:5	80 (*R*)

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by GC or SFC on a chiral stationary phase. [c] Conversion [%].

Table 5: Stereogenic quaternary carbon center formation.



Entry	R^1	R^2	Yield [%][a]	γ/α[b]	*ee* [%][c]
1	4-MeOC_6H_4[d]	Et	77	62:38	0
2	Ph[d]	Et	70	>98:2	89 (*R*)
3	Ph[e]	Et	27[g]	>98:2	39 (*R*)
4	Ph[f]	Et	100[g]	>98:2	72 (*R*)
5	Ph[d]	$Me_2C{=}CH(CH_2)_2$	94	>98:2	84 (*R*)
6	4-$CF_3C_6H_4$[h]	Et	55	>98:2	86 (*R*)
7	Cy[i]	$Ph(CH_2)_2$	86	>98:2	64 (*R*)
8	*t*Bu	$Ph(CH_2)_2$	65	>98:2	73 (*R*)

[a] From the *E* substrate. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC or SFC on a chiral stationary phase. [d] Mixture of *E*/*Z* isomers (8:2). [e] Cinnamyl chloride derivative as a mixture of *E*/*Z* isomers (8:2). [f] Cinnamyl iodide derivative as a mixture of *E*/*Z* isomers (75:25). [g] Conversion from the mixture [%]. [h] Mixture of *E*/*Z* isomers (9:1). [i] Mixture of *E*/*Z* isomers (8:2) and *ee* value was determined after epoxidation.

with the *E* substrate, and could be stopped with minimum conversion of the *Z* substrate.[13] In fact, the *Z* isomer decreased the enantiomeric excess, presumably because, with the same facial selectivity, it affords the opposite enantiomer.

The trend in regioselectivity observed above with the bulkiest substrates is also followed here. Almost complete γ regioselectivity was observed and was independent of the substrate. An exception is the substrate with an electron-donating group, which is associated to a dramatic loss of enantioselectivity (Table 5, entry 1), probably through an S_N1 mechanistic pathway. The stereoselectivity was also quite good, up to 89%, using aromatic compounds (Table 5, entries 2, 4–6). The aliphatic substrates offered a slight decrease in the enantiomeric excess (Table 5, entries 7 and 9). Again, copper-catalyzed reactions have never afforded such high γ selectivities using Grignard reagents.[1]

In conclusion, a copper-free allylic alkylation reaction with Grignard reagents was performed with up to 91% *ee*. The enantioselectivity (around 85% *ee*) is independent of substrate and Grignard reagent. The formation of stereogenic quaternary centers is completely regioselective with good enantiomeric excesses (up to 89% *ee*) observed with aromatic substrates. This methodology seems complementary to the copper-catalyzed analogue. Further work is underway to improve the enantioselectivity with new NHCs.

Experimental Section

Cinnamyl bromide (0.5 mmol) and **L1** (1 mol%) were suspended in dry Et_2O (2 mL) in a flame-dried Schlenk flask, under a nitrogen atmosphere, and cooled to −15 °C. EtMgBr (3 M in Et_2O; 0.3 mL, 1.8 equiv) was added dropwise over 4 minutes. After conversion was complete, the mixture is quenched by addition of a saturated solution of NH_4Cl (2 mL) and stirred at room temperature for 15 minutes. The aqueous layer was separated and extracted with Et_2O (3 × 3 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography and gave a mixture of γ and α products (76:24) and 85% *ee* (*R*; Table 1, entry 1). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.26 (m, 5H), 6.49 (d, α), 6.33 (m, α), 6.06 (m, γ), 5.13 (m, γ′), 3.24 (q, $J = 7.4$ Hz, γ), 2.29 (q, $J = 7.0$ Hz, α), 1.86 (m, γ), 1.59 (m, α), 1.07 (t, 3H, $J = 7.32$ Hz, α), 0.98 ppm (t, 3H, $J = 7.32$ Hz, γ). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 144.4$ (γ), 142.2 (γ), 130.9 (α), 129.9 (α), 128.4 (γ), 128.3 (α), 127.6 (α), 126.7 (γ), 126.1 (γ), 125.9 (α), 114.0 (γ), 51.7 (γ), 35.1 (α), 28.3 (γ), 22.5 (α), 13.7 (α), 12.1 ppm (γ). $[\alpha]_D^{20} = -30\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.6\ \mathrm{g\,cm^{-3}}$ $CHCl_3$) for the mixture. The *ee* values were measured by SFC on a chiral stationary phase (chiralcel OJ column, 2 mL min^{-1}, 200 bar, MeOH, 1% for 2 min then 2% min^{-1}): 5.56 min (*R*), 6.11 min (*S*).

Received: January 31, 2010
Published online: April 6, 2010

Keywords: allylic substitution · asymmetric catalysis · carbene ligands · Grignard reagents

[1] For reviews, see: a) A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola, *Chimia* **2006**, *60*, 124–130; b) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765–3780; c) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823; d) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824–2852.

[2] a) F. Guillen, C. L. Winn, A. Alexakis, *Tetrahedron: Asymmetry* **2001**, *12*, 2083; b) J. Pytkowicz, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2001**, *12*, 2087; c) A. Alexakis, C. L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, *Adv. Synth. Catal.* **2003**, *345*, 345–348.

[3] a) S. Tominaga, Y. Oi, T. Kato, D. K. An, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 5585–5588; b) S. Okamoto, S. Tominaga, N. Saino, K. Kase, K. Shimoda, *J. Organomet. Chem.* **2005**, *690*, 6001–6007.

[4] a) H. Seo, D. Hirsch-Weil, K. A. Abboud, S. Hong, *J. Org. Chem.* **2008**, *73*, 1983–1986; b) D. Hirsch-Weil, D. R. Snead, S. Inagaki, H. Seo, K. A. Abboud, S. Hong, *Chem. Commun.* **2009**, 2475–2477.

[5] K. B. Selim, Y. Matsumoto, K. Yamada, K. Tomioka, *Angew. Chem.* **2009**, *121*, 8889 – 8891; *Angew. Chem. Int. Ed.* **2009**, *48*, 8733 – 8735.
[6] a) A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130 – 11131; b) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877 – 6882; c) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 4638 – 4642; *Angew. Chem. Int. Ed.* **2007**, *46*, 4554 – 4558; d) D. G. Gillingham, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 3934 – 3938; *Angew. Chem. Int. Ed.* **2007**, *46*, 3860 – 3864; e) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 446 – 447.
[7] A. Alexakis, C. Malan, L. Lea, C. Benhaim, X. Fournioux, *Synlett* **2001**, 927 – 930.
[8] a) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416; b) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem.* **2008**, *120*, 9262 – 9264; *Angew. Chem. Int. Ed.* **2008**, *47*, 9122 – 9124.
[9] T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2009**, *50*, 4741 – 4743.
[10] Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 15604 – 15605.
[11] Y. Lee, B. Li, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 11625 – 11633.
[12] S. E. Denmark, G. L. Beutner *Angew. Chem.* **2008**, *120, 1584–1663; Angew. Chem. Int. Ed.* **2008**, 47, 1560 – 1638; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560 – 1638.
[13] For further details, see the Supporting Information.

