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Synthesis of Arylzinc Thiolates Containing Perfluoroalkyl Chains. Model Catalyst Precursors for the Enantioselective Zinc-Mediated 1,2-Addition of Dialkylzincs to Aldehydes in Fluorous Biphase Systems

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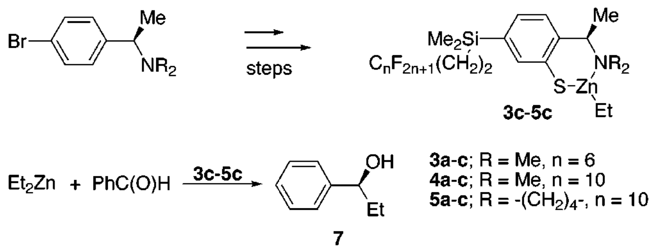
ABSTRACT



The synthesis of perfluoroalkyl-functionalized arene trimethylsilyl ethers and their conversion to ethylzinc thiolates is described. These compounds have been successfully applied as catalysts in the enantioselective addition of diethylzinc to benzaldehyde. This is the first example of a two-phase organic/perfluorous enantioselective catalytic system.

One of the major issues in applying homogeneous catalysis in fine-chemical synthesis is the design of reaction systems that enable separation of the catalyst from the product. Recent examples are the immobilization of catalytically active sites onto soluble polymers or dendrimers[1] and the use of two-phase systems, usually organic solvent/water as in the Ruhr-Chemie hydroformylation process.[2] A disadvantage of the latter approach is the incompatibility of many organometallic catalyst, and also of reagents, with water.

Pioneering work by Horváth et al.[3] led to a new type of two-phase catalytic system, based on the temperature-dependent phase separation of a common organic and a perfluorous solvent. These so-called fluorous biphase systems (FBS) have the advantage that most organometallic reagents are inert toward the solvents involved. A prerequisite is the use of a fluorinated catalyst that shows preferential solubility in the perfluorous solvent. Nowadays an increasing number of academic and industrial groups are working on the design of ligands containing perfluoroalkyl groups and their application in catalysis. This topic has been reviewed recently.[1]

Previously, we[4] and others[5] have shown that chiral *o*-aminoarenethiolates are excellent catalyst for the enantio-

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[1] de Wolf, A. C. A.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37 and references therein.

[2] Hermann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.

[3] Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.

[4] Rijnberg, E.; Hovestad, N. J.; Kleij, A. W.; Jastrzebski, J. T. B. H.; Boersma, J.; Janssen, M. D.; Spek A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2847.

[5] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. *Tetrahedron: Asymmetry* **1994**, *5*, 31.

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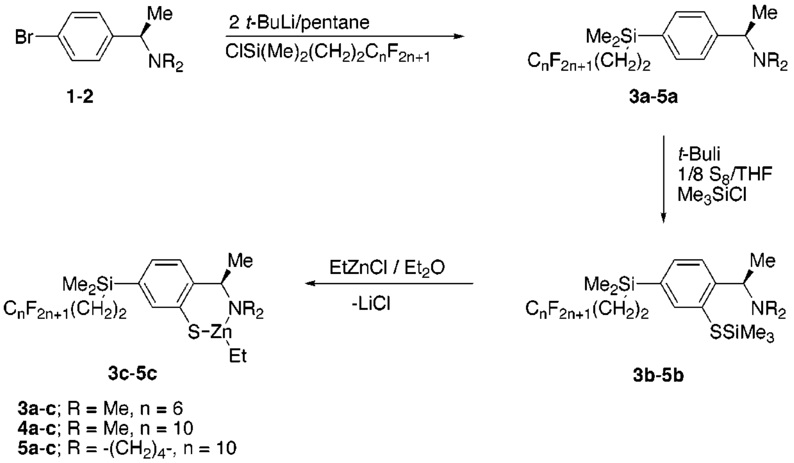
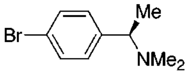
Scheme 1

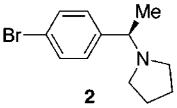


selective addition of dialkylzincs to aldehydes. It is thus a challenge to modify these catalyst in such a way that they become applicable in FBS.

For the introduction of perfluoroalkyl chains in the aminoarenethiolate precursors we used the building block $R_FCH_2CH_2SiMe_2Cl$, ($R_F = C_6F_{13}$ or $C_{10}F_{21}$), reported previously for the functionalization of the 1,3-bis[(dimethylamino)methyl]benzene ligand system.[6] The $CH_2CH_2SiMe_2$ unit serves as a spacer to minimize the electron-withdrawing effect of the perfluoroalkyl groups that might influence the catalytic properties of the ligand system, and a suitable reactive functionality (SiCl) is present for coupling with the arylamine.

The first step of the synthesis involves the conversion of enantiomerically pure (ee = 98.9%) (*R*)-(+)-4-bromo-1-phenylethylamine[7] into the corresponding dimethyl-and pyrrolidine derivatives **1** and **2**.


1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Introduction of the perfluoroalkyl-containing substituent was carried out by reacting **1** and **2** with 2 equiv of *t*-BuLi at −70 °C in diethyl ether. The resulting lithium compounds were reacted with the appropriate triorganosilicon chloride; see Scheme 1.

