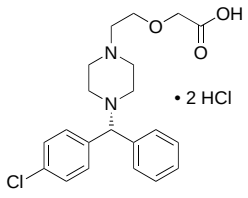
Asymmetric, Catalytic Phenyl Transfer to Imines: Highly Enantioselective Synthesis of Diarylmethylamines**

Nina Hermanns, Stefan Dahmen, Carsten Bolm, and Stefan Bräse*

Enantiomerically pure diarylmethylamines are important intermediates in the synthesis of biologically active compounds.[1] Cetirizine hydrochloride (**1**) stands out from several drug candidates as a commercially important nonsedating antihistamine agent. Binding studies indicate that the *R* enantiomer displays a better pharmacological profile than the racemate.[2] Despite the importance of enantiopure diarylmethylamines, synthetic accesses and especially asymmetric (catalytic) processes for their synthesis are rather limited.[3] While there are several synthetic routes to, for example, enantiopure cetirizine that utilize resolution techniques,[4] stoichiometric amounts of chromium complexes,[5] or diastereoselective approaches with chiral auxiliaries,[6] to the best of our knowledge there is only a single report on an asymmetric catalytic addition of an organometallic arylation agent to an imine derivative. Hayashi and Ishigedani described a highly enantioselective rhodium-catalyzed process for the arylation of *N*-sulfonylimines with aryl stannanes (up to 96% *ee*).[7]



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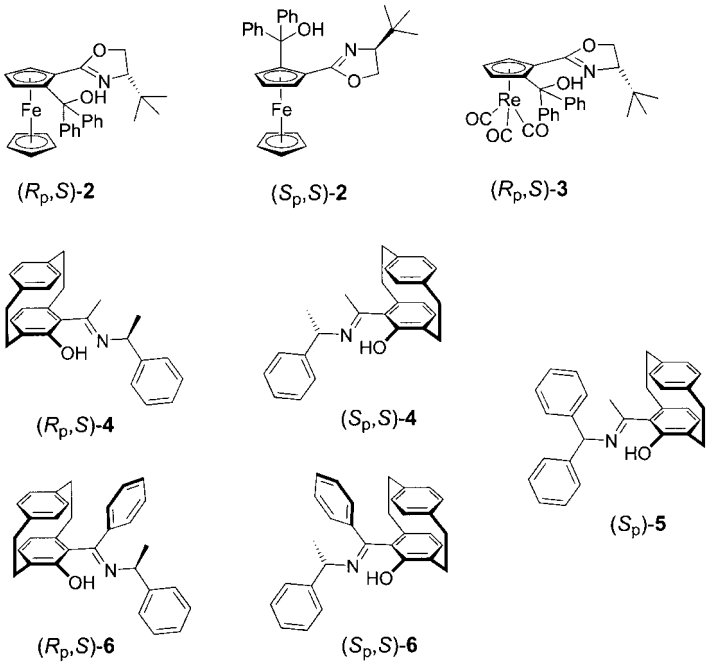
For quite some time we have been engaged in the asymmetric transfer of a phenyl group from organozinc reagents and have developed a protocol for the highly enantioselective transfer of a phenyl group to aldehydes using ferrocene (R_p,*S*)-**2** and cyrhetrene (R_p,*S*)-**3**.[8] However, a major difficulty in the development of asymmetric processes for the transfer of a phenyl group remains the much higher reactivity of diphenylzinc relative to dialkylzinc and the concomitant rapid uncatalyzed background reaction.

Recently, we developed a catalytic procedure for the enantioselective addition of diethylzinc to masked *N*-formylimines by employing catalytic amounts of [2.2]paracyclophane-based ketimines.[9,10] We now report on the combination of both methods, which leads to the first highly enantioselective addition of phenylzinc to imines and gives rise to optically active diarylmethylamines in very high enantiomeric excesses.

