

Asymmetric Radical Reduction with Planar Chiral Organotin Hydrides

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The catalytic enantioselective quenching of a trigonal sp^2 intermediate such as free radicals may be quite challenging since only the steric matching between the catalyst and the substrate is important. Consequently, catalytic asymmetric radical reactions are rare¹ and all the known asymmetric radical reductions with tin hydrides have been carried out in stoichiometric sense. Curran and Metzger independently used binaphthyl tin compounds.² Later, Metzger and Thomas reported other tin hydrides, which gave rather poor enantioselectivity.³ Thus, we conceptually devised a system, in which the four 3-dimensional quadrants around the metal are occupied by open space and 3 substituents of small, medium and large sizes, which may be satisfied by planar chiral metallocene tin hydrides with a bulky screen underneath (Figure 1).

Preparation is straightforward. Enantioselective ethylation of the aldehyde **2**⁴ in the catalytic presence of an amino thiol⁵ gave the alcohol **4** in 98% yield and 98.5% ee. Subsequent acetylation, amination and directed lithiation and

stannylation with trimethyltin chloride (to **8**) and finally, redistribution of the tin compound with trimethyltin chloride at 150 °C (to **10**),⁶ followed by $LiAlH_4$ reduction, gave the tin hydride **12**. The unsubstituted ferrocene analog **11** was prepared in a similar way (Scheme 1).

The reduction of a racemic α -bromoester **13**, with stoichiometric Cp* tin hydride **12** led to the formation of (*R*)-**14**⁷ of 87% ee as determined by HPLC analysis (Chiralcel OJ, 5 % IPA/*n*-Hex, 0.3 mL/min, (*R*)-**14** 44 min, (*S*)-**14** 52 min). As far as we know, the enantioselectivity of this level, namely 87% ee, was the highest among the reported examples. As expected, the reactions with the unsubstituted cyclopentadienyl tin hydride **11** gave very low enantioselectivity. This should indicate that our a priori assumption that a severe face-blocking from any one quadrant was necessary for good enantioselectivity was correct (Table 1).

With the outstanding results in hand, a catalytic version of the free radical reduction of **13** with 0.1 equiv of **12** and 1.1 equiv of commercially available poly(methylhydrosiloxane)

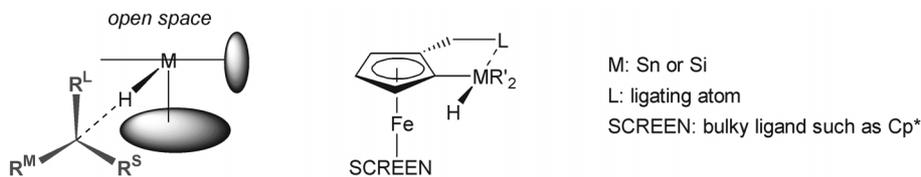
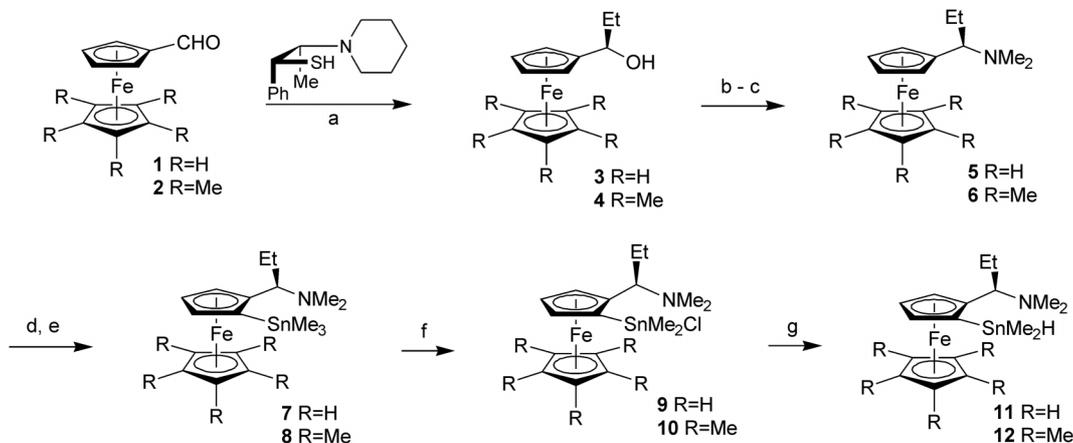
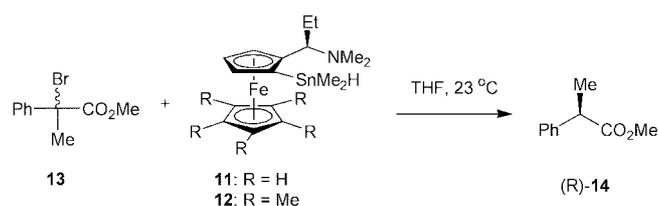


Figure 1. Conjecture.



