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Asymmetric, Catalytic Phenyl Transfer to Aldehydes: Enantioselective Synthesis of Diarylmethanols**

Carsten Bolm,* Nina Hermanns, Jens P. Hildebrand, and Kilian Muñiz

Chiral diarylmethanols are important intermediates for the synthesis of biologically and pharmaceutically active substances.[1] Two major approaches exist for their enantioselective synthesis: the asymmetric reduction of unsymmetrical diaryl ketones and the enantioselective aryl transfer to benzaldehydes. The most prominent examples of the former are based on Corey's CBS reduction methodology[2] and Noyori's enantioselective ketone hydrogenation catalyzed by 2,2′-bis(diphenylphosphanyl)-1,1′binaphthyl (BINAP)/diamine ruthenium complexes.[3] Both reactions work well but also require certain substrate attributes such as electronically very different aryls or *ortho*-substitution of one of the aryl groups. Successful examples of the second strategy have only recently been described.[4] In organozinc chemistry,[5] enantioselective phenyl transfers to aldehydes were first reported by Soai and co-workers who employed a zinc reagent prepared in situ from $ZnCl_2$ and phenylmagnesium bromide and stoichiometric amounts of *N*,*N*-dibutylnorephedrine as chiral ligand (up to 82 % *ee*).[5b, 6] Interestingly, salt-free diphenylzinc behaved differently and gave unsatisfactory results. The first successful application of isolated diphenylzinc in this reaction was described by Fu and co-workers in 1997 who demonstrated that a chiral azaferrocene catalyzed its addition to 4-chlorobenzaldehyde affording the corresponding diarylmethanol with 57 % *ee*.[7] Soon after, Pu and co-workers[8] and Bolm and Muñiz[9] independently developed other catalysts for the asymmetric phenylation of aldehydes based on 2,2′-dihydroxy-1,1′-biphenyl (BINOL) derivatives and planar-chiral ferrocenyl oxazoline **3**,[10] respectively. Here we report on an improvement of the existing methodology which allows the catalytic synthesis of a wide range of arylphenylmethanols **2** from benzaldehydes **1** with very high enantioselectivities.

A major difficulty in the development of an efficient asymmetric phenyl transfer from diphenylzinc to aldehydes **1** is the rapid competitive uncatalyzed pathway, which diminishes the enantioselectivity. To compensate this effect some

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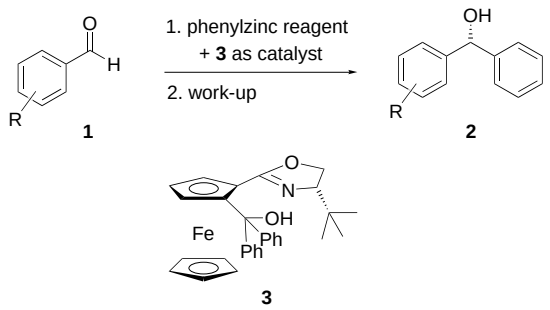
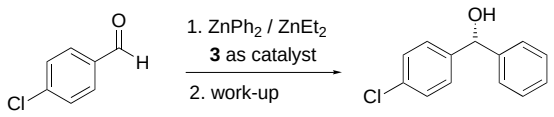


1 **2** **3**

known catalytic systems rely on the use of high catalyst loadings or high dilution conditions. Furthermore, the loss of one phenyl as nontransferable aryl group on zinc has to be accepted. Based on literature data[11, 12] we reasoned that the use of a modified phenylzinc reagent might help to suppress the undesired background reaction and even allow transfer of both phenyl groups.[13] To our delight and supporting our hypothesis we found that employing an organozinc species formed in situ by mixing diphenylzinc and diethylzinc (in a ratio of 1:2)[14] led to a dramatic increase in enantioselectivity. Thus, with 10 mol % of **3** the phenylation of 4-chlorobenzaldehyde now afforded the product alcohol with 97 % *ee* compared to 88 % *ee* with the original system[9] employing diphenylzinc only (Table 1, entry 4). Under these conditions the catalyst loading could even be reduced to 2.5 mol % giving the product with 93 % *ee* (Table 1, entry 2).

Table 1. Phenyl transfer to 4-chlorobenzaldehyde (**1a**) in the presence of catalytic amounts of ferrocene **3**.[a]



1a **2a**

Entry	**3** [mol %]	$ZnPh_2/ZnEt_2$ [equiv]	Yield [%][b]	*ee* of **2a** [%][c,d]	Absolute config.[e]
1	1	0.65/1.3	84	79	*R*
2	2.5	0.65/1.3	86	93	*R*
3	5	0.65/1.3	92	95 (82)	*R*
4	10	0.65/1.3	89	97 (88)	*R*
5	15	0.7/1.4	68	97	*R*
6	40	1.0/2.0	94	99 (90)	*R*
7	100	1.5/3.0	81	99 (94)	*R*

[a] Reactions were carried out in toluene at 0 °C. [b] After column chromatography. [c] Determined by HPLC using a chiral stationary phase. [d] Values in parentheses refer to the results of reactions with pure $ZnPh_2$. [e] Determined by comparison of the order of peak elution during HPLC with literature values.