At the outset of our study we examined the use of different N,O-ligands (Scheme 1) in the phenylation of *N*-[*p*-tolylmethyl-(toluene-4-sulfonyl)]formamide (**7a,** Table 1). This class of *N*-acylimine precursors is readily available in a one-pot synthesis from benzaldehyde, amide, and *p*-tolylsulfinic acid.[11] The addition to the imine then proceeds by deprotonation of amide **7a**, followed by elimination of the sulfinate to form *N*-formylimine **8a**. Addition of the zinc reagent gives rise to the *N*-formylamine **9a**. We started out by employing the reaction conditions developed for the enantioselective transfer of a phenyl group to aldehydes using a mixed zinc reagent formed in situ from diphenylzinc and diethylzinc. This reagent selectively transfers only the phenyl moiety to the substrate to afford *N*-formylamine **9a** in very high yield without formation of the corresponding ethylation product.[12]



(R_p,*S*)-**2** (S_p,*S*)-**2** (R_p,*S*)-**3**

(R_p,*S*)-**4** (S_p,*S*)-**4** (S_p)-**5**

(R_p,*S*)-**6** (S_p,*S*)-**6**

Scheme 1. N,O-Ligands employed in the asymmetric transfer of a phenyl group to imines.

The ligand screening (Table 1) showed that ferrocene (R_p,*S*)-**2** and cyrhetrene **3**, which represent the best ligands for the enantioselective transfer of a phenyl group to aldehydes (up to 99% *ee*) so far, gave only moderate enantioselectivities in the addition to imine **8a** (entries 1 and 3). The catalysis with diastereomeric ferrocene (S_p,*S*)-**2** did not lead to any improvement (entry 2). In contrast, the use of [2.2]paracyclophane-based ketimines **4**–**6**[13] gave rise to *N*-formyldiarylmethylamines in good to excellent enantioselectivities (up to 97% *ee*, entry 11). Ketimine (R_p,*S*)-**6** showed the best results in the ligand screening and was chosen for further optimization studies. Interestingly, (S_p)-**5** bearing only the element of planar chirality, also gave rise to the product amine in very high enantioselectivity (entry 6). Within our ongoing study of [2.2]paracyclophane-based N,O-ligands, this

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[**] We are grateful to the Fonds der Chemischen Industrie and to the Deutsche Forschungsgemeinschaft (DFG) within the SFB 380 "Asymmetric Synthesis by Chemical and Biological Methods" for financial support.

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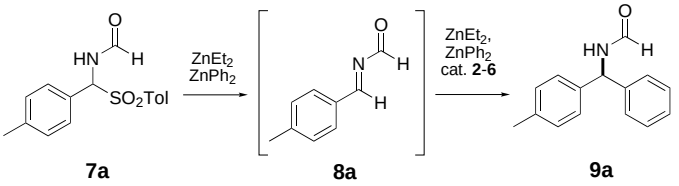
Table 1. Ligand screening for the transfer of a phenyl group to imines.[a]



7a **8a** **9a**

Entry	Ligand (10 mol %)	T [°C]	$ZnPh_2/ZnEt_2$ [equiv]	Yield [%][b]	*ee* [%][c]
1	(R_p,*S*)-**2**	0	2/2	98	54 (−)
2	(S_p,*S*)-**2**	0	2/2	99	48 (−)
3	(R_p,*S*)-**3**[d]	−20	2/2	98	41 (−)
4	(R_p,*S*)-**4**	0	2/2	99	89 (+)
5	(S_p,*S*)-**4**	0	2/2	97	72 (−)
6	(S_p)-**5**	0	2/2	94	91 (−)
7	(S_p,*S*)-**6**	0	2/2	98	71 (−)
8	(R_p,*S*)-**6**	0	2/2	99	93 (+)
9	(R_p,*S*)-**6**	−10	2/2	99	95 (+)
10	(R_p,*S*)-**6**	−10	1.2/1.2	96	92 (+)
11	(R_p,*S*)-**6**	−20	1.5/1.5	98	97 (+)
12	(R_p,*S*)-**6**	−20	1.2/1.2	85	87 (+)
13	(R_p,*S*)-**6**	−20	2.5/–	99	92 (+)
14	(R_p,*S*)-**6**	−40	2/2	51	67 (+)

[a] Reactions were carried out in toluene for 12 h with 0.25 mmol of imine precursor **7a**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information). [d] 9 mol % of (R_p,*S*)-**3** was used.

is the first example of a ligand in which the combination of both planar and central chirality is not required to achieve high enantioselectivity.

