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Memory of Axial Chirality in Aryl Radical Phosphanylations

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Abstract: The rate constant for phosphanylation of an aryl radical with trimethylstannyl diphenylphosphane (Me_3SnPPh_2) has been measured as $k_{phos} \approx 9 \times 10^8$ M^{-1} s^{-1}. Aryl radicals derived from several axially chiral *o*-haloanilides are trapped by Me_3SnPPh_2 with complete retention of axial chirality as shown by oxidation of the phosphanes to give stable, easily analyzed phosphane oxides or sulfides. Double phosphanylations of *o*,*o*′-dihaloanilides followed by treatment with H_2O_2 or S_8 in either order give enantiomers of a mixed diphosphane oxide sulfide. Chemodivergent trapping of diastereomers of an *N*-(cyclohex-2-enyl)anilide anilide is observed. For one isomer, the cyclization precedes the Me_3SnPPh_2 trapping, while for the other isomer direct trapping with Me_3SnPPh_2 supersedes the cyclization. The products are chiral triaryl phosphanes, oxides, and sulfides that are potentially interesting ligands in asymmetric catalysis.

Memory of chirality has been observed for various types of reactions.[1] Radical reactions are fast and are therefore prime candidates for this kind of chirality transfer, yet examples are rare. Ring strain[2] and conformational effects[3] have been elegantly used to transfer chirality from a radical or diradical precursor to the corresponding product starting with centrosymmetric C-radicals (Figure 1, top). However, chirality transfer from axially chiral radicals to axially chiral products has not been reported (Figure 1, bottom). Central to the challenge is that the intermediate axially chiral radical must have a significantly lower rotation barrier than both the precursor and the product.

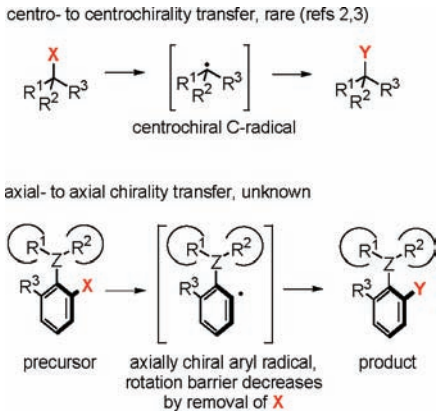


Figure 1. Memory of chirality in radical reactions.

Chiral information in axially chiral aryl radicals derived from iodoanilides of type **1**[4] can be relayed via fast radical cyclizations to centrochiral compounds **2** with high fidelity (Figure 2).[5−7] This success shows that cyclization of the intermediate aryl radicals occurs faster than racemization by rotation around the N−Ar bond. Clearly, stereospecific intermolecular trapping of axially chiral aryl radicals as outlined in Figure 1 requires an extremely fast bimolecular reaction.

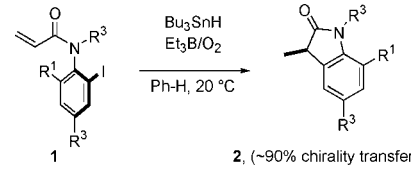
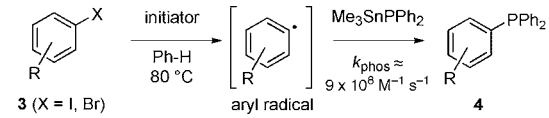


Figure 2. Axial chirality to centrochirality transfer in aryl radical cyclizations.

Radical phosphanylations of aryl halides **3** with trimethylstannyl diphenylphosphane produce phosphanes **4** in high yields (eq 1).[7,8] DFT calculations show that the rate-limiting addition of Me_3SnPPh_2 to a phenyl radical has a high negative reaction enthalpy ($\Delta E_{add} = -28.2$ kcal mol^{-1}). We therefore envisioned that radical phosphanylation might be suited for stereospecific trapping of axially chiral aryl radicals.



