Zirconocene−Zinc Transmetalation and in Situ Catalytic Asymmetric Addition to Aldehydes

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The direct generation of organometallic reagents from alkenes and alkynes is a useful strategy for efficient C,C bond formation, since unsaturated substrates are readily available. Hydrozirconation with Cp_2ZrHCl (Schwartz reagent)[1,2] provides organozirconocene reagents that can readily be added to enones,[3] aldehydes,[4,5] epoxides,[6] and isocyanates,[7] but enantioselective protocols have so far been rare.[8] We have recently reported[5] a high-yielding protocol for the in situ transmetalation of alkenylzirconocenes to alkylzinc species and have now succeeded in developing a catalytic asymmetric protocol for subsequent additions to aldehydes.

The alkenylzirconocene complex **2**, obtained by treatment of a solution of alkyne **1** in CH_2Cl_2 with Cp_2ZrHCl, rapidly undergoes transmetalation at −65 °C to generate the alkenylzinc intermediate **3** (Scheme 1). The resulting zirconocene byproducts are efficient promoters for the 1,2-addition of organozinc derivatives to aldehydes.[9] Accordingly, even in the absence of the usual amino alcohol ligands,[10] addition of aldehydes **4** results in rapid formation of racemic allylic alcohols (±)-**5**. We were interested to see if upon addition of chiral zinc ligands pioneered by Noyori[10,11] an asymmetric pathway was capable of competing with the achiral, zirconocene-induced aldehyde addition. Our initial attempts with 1-hexyne, benzaldehyde, and 8 mol % of the proline-derived amino alcohol **6**[12] furnished 1-phenyl-2-hepten-1-ol in a disappointing 38% ee (Table 1).[5a] We later found that this reaction could be optimized by allowing for 1 h of equilibrating time at −65 to −30 °C before addition of the aldehyde. Under these conditions, the desired product was obtained in an improved 81% ee in the presence of 10 mol % of **6** (entry 2). However, a decrease in the catalyst loading to 2 mol % reduced the enantioselectivity to 19% ee (entry 3).[13]

Scheme 1

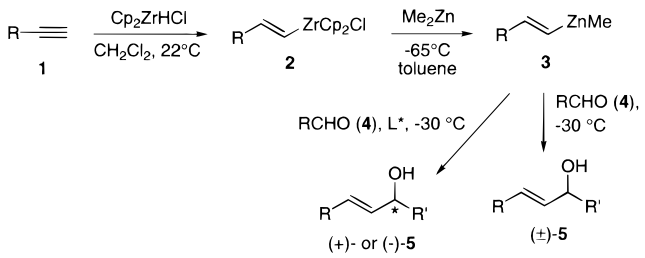
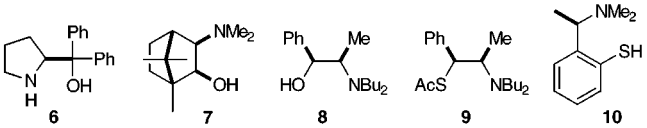


Table 1. Asymmetric Addition of 1-Hexenylzirconocene (2, R = C_4H_9) to Benzaldehyde in the Presence of Catalytic Ligands L* (6−10) To Give (*S*)-1-Phenyl-2-hepten-1-ol



6 7 8 9 10

entry	L* (mol %)	yield (%)	ee (%)
1[5a]	**6** (8)	92	38
2	**6** (10)	88	81
3	**6** (2)	99	19
4	**7** (10)	77	3
5	**8** (10)	85	1
6	**9** (10)	80	70
7	**10** (10)	76	89
8	**13** (10)	80	95
9	**13** (5)	73	90
10	**13** (2)	88	78
11[a]	**13** (10)	90	83

[a] This reaction was run at 0 °C; all other reactions were run at −30 °C.

Since addition of nucleophiles such as MeLi that were envisioned to neutralize the achiral pathway mediated by $Cp_2ZrMeCl$ formed in the transmetalation with dimethylzinc[14] did not improve enantioselectivity, we turned our attention to chiral ligands **7**,[11] **8**,[15] **9**,[16] and **10**.[17] Surprisingly, amino alcohols **7** and **8** gave very low or no asymmetric induction (Table 1, entries 4 and 5). Ligand **7** ((+)-DAIB), for example, has been successfully used in the catalytic 1,2-addition of alkenylzinc reagents, prepared similarly by in situ borane−zinc transmetalation.[18] However, in the zirconocene−zinc manifold only 3% ee was obtained. Thioacetate **9** led to a considerable improvement (70% ee, entry 6), but the best results were achieved with van Koten's thiol amine **10** (89% ee, entry 7). Encouraged by the results