Scheme 1. Synthesis of the planar chiral tin hydride.

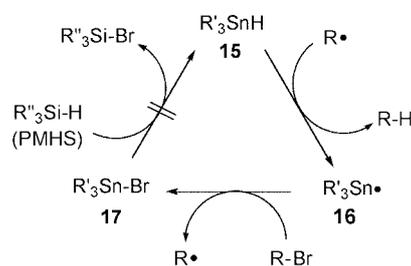
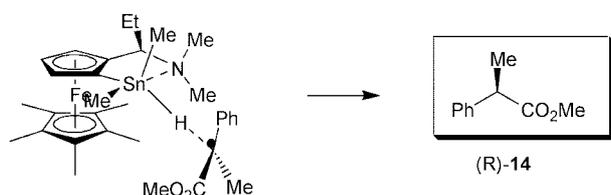
Reagents and conditions: (a) β -aminothiol (5 mol%), Et_2Zn , Et_2O , 0 °C, 12 h (98%, 98.5% ee); (b) Ac_2O , TEA, DMAP, MC, rt, 12 h (100%); (c) $HNMe_2$, THF, 3 d (80%); (d) *t*-BuLi, Et_2O , reflux, 2 h; (e) Me_3SnCl , Et_2O , reflux, 12 h (50% from **6**); (g) Me_3SnCl , 150 °C, 2 h (80%); (h) $LiAlH_4$, Et_2O , rt, 18 h (95%).

**Table 1.** Enantioselective reduction

entry	Ligand	time	ee	conversion
1	12 (1.0 eq)	20 h	87%	65%
2	11 (1.5 eq)	5 h	9%	100%

(PMHS) as a hydride source was attempted. The reaction furnished 90% ee, even though the amount of the (*R*) product formed (9%) just paralleled the amount (10 mol%) of the tin hydride employed. Various fluoride (anhydrous, or saturated aqueous KF, *n*-Bu₄NF)⁸ did accelerate the reaction, but with a drastic drop of enantioselectivity presumably due to epimerization by basic fluoride ion (13–31% ee). The failure of catalytic reduction with the same level of enantioselectivity seemed to be originated from the inability of PMHS to reduce the Sn-Br intermediate **17** formed during the reaction. (Scheme 2) The addition of a carbonate to the reaction mixture in the hope of forming stannyl carbonate, which undergoes reduction with PMHS,^{8c} did not lead to improvement.⁹

The enantioselectivity seems to be a result of differentiation of enantiotopic faces of the prochiral radical. Assuming a trigonal bipyramidal arrangement of the tin atom with one of the methyl groups and the nitrogen at axial position¹⁰ and that the largest phenyl group swings away from the ferrocene moiety, more favorable may be the one in which the methyl group, the smallest group, is in the same side of the dimethylamino group, the largest steric factor on the upper ring. A CaCHE calculation showed that the transition state is more stable by *ca.* 3 kcal/mol than the alternative, which

**Scheme 2.** The sequence initially projected.**Figure 2.** The working model.

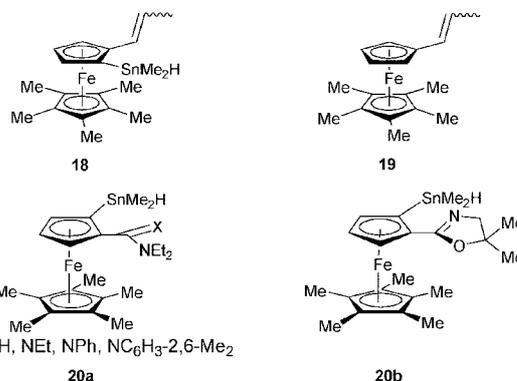
predicts the formation of (*R*) compound (Figure 2).

In conclusion, it has been shown that the enantioselectivity of hydrogen transfer from the chiral tin hydrides to prochiral radicals is determined by steric interactions between the hydrogen donors and the prochiral radicals.

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- Although the tin hydride **12** is a highly enantioselective agent, it slowly decomposed to **18** and **19** during the reaction, due to which the conversion might have been always low. The amides and amidines, **20**, with similar steric setting but with stronger donor character were stable but the enantioselectivity with these trigonalized reagents was less than 25%. Details of preparation will be reported in due course.



- ¹H-NMR spectral data of the tin chloride **10** and the hydride **12** indicated that the two methyl groups on the tin atom are diastereotopic in each case. (**10**: $\delta = 0.88$ (s) and 0.58 (s). **12**: $\delta = 0.22$ (d) and 0.18 (d)) This may be the evidence for intramolecular penta-coordination of the tin atom with the amine nitrogen. (a) Hoppe, S.; Weichmann, H.; Jurkschat, K.; Koglin, C. S.; Drager, M. *J. Organomet. Chem.* **1995**, *505*, 63. (b) Azizian, J.; Roberts, R. G. M.; Silver, J. *J. Organomet. Chem.* **1986**, *303*, 397.