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Reprint

Enantioselective Hydrogen Transfer from a Chiral Tin Hydride to a Prochiral Carbon-Centered Radical

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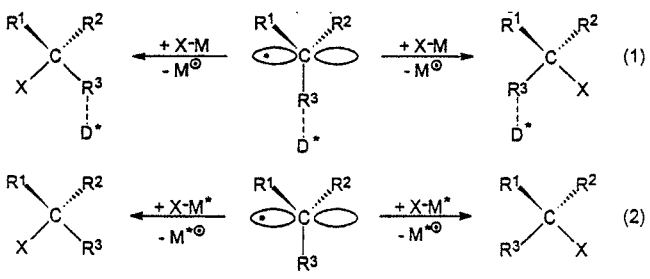
Radical reactions can proceed with high stereoselectivities.[1] Enantioselective radical reactions, however, continue to be a challenging concept. Currently, this problem is being explored by using two principally different approaches [Eqs. (1), (2)]. In analogy to carbanion chemistry, a chiral auxiliary can be attached to an existing radical to control the configuration of the new stereogenic center [Eq. (1)].[1b] The chiral auxiliary used in this approach does not have to be covalently bound to the radical. Murakata et al., for instance, reported the enantioselective radical reduction of an α-iodolactone with tributyltin hydride in the presence of stoichiometric amounts of a chiral



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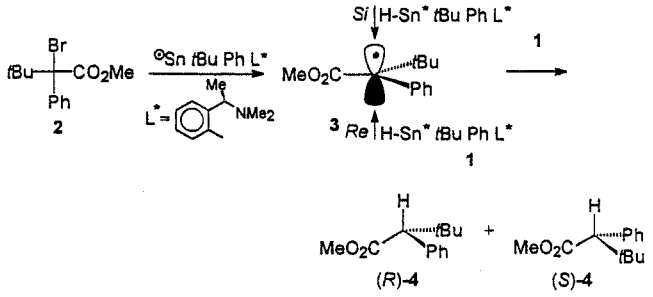
amine and a Lewis acid. In this case, the hydrogen atom is transferred to a chiral radical, which is formed in situ by complexation to the chiral auxiliary.[2] Analogous enantioselective hydrogen transfers[3] as well as intra-[4] and intermolecular[5] additions have also been reported. The prerequisite for such enantioselective reactions is that the substrate contains suitable coordination sites for the chiral auxiliary. These are not required for reactions in which, according to Equation (2), a chiral reagent distinguishes between enantiotopic faces of a radical in diastereomeric transition states.[6]

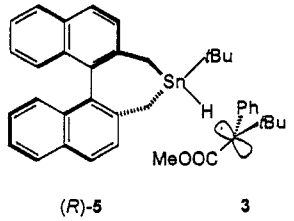
Tin hydrides that contain chiral ligands are hydrogen donors which, in principle, can trap prochiral radicals enantioselectively.[7] Since the chirality of these tin compounds is maintained under conditions of a radical chain reaction,[8] catalytic enantioselective transformations appear feasible.

We have demonstrated that chiral tin hydrides such as **1** reduce the α-bromoester **2** enantioselectively to the ester **4** via the prochiral radical **3** with enantiomeric excesses of up to 25%.[9]



Although the enantioselectivity was low due to the fact that **1** was used as a diastereomeric mixture, the outcome clearly showed for the first time that enantioselective radical transfers of hydrogen atoms according to Equation (2) are possible,[10] and furthermore that high and synthetically useful enantioselectivities can be achieved when suitable, sterically uniform tin hydrides are employed.

Chiral C_2-symmetric tin hydrides are hitherto unknown. However, three 2,2′-dimethyl-1,1′-binaphthyl-substituted tin compounds have been described[11] that could potentially be used as precursors for the synthesis of such a hydride. To explore this possibility, we used MOPAC[12]/PM3 to calculate the structure of the tin hydride (*R*)-**5**, which contains a C_2-symmetric substituent and a rigid conformation with respect to the stannepine ring. Based on steric effects, in the transition state of the H-transfer, in which the donor, hydrogen, and acceptor atoms assume a linear arrangement (Sn···H···C), (*R*)-**5** should be able to distinguish between the enantiotopic faces of a prochiral radical such as **3** (Scheme 1). In this transition state, the small substituent S at the radical center is presumably oriented beneath the binaphthyl substituent, the medium-sized substituent M is oriented to the back, and the large substituent L is oriented to the front in the least sterically hindered space. Based on this model, the selective formation of (*S*)-**4** is expected upon reduction of the α-bromoester **2** via radical **3** (S = COOMe, M = Ph, L = *t*Bu).



Scheme 1. Preferred approach of radical **3** to the tin hydride (*R*)-**5**.