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(5) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205.
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(7) Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631.
(8) For the Cu(I)-catalyzed asymmetric addition of organozirconocenes to α,β-unsaturated acyloxazolidinones, see: Wipf, P.; Takahashi, H. *Chem. Commun.* **1996**, 2675.
(9) In fact, Cp_2ZrCl_2 is a catalyst for diethylzinc addition to aldehydes. At 0 °C, the addition of Et_2Zn to benzaldehyde proceeds in 4 h to 50% in the presence of 10 mol % of zirconocene dichloride. In the absence of zirconocene catalyst, only 0−5% conversion is observed.
(10) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(11) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
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(13) Enantioselectivities in entries 1−7 in Table 1 were determined by polarimetry; the % ee for entry 5 in Table 2 was determined via the Mosher ester derivative; all other ee's were obtained by chiral HPLC using a Chiracel OD column. The absolute configurations of (*S*)-1-phenyl-2-hepten-1-ol and (*S*)-4,4-dimethyl-1-phenylpent-2-en-1-ol were assigned on the basis of comparison with the literature $[\alpha]^{18}_D$; all other products were assigned correspondingly.
(14) The use of diethylzinc in place of dimethylzinc provided essentially identical yields and asymmetric inductions.
(15) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
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Scheme 2

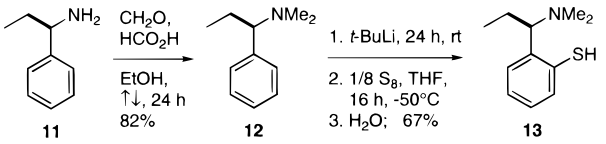

Table 2. Catalytic Asymmetric Addition of Alkynes 1 to Aldehydes 4 in the Presence of 10 mol % of Chiral Ligand 13[22]

entry	alkyne **1**, R =	aldehyde **4**, R =	yield (%)	ee (%)
1	n-C_4H_9	(p-Cl)C_6H_4	83	97
2	n-C_4H_9	(p-CF_3)C_6H_4	71	93
3	n-C_4H_9	(p-OMe)C_6H_4	75	63
4	n-C_4H_9	(m-OMe)C_6H_4	79	99
5	n-C_4H_9	c-C_6H_{11}	63	74
6	n-C_4H_9	$PhCH_2CH_2$	71	64
7	$(CH_3)_3C$	Ph	73	83
8	3-hexyne	Ph	66	99
9	$TIPSOC(O)CH_2CH_2$	Ph	67	92

obtained with this amino thiol ligand,[19] we sought to enhance stereoselectivity by increasing the steric bulk at the benzylic position of **10**. Starting from (*R*)-ethylbenzylamine **11**,[20] Eschweiler−Clark methylation followed by ortho lithiation and trapping with elemental sulfur yielded amino thiol **13** in 54% overall yield (Scheme 2).[17] Addition of 10, 5, and 2 mol % of this catalyst to the test reaction provided chiral benzylic alcohol in very satisfactory 95%, 90%, and 78% ee, respectively (Table 1, entries 8−10). As expected, an increase in the reaction temperature from −30 to 0 °C led to a decrease in ee from 95% to 83% (entry 11).

The scope of the asymmetric aldehyde addition of zirconocene-derived organozinc reagents with 10 mol % of catalyst **13** is illustrated in Table 2. Electron-withdrawing substituents on aromatic aldehydes are well tolerated and, in general, lead to increases in % ee's up to 97% for *p*-chlorobenzaldehyde (entry 1). Interestingly, the electron-rich *p*-methoxybenzaldehyde provides a low ee of 63%, whereas the *m*-methoxy substituent boosts selectivity to 99% (entries 3 and 4). Aliphatic aldehydes are poorer substrates in terms of enantioselectivity, and with cyclohexylcarboxaldehyde and hydrocinnamaldehyde the enantioselectivity drops to 64−74% ee. Very promising preliminary results were obtained with the internal alkyne 3-hexyne and a silyl ester functionalized terminal alkyne that provided benzaldehyde addition products in 99 and 92% ee, respectively (entries 8 and 9).

Initially, we rationalized the successful catalysis with amino thiols **10** and, in particular, **13**, vs amino alcohols such as **7** and **8** with the greater oxophilicity of zirconium over zinc species that would lead to an unfavorable complexation equilibrium with amino alcohols. However, kinetic GC experiments actually established that in the presence of amino alcohol **8** the addition of zirconocene-derived hexenylzinc to benzaldehyde actually proceeded considerably faster to 50% completion than the reaction catalyzed by amino thiol **13** (Figure 1). Product formation in the presence of **13** is comparable to the rate obtained in the absence of chiral ligand, e.g., for the reaction entirely mediated by achiral or racemic zirconocene byproducts. Therefore, the high enantioselectivity observed with amino thiol **13** is not based on faster kinetics for the asymmetric reaction,[21] and