(1)

We first measured the rate constant for phosphanylation of an aryl radical by competition kinetics[9] with Bu_3SnH reduction as the "clocked" competition process.[10] *o*-Iodoanisole (**3**, R = *o*-OMe, X = I) was treated with Bu_3SnH (1.0 equiv), Me_3SnPPh_2 (1.0 equiv), and initiator V-40 in benzene at 80 °C to give a mixture of anisole and *o*-anisyldiphenylphosphane (**4**, R = *o*-OMe). From the product ratio and the known rate constant for reduction of an aryl radical by Bu_3SnH ($k_{red} = 1.2 \times 10^9$ M^{-1} s^{-1}),[10] k_{phos} for phosphanylation was calculated to be 9.4×10^8 M^{-1} s^{-1}. This large rate constant encouraged us to study stereospecific trapping of axially chiral aryl radicals with stannylated phosphines.

Aryl iodides **5a**,**b** were readily prepared as described in the Supporting Information (SI). They were resolved by preparative HPLC and were configurationally stable even at 80 °C. To our delight, treatment of **5a** (er = 96:4) with Me_3SnPPh_2 (3 equiv) and AIBN at 75 °C followed by oxidation with H_2O_2 afforded the phosphine oxide **6a** in 65% isolated yield with perfect memory of chirality (er = 96:4, eq 2). The absolute configuration of the precursor **5a** was assigned by X-ray analysis, and the product configuration follows because the reaction must occur with retention. In contrast, AIBN-initiated phosphanylation of enantiopure anilide **5b** under the same conditions furnished after S_8 oxidation[11]

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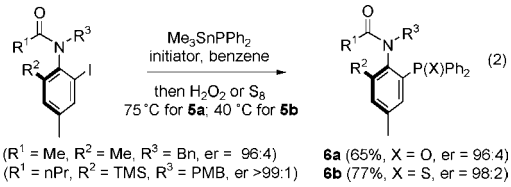
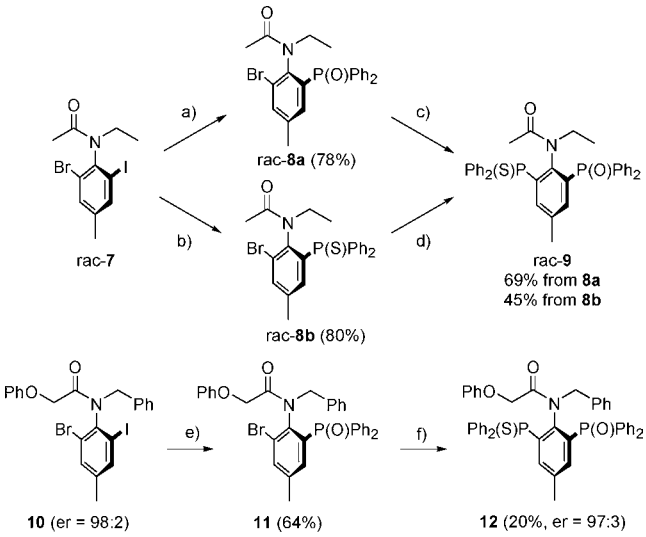
thiophosphine oxide **6b** in 60% yield with an enantiomeric ratio of only 77:23.[12] However, phosphanylation at 40 °C by using di-*tert*-butyl hyponitrite (DTBH) as an initiator afforded **6b** in a 77% yield with high memory of chirality (98/2).[13]



To document the power of the method, we focused on sequential double phosphanylations of axially chiral *ortho*,*ortho*′-bishaloanilide **7** (Scheme 1). Selective substitution of iodine and subsequent H_2O_2 oxidation afforded **8a** in 78% yield. Renewed radical phosphanylation and S_8 treatment provided **9** in a good yield. By reversing the order of the oxidation processes (S_8 oxidation prior to peroxide treatment) **9** was accessible via **8b**, presumably in a stereodivergent way. Compounds like **9** are potential ligands with soft and hard Lewis basic coordination sites.

These reactions were performed with racemic **7**, which proved difficult to resolve. However, highly enantiomerically enriched amide **10** (98:2) was prepared and reacted via **11** to amide **12**, which was isolated with high er (97:3). This proves that excellent memory of chirality can be achieved in both transformations.