The heteroatom-assisted ortho-lithiation of the chiral α-substituted benzylamine derivatives has been well established and usually produces the corresponding lithiated compounds within a few hours in quantitative yield.[8] However, quantitative lithiation of the perfluorosilicon functionalized α-methylbenzylamines **3a**−**5a** with *t*-BuLi in pentane requires at least 120 h. The lithiated compounds were not isolated as such, but directly converted into the thiol derivatives by reaction with a stoichiometric amount of elemental sulfur at −70 °C in the presence of added THF. Subsequent treatment of the resulting lithium thiolate with excess Me_3SiCl afforded the trimethylsilyl thioethers **3b**−**5b**. The LiCl that had formed was removed by centrifugation. Evaporation of the solvent afforded the trimethylsilyl thioethers **3b**−**5b** almost pure, and they were used as such. The extreme sensitivity of trimethylsilyl thioethers toward hydrolysis precludes elemental analysis and **3b**−**5b** were therefore characterized by ^1H and ^{13}C NMR spectroscopy.

Previously, we had shown that *o*-aminoaryl trimethylsilyl thioethers can be easily converted into metal arylthiolates by a 1:1 reaction of, e.g., Cu(I)[9] and Zn(II) chlorides[4] with formation of trimethylsilyl chloride. Thus, treatment of the trimethylsilyl thioethers **3b**−**5b** with EtZnCl gave the crude ethylzinc arenethiolates **3c**−**5c** in quantitative yield.

Crystallization from hexane gave **4c** and **5c** as colorless solids, while **3c** was isolated as an orange oil. The new ethylzinc arenethiolates were fully characterized by ^1H and ^{13}C NMR spectroscopy and elemental analysis.[10] The ^1H and ^{13}C NMR spectra are closely comparable to those of the parent ethylzinc arenethiolates that we reported previously.[4]

Monophase experiments[11] in hexane as a solvent have shown that these enantiomerically pure fluorous ethylzinc arenethiolates are active catalysts in the 1,2-addition of diethylzinc to benzaldehyde at a concentration of merely 2.5 mol %. To establish the effect of the perfluoroalkyl chain on the activity and enantioselectivity of these catalysts, we

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(6) Kleijn, H.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Kooijman, H.; Spek A. L.; van Koten, G. *Tetrahedron* **1998**, *54*, 1145.

(7) Obtained from Syncom BV, The Netherlands. Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2349.

(8) Jones, F. N.; Vaulx, R. L.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 3461.

(9) Knotter, D. M.; van Maanen, H. L.; Grove, D. M.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1991**, *30*, 3309.

(10) Analytical data of compounds **3a**−**5c** are available as Supporting Information.

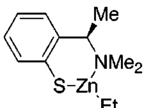
(11) A 0.125 mmol portion of catalyst **3c**, **4c**, **5c**, or **6** was dissolved in 10 mL of hexanes. Subsequently, 6 mL of a 1 M solution of Et_2Zn in hexanes and 5 mmol of benzaldehyde were added. The mixture was stirred for 6 h at room temperature. After aqueous workup, the products were isolated and analyzed by HPLC and ^1H and ^{13}C NMR.

Table 1. Monophase 1,2-Addition of Et_2Zn to PhC(O)H in Hexane with 2.5 Mol % of Catalyst

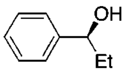
catalyst	conversion (%) after 6 h	ee of (*S*)-**7**[b] (%)
3c	94	87
4c	90	82
5c	100	94
6[a]	81	72

[a] 4 mol % in toluene; conversion >99% after 18 h; ee 92%.[4] [b] Ee was determined by HPLC analysis; Daicel chiralcel OD column, 25 cm × 4.6 mm, eluents 2-propanol/hexane 2/98, flow 1 mL/min; t_R (*R*)-enantiomer, 516 s; t_R (*S*)-enantiomer, 582 s.

compared them with the parent arenethiolate zinc catalyst **6**[4](Table 1).



6



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These results show that both the activity and enantioselectivity are even better than that of the parent catalyst **6**.

Although the introduction of only one perfluoroalkyl chain cannot be expected to result in a good catalyst for a perfluorous biphase system (FBS), such as octane/perfluoromethylcyclohexane, we performed some preliminary experiments[12] in this medium to demonstrate the principle; see Table 2.

Table 2. Enantiomeric Excess of **7** Obtained after 1−2 Addition Reaction of Et_2Zn to PhC(O)H with 2.5 Mol % Catalyst in a FBS Medium

catalyst	run 1	run 2	run 3	run 4	run 5
3c	84	72	37	9	3
4c	79	78	61	36	11
5c	92	92	76	43	28

These experiments show that lengthening of the perfluoroalkyl chain does have a positive effect on the number of runs that the catalyst can be reused (cf. **3c** and **5c**). Moreover, the runs with catalyst **5c** show that also as a fluorous catalyst the pyrrolidine-functionalized arenethiolate gives the best result.

We are currently studying the synthesis of highly branched derivatives of **3c** and **5c** to improve the reusability of the fluorous catalyst with preservation of enantioselectivity.

Supporting Information Available: Full characterization for compounds **3a**−**5c**, ^1H, ^{13}C NMR spectroscopic data and elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] A 0.125 mmol portion of the appropriate catalyst **3c**, **4c**, or **5c** was dissolved in 6 mL of perfluoromethylcyclohexane. Subsequently, 6 mL of a 1 M solution of Et_2Zn in hexanes and 5 mmol of benzaldehyde were added. The two-phase mixture was stirred for 15 h. After this period, the hexane layer was separated. Aqueous workup of this solution gave the product in almost quantitative yield. The product was analyzed by HPLC and ^1H and ^{13}C NMR. To the remaining perfluorous solution a new portion of Et_2Zn in hexanes and 5 mmol of benzaldehyde were added. Again after 16 h the two phases were separated and the product in the hexane layer was analyzed. This procedure was repeated five times; see Table 2.