Toluene proved to be the solvent of choice; in hexane only moderate yields were obtained. The amount and ratio of zinc reagents was varied and found to be optimal with respect to yield and enantioselecitity when 1.5 equivalents of both $ZnPh_2$ and $ZnEt_2$ were used (entries 9–12). If diphenylzinc was used alone, the *ee* value was slightly lower relative to that obtained with the mixed reagent (entries 11 and 13). This observation can be explained by a faster and, therefore, more competitive uncatalyzed background reaction of diphenylzinc occurring relative to when the modified reagent formed from diphenylzinc and diethylzinc was used.

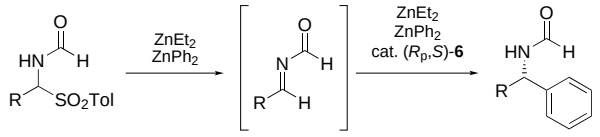
The reaction temperature had a significant impact on the stereochemical outcome of the process as well. With **7a** as the substrate, the highest *ee* value of 97 % was obtained at −20 °C. At −40 °C not only did the *ee* value drop significantly, but the yield was also diminished (entry 14).

A wider range of substrates was applied in the title reaction to demonstrate the broad applicability of the method (Table 2). The results reveal that aromatic imine precursors with different electronic properties as well as different substitution patterns are equally well tolerated. The substrates can be electron rich or electron poor, and even sterically hindered imines with a double *ortho* substitution gave excellent results (95 % *ee*, entry 8). Only a *meta*-substituted starting material gave a product with a slightly lower *ee* value (89 % *ee*, entry 7). Interestingly, the same effect was observed in the addition of diethylzinc to imines using (R_p,*S*)-**4** and (R_p,*S*)-**6**.[9] A decrease in the catalyst loading resulted in the formation of products with slightly or significantly lower enantiomeric excesses depending on the substrate (entries 2, 4, and 5).

The deprotection of *N*-formylamines **9** to the free amines can easily be achieved by acidic methanolysis (Scheme 2). The deprotection of *N*-formylamine **9b** proceeds quantitatively and without racemization. The absolute configuration of **9b** was assigned to be *R* by comparison of the specific optical rotation of free amine (−)-**10b** with the literature value.[14,15] This configuration is consistent with the asymmetric induction observed in the addition of diethylzinc to imines in the presence of (R_p,*S*)-**4** and (R_p,*S*)-**6**.[9] The *ee* value of *C*-(4-chloro-phenyl)-*C*-phenylmethylamine **10b** was determined by HPLC analysis of *N*-[(4-chlorophenyl)phenylmethyl]acetamide (**11b**) obtained by treatment of **10b** with acetic anhydride and triethylamine.[16]

In summary, we have presented the first catalytic and highly enantioselective process for the asymmetric addition of a phenylzinc reagent to imines that gives rise to diarylmethyl-

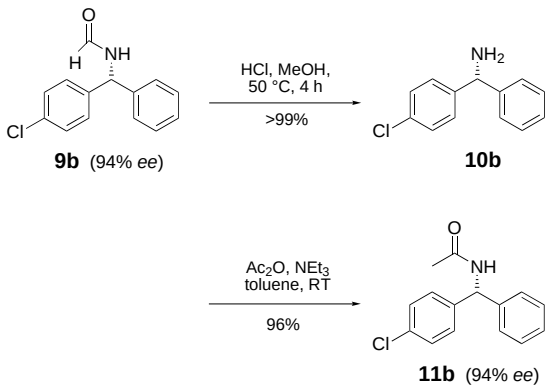
Table 2. Substrate spectrum for the transfer of a phenyl group to imines.[a]