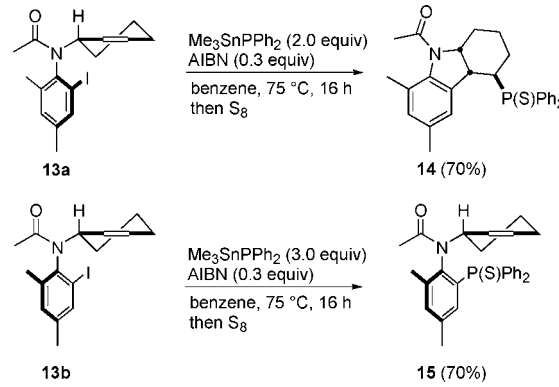
Scheme 1. Double Phosphanylations[a]



[a] (a) Me_3SnPPh_2 (1.1 equiv), AIBN (0.3 equiv), 75 °C, 16 h, then H_2O_2. (b) Me_3SnPPh_2 (1.1 equiv), AIBN (0.3 equiv), 75 °C, 16 h, then S_8. (c) Me_3SnPPh_2 (2.0 equiv), AIBN (0.3 equiv), 75 °C, 24 h, then S_8. (d) Me_3SnPPh_2 (3.0 equiv), AIBN (0.3 equiv), 75 °C, 24 h, then H_2O_2. (e) Me_3SnPPh_2 (4 equiv), DTBH (0.3 equiv.), 40 °C, 17 h, then H_2O_2. (f) Me_3SnPPh_2 (9 equiv), DTBH (0.3 equiv), 40 °C, 63 h, then S_8.

We also pitted this rapid phosphanylation method against a cyclization. 5-*Exo*-aryl cyclizations of radicals derived from *N*-allyl *ortho*-iodoanilides occur with rate constants on the order of 10^9 s^{-1}.[4c] Hence with appropriate tuning, the radical phosphanylation and 5-*exo* cyclization might compete. Highly interesting is the case where the *N*-allyl moiety bears an additional stereogenic center because the 5-*exo*-radical cyclization of the axially chiral radicals will occur via two diastereomeric transition states. Phosphanylation might filter out the higher energy 5-*exo* pathway resulting in a chemodivergent process.

Scheme 2. Chemodivergent Phosphanylations



To test that hypothesis, we prepared the readily separable diastereomeric *ortho*-iodoanilides **13a** and **13b** (see SI). Iodide **13a** was reacted with Me_3SnPPh_2 under radical conditions to provide after oxidation tricycle **14** as the only detectable isomer in 70% overall yield (Scheme 2). No product of direct phosphanylation was detected. Pleasingly, diastereoisomer **13b** underwent aryl radical phosphanylation to give after oxidation **15** in 70% yield. None of the 5-*exo*-cyclization product was obtained.[14] Under these conditions, phosphanylation is much slower than cyclization of the radical derived from **13a** but much faster than cyclization of the radical from **13b**. All of these processes are faster than the N−Ar bond rotation that would interconvert the aryl radicals.

In conclusion, we show the first examples of stereospecific intermolecular trapping of axially chiral aryl radicals. The chiral triarylphosphane products and their derived oxides and sulfides are potentially interesting ligands in asymmetric catalysis.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (DFG) and the U.S. National Science Foundation (NSF) for funding. We dedicate this paper to Prof. Bernd Giese on the occasion of his 70th birthday.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) H_2O_2 oxidation worked equally well; however, the phosphine oxide could not be resolved with the HPLC columns tested.
(12) Evidently, the silyl group lowers the rotation barrier in this series, perhaps by complexation with the amide oxygen. See Keller, A. I. Ph.D. Thesis, University of Pittsburgh, 2007, Chapter 2.
(13) The amide C(O)−N bond rotation energy is rather high for compounds **6a** and **6b**, and the amide *cis-trans* isomers could be separated by HPLC; see also: Ototake, N.; Nakamura, M.; Dobashi, Y.; Fukaya, H.; Kitagawa, O. *Chem.—Eur. J.* **2009**, *15*, 5090–5095.
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