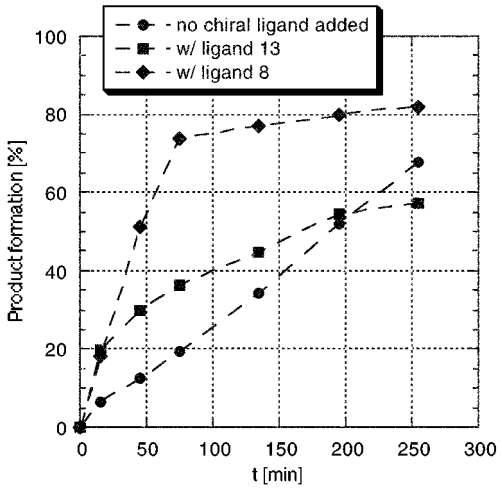

Figure 1. Kinetic studies (GC) for 1-phenyl-2-hepten-1-ol formation in a mixture of hexenylzirconocene/Me_2Zn at −30 °C in the absence of chiral ligand and in the presence of 10 mol % of **8** and **13**. Rates for disappearance of benzaldehyde (not shown) were analogous to the product formation kinetics. All measurements were reproduced two to four times.

the significant increase in reaction rate observed with amino alcohol **8** does not support the hypothesis that preferential complex formation between **8** and zirconocene is mainly responsible for the decrease in asymmetric induction. The presence of both zirconium and zinc species in the reaction mixture clearly complicates the interpretation of kinetic data, and more mechanistic studies will be needed to elucidate the role that the zirconocene byproducts play in the catalytic cycle.

In conclusion, in situ hydrozirconation of alkynes, transmetalation to dimethylzinc, and chiral amino thiol-catalyzed addition to aldehydes provides an efficient protocol for the asymmetric preparation of (*E*)-allylic alcohols. Highlights of this reaction are the excellent enantioselectivities observed with the new chiral ligand **13** and aromatic aldehydes as well as the efficiency of the reaction with the internal alkyne 3-hexyne and the functionalized substrate 4-pentynoate. Further structural modifications of **13** will be explored in order to improve enantioselectivities with aliphatic aldehydes.

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Supporting Information Available: Experimental details and characterization for all new compounds. Copies of ^1H and ^{13}C NMR spectra (10 pages).

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(19) For other applications of amino thiols as ligands in zinc-mediated aldehyde additions, see ref 16 and: (a) Kang, J.; Lee, J.; Kim, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2009. (b) van Koten, G.; Rijnberg, E.; Jastrzebski, J.; Janssen, M.; Boersma, J. *Tetrahedron Lett.* **1994**, *35*, 6521.

(20) This compound was obtained in 98% ee from BASF. We thank Drs. Dietrich and Ritter for a generous sample of **11**.

(21) In the addition to hydrocinnamaldehyde (Table 2, entry 6), we also analyzed the dependence of the % ee on conversion and found it to be consistent at 65 ± 2% throughout the course of the reaction.

(22) In a typical protocol, a suspension of 0.21 g (0.81 mmol) of zirconocene hydrochloride in 2 mL of dry CH_2Cl_2 under N_2 was treated with 94 μL (0.81 mmol) of 1-hexyne at room temperature. The mixture was allowed to stir for 5 min before the removal of all volatiles in vacuo. The resulting light yellow solid was then dissolved in 2 mL of dry toluene, cooled to −65 °C, and then treated with 0.41 mL (0.82 mmol) of Me_2Zn (2.0 M in toluene). To this mixture was added 16.6 mg (0.085 mmol) of ligand **13**. After a period of 1 h, accompanied by slow warming to −30 °C, a solution of 115 mg (0.81 mmol) of 4-chlorobenzaldehyde in 2 mL of dry toluene was added. The reaction mixture was stirred overnight (12 h) before being quenched with saturated $NaHCO_3$. The solution was extracted (3×) with EtOAc, washed with brine, dried ($MgSO_4$), filtered through a pad of SiO_2, and chromatographed on SiO_2 (9:1 hexanes/EtOAc) to yield 151 mg (83%) of (*S*)-1-(4-chlorophenyl)hept-2-en-1-ol as a colorless oil: $[\alpha]_D$ +48.0 (*c* 1.51, $CHCl_3$). Chiral HPLC (Chiralcel OD column) analysis using 0.5% *i*-PrOH in hexane as the eluent indicated 97% ee: ^1H NMR δ 7.25−7.31 (m, 5 H), 5.72 (dt, 1 H, J = 15.3, 6.5 Hz), 5.56 (dd, 1 H, J = 15.3, 6.8 Hz), 5.09 (d, 1 H, J = 6.8 Hz), 2.34 (bs, 1 H), 2.08−2.01 (m, 2 H), 1.41−1.25 (m, 4 H), 0.89 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 142.0, 133.5, 133.2, 132.1, 128.7, 127.7, 74.7, 32.0, 31.4, 22.4, 14.1; HRMS (EI) calcd for $C_{13}H_{17}OCl$ 224.0968, found 224.0971.