7a-g **8a-g** **9a-g**

Entry	R	Product	(R_p,*S*)-**6** [mol %]	Yield [%][b]	*ee* [%][c]
1	4-MeC_6H_4	**9a**	10	99 (85)	97 (+)
2	4-MeC_6H_4	**9a**	5	99	94 (+)
3	4-ClC_6H_4	**9b**	10	99 (82)	94 (+)-(*R*)
4	4-ClC_6H_4	**9b**	5	99	81 (+)-(*R*)
5	4-ClC_6H_4	**9b**	1	98	69 (+)-(*R*)
6	4-$MeOC_6H_4$	**9c**	10	99 (75)	97 (+)
7	3-MeC_6H_4	**9d**	10	98	89 (+)
8	2,6-$Cl_2C_6H_4$	**9e**	10	99 (89)	95 (+)
9	4-*t*BuC_6H_4	**9f**	10	98 (81)	96 (+)
10	4-$COOMeC_6H_4$	**9g**	10	99 (80)	95 (−)

[a] Reactions were carried out in toluene at −20 °C for 12 h, 1.5 equiv $ZnPh_2$, 1.5 equiv $ZnEt_2$, with 0.25 mmol of imine precursor **7a**–**g**. [b] Determined by ^{1}H NMR spectroscopy. Yields in parenthesis refer to yields after column chromatography. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information).



9b (94% *ee*) **10b**

11b (94% *ee*)

Scheme 2. Deprotection of *N*-formylamine **9b**.

  0044-8249/02/11419-3845 $ 20.00+.50/0

amines in excellent yields and enantioselectivities. Further optimizations and applications of this methodology as well as a detailed mechanistic study are in progress.

Received: June 4, 2002 [Z19442]

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[15] The absolute configurations of all other products should be *R* as well if an analogous stereochemical reaction pathway is assumed.

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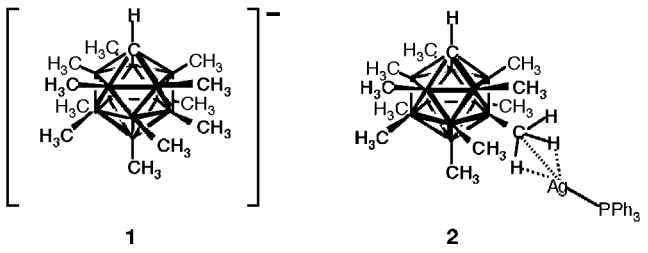
$[(PPh_3)Ag(HCB_{11}Me_{11})]$: A Complex with Intermolecular Ag···H_3C Interactions**

Michael J. Ingleson, Mary F. Mahon, Nathan J. Patmore, Giuseppe D. Ruggiero, and Andrew S. Weller*

Dedicated to Professor Thomas P. Fehlner on the occasion of his 65th birthday

The "least-coordinating" peralkylated monoanionic carboranes based around $[1\text{-}closo\text{-}CB_{11}R_{12}]^-$ (R = alkyl)[1,2] are of significant technological interest. They can form stable, lipophilic, free radicals that are also strong oxidants,[3] novel electrolytes,[2] act as partners with lithium ions as catalysts for pericyclic rearrangements,[4] or can be used to isolate reactive cations such as $[nBu_3Sn]^+$[5] or Me^+.[6] They constitute some of weakest nucleophiles within the family of icosahedral monocarborane anions,[7] and also have the attractive properties of being relatively chemically robust[8] and available in gram quantities. Given that much of the interest in least-coordinating anions, such as the perfluorinated tetraaryl borates, is based around the generation of cationic Lewis acidic metal centers that show enhanced catalytic properties,[9] analogous complexes partnered with peralkylated carborane anions are of significant interest. The fact that peralkylated anions such as **1** can be considered as being negatively charged "alkane balls" is of particular relevance as there is considerable interest in the isolation and structure of metal–alkane complexes.[10] The structures of simple alkali-metal salts of $[1\text{-}closo\text{-}CB_{11}Me_{12}]^-$ have been reported,[11] while the main-group-metal complex $[nBu_3Sn][1\text{-}closo\text{-}CB_{11}Me_{12}]$ is a closely associated ion-pair in the solid state, a structure that is thought to be retained in solution.[5] However, no analogous transition-metal complexes have been described. We have a current interest in the chemistry of metal–ligand complexes partnered with monoanionic carborane anions[12] and report here the first example of a d-block-metal complex containing



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[**] This work was supported by the Royal Society (A.S.W.), the EPSRC (GR/R36824), and the University of Bath. Dr. M. A. Fox (University of Durham) is thanked for his help and useful discussions.

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