Further optimization was accomplished by varying the reaction temperature, solvent, and the amount and ratio of zinc reagents: toluene was found to be the solvent of choice and the temperature could be raised to 10 °C without loss of selectivity. As hoped for, use of the $ZnPh_2/ZnEt_2$ mixture had the additional benefit that the amount of diphenylzinc could be reduced, and even with only 0.65 equivalents of this zinc reagent high conversion of the aldehyde was achieved. For maximum selectivity a twofold excess of $ZnEt_2$ was essential, presumably to shift the equilibrium towards a mixed zinc species.[14] Under the optimized conditions several aldehydes were submitted to the aryl transfer reaction (Table 2).

Table 2 shows that for a wide range of aromatic aldehydes the addition proceeds with excellent enantioselectivities of up

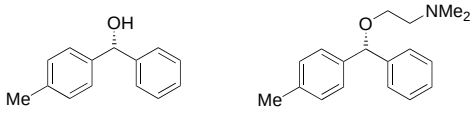
Table 2. Catalyzed phenyl transfer to various aldehydes.[a]

Entry	R in RCHO	Yield [%][b]	*ee* of **2** [%][c,d]	Absolute config.[e]
1	4-Cl-C_6H_4	86	97 (88)	*R*
2	4-H_3CO-C_6H_4	82	98 (87)	*R*
3	3-H_3CO-C_6H_4	99	96	*R*
4	4-H_3C-C_6H_4	86	98 (85)	*R*
5	4-C_6H_5-C_6H_4	98	97 (91)	*R*
6	2-$C_{10}H_9$	70	96 (89)	*R*
7	2-Br-C_6H_4	64	91 (73)	*R*
8	2-Furyl	99	95 (80)	*R*
9	*E*-C_6H_5CH=CH	97	90 (73)	*S*
10	$C(CH_3)_3$	68	94 (56)	*S*
11	C_6H_5-CH_2	82	83	*S*
12	$CH(CH_3)_2$	75	91	*S*

[a] Reactions were carried out in toluene at 10 °C in the presence of 10 mol % of ferrocene **3** using a mixture of 0.65 equivalents of $ZnPh_2$ and 1.3 equivalents of $ZnEt_2$. [b] After column chromatography or purification using preparative HPLC. [c] Determined by HPLC using a chiral stationary phase. [d] Enantiomeric excess in parentheses refers to the reaction performed with 1.5 equivalents of $ZnPh_2$ instead of the $ZnPh_2/ZnEt_2$ combination (for entries 1–7: 10 mol % of **3;** for entries 8–10: 5 mol % of **3**). [e] Determined by comparison of the order of peak elution during HPLC with literature values, or tentatively assigned by assumption of an identical reaction pathway (entries 3–5, 11, 12)

to 98 % *ee*. It should also be emphasized that with the new protocol the range of substrates is no longer limited to *para*-substituted aromatic aldehydes; *meta*- and even *ortho*-substitutions which have so far resulted in only moderate enantioselectivities[9] are well tolerated and the corresponding chiral diarylmethanols are formed with high enantioselectivities (Table 2, entries 3 and 7). Furyl carbaldehyde and cinnamyl aldehyde also react highly selectively and give the corresponding alcohols with 95 % *ee* and 90 % *ee*, respectively (Table 2, entries 8 and 9).

Noteworthy is that product **2b**, which is obtained in a single step from 4-methylbenzaldehyde with 98 % *ee*, is the direct precursor of antihistaminic (*R*)-neobenodine **4.**[15] By reduction of the corresponding unsymmetrical diketone this compound is not directly available with high enantioselectivity.[3]



2b **4**

The addition of diphenylzinc to aliphatic aldehydes was also briefly examined. For selected examples good to excellent enantioselectivities have been obtained (Table 2, entries 10–12). Compared to the previous results the new protocol proved superior again, giving, for example, the addition product of pivalaldehyde with 94 % *ee*.

Experimental Section

In a glovebox a well-dried Schlenk flask was charged with diphenylzinc (36 mg, 0.16 mmol). The flask was sealed and removed from the glovebox. Freshly distilled toluene (3 mL) was added followed by diethylzinc (33 μL,

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0.33 mmol). After the mixture had been stirred for 30 min at room temperature, ferrocene **3** (12 mg, 0.025 mmol) was added, and the resulting solution was then cooled to 10 °C. Stirring was continued for an additional 10 min at this temperature, and the aldehyde (0.25 mmol) was then added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at 10 °C overnight. Quenching with water followed by extracting with dichloromethane, drying of the combined organic phase over $MgSO_4$, and evaporating the solvent under reduced pressure gave the crude product. Column chromatography (silica gel; eluents: hexanes/diethyl ether) afforded the pure secondary alcohol (for *ee* analyses by HPLC see Supporting Information).

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[12] An example of the use of a combination of $ZnPh_2$ and $ZnMe_2$ in this reaction has been described before: Phenyl transfer to nicotinaldehyde catalyzed by *N*,*N*-diethylnorephedrine resulted in phenyl transfer with 20:1 selectivity to give 3-phenylpyridylmethanol in 70% *ee*, while the addition of $ZnPh_2$ only afforded the product alcohol in 73% *ee*; J. Blacker in *Third International Conference on the Scale Up of Chemical Processes* (Conference Proceedings) (Ed.: T. Laird), Scientific Update, UK, **1998**, p. 74.

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A Synthetic Azinomycin Analogue with Demonstrated DNA Cross-Linking Activity: Insights into the Mechanism of Action of this Class of Antitumor Agent**

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Chemical agents capable of inducing DNA interstrand cross-links (ISCs) comprise an extremely important class of clinical cancer chemotherapeutic agents.[2] The azinomycins (**1**

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