We now report on the synthesis of both enantiomers (*R*)- and (*S*)-**5** of the first chiral tin hydride containing a C_2-symmet-

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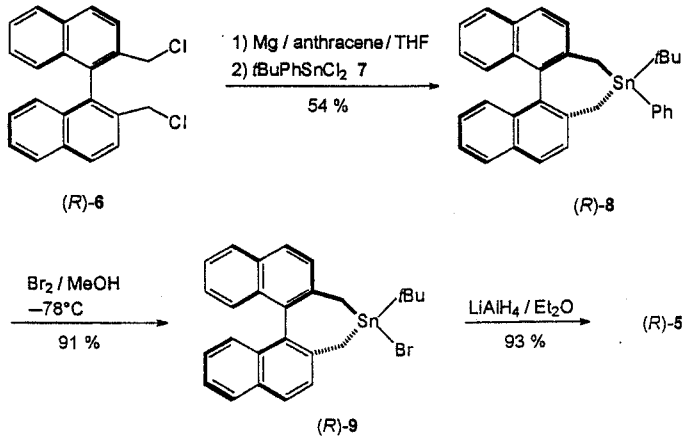
ric binaphthyl substituent,[13] and their application in the enantioselective reduction of the α-bromoester **2**. Furthermore, we demonstrate for the first time that these enantioselective reductions can also be performed with catalytic amounts of the respective chiral tin hydride.

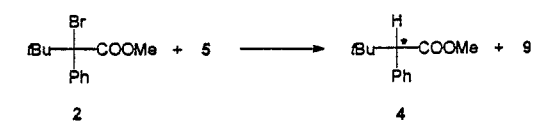
The tin hydrides (*R*)-**5** and (*S*)-**5** were prepared in three steps starting from (*R*)- and (*S*)-2,2′-bis(chloromethyl)-1,1′-binaphthyl **6**, respectively.[14] Compound **6** was first allowed to react with magnesium–anthracene to give the di-Grignard compound, which, upon treatment with *tert*-butylphenyltin dichloride (**7**), afforded stannepine **8**.[14] Bromination to bromostannepine **9** and subsequent reduction with lithium aluminum



hydride gave **5** in an overall yield of 46%. This sequence can be used for a wide variety of different alkyl substituents at the tin atom. In an inert gas atmosphere, the solid tin hydride **5** can be stored for several weeks at room temperature without notable decomposition.

The reduction of the bromoester **2** proceeded smoothly. Only at −78 °C did it become necessary to add triethylborane as an initiator (Table 1).[15] The reaction of (*R*)-**5** at −78 °C led to the reduction product in a ratio of [(*S*)-**4**]:[(*R*)-**4**] = 76:24 (52% *ee*) (Table 1, entry 1). More significantly, the major and minor enantiomers of this reaction could be determined a priori by a simple examination of the steric interactions present in the transition state (Scheme 1). The selectivity decreases with increasing temperatures and was found to be 66:34 (32% *ee*) at −10 °C (entry 2), and 64:36 (28% *ee*) at 24 °C (entry 4). The enantiomeric tin hydride (*S*)-**5** reduces **2** with reversed selectivity (entry 3). A kinetic resolution of **2** was not observed.

Table 1. Enantioselectivity of the reduction of **2** with **5** [a].



2 **4**

Entry	H-donor	*T* [°C]	Yield [%]	[(*S*)-4]:[(*R*)-4]
1	(*R*)-**5**	−78 [b]	93 [d]	76:24
2	(*R*)-**5**	−10	94 [d]	66:34
3	(*S*)-**5**	−15	96 [d]	32:68
4	(*R*)-**5**	24	97 [d]	64:36
5	$NaB(CN)H_3$, (*R*)-**9** [c]	24	98 [e]	63:37

[a] See *Experimental Section* for reaction conditions. [b] Addition of an equimolar amount of Et_3B as an initiator [15]. [c] See *Experimental Section* for catalytic reaction conditions. [d] Based on **5**. [e] Based on **2**.

In general, reductions with tin hydrides can also be performed catalytically; the tin hydride reducing agent can be regenerated by the addition of sodium cyanoborohydride.[16] Particularly noteworthy is the observation that the enantioselective reductions discussed herein proceed with the same selectivities when the catalytic variant is used (entry 5) in which **5** is formed in situ from tin bromide **9**.

Experimental Section

Reduction of **2**: **2** (7 mg, 0.16 mmol), dodecane (3.6 mg, 0.02 mmol) as internal standard, and **5** (30–40 mg, 0.07–0.09 mmol) were stirred for 13–25 h in diethyl ether (5 mL) under argon at the temperatures listed in Table 1. Triethylborane (1 equiv in hexane) was added at −78 °C (entry 1). For entry 5, **9** (1 mg) and $NaB(CN)H_3$ (30 mg, 0.48 mmol) were used. After a saturated NH_4Cl solution had been added, the mixture was dried over $MgSO_4$ and filtered through silica gel. The reaction product was analyzed by using a 25 m heptakis(2,6-di-*O*-pentyl)-β-cyclodextrin-OV1701 capillary (temperature program: 90 °C (5 min), 0.2 degrees per min, 100 °C (5 min): (*S*)-**4**: 25.44 min, (*R*)-**4**: 26.04 min).

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