Catalytic enantioselective aryl transfer: asymmetric addition of diphenylzinc to aldehydes

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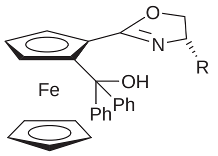
The asymmetric addition of diphenylzinc to aldehydes in the presence of catalytic amounts of a planar chiral ferrocene-based hydroxy oxazoline affords products with enantiomeric excesses of up to 96%.

The asymmetric addition of organozinc reagents (ZnR_2) to aldehydes is a well understood process in which the transferred moiety R is generally an alkyl group such as methyl, ethyl or isopropyl. A variety of chiral compounds catalyse this process yielding the corresponding secondary alcohols with excellent enantiomeric excesses.[1] In contrast, asymmetric transition metal catalysed C–C bond formations between aldehydes and suitable *aryl* transfer reagents are still rare.[2] In this context, Fu described the addition of diphenylzinc to 4-chlorobenzaldehyde which, in the presence of 3 mol% of a planar chiral azaferrocene, gave the product with 57% ee.[3] So far, this has been the only report on this type of arylation.[4,5] In a complementary approach, Miyaura recently described the rhodium catalysed addition of phenylboronic acid to naphthaldehyde. In the presence of an axially chiral monophosphine as ligand, an enantiomeric excess of 41% ee was obtained for the product.[6]

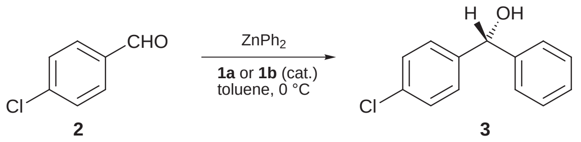
We have recently investigated the influence of planar chirality on asymmetric alkylation reactions catalysed by a series of ferrocenyl hydroxy oxazolines.[7–9] Within this project, the syntheses and catalytic applications of compounds **1a** and **1b** have been described.[7b] We have now employed these ferrocenes in asymmetric arylations by catalysed addition of diphenylzinc to aldehydes.[10] First, the reaction conditions were optimised using 4-chlorobenzaldehyde (**2**) as substrate (Table 1).



1a R = Bu^t
b R = Ph

Even with as little as 3 mol% of ferrocene **1a** quantitative formation of **3** was observed, indicating the efficiency of this catalysis (Table 1, entry 1). HPLC using a chiral stationary phase revealed an enantiomeric excess of 64% for the resulting secondary alcohol. By incresing the catalyst loading to 5 and 10 mol%, the ee of **3** was raised to 82 and 88% ee, respectively (entries 2, 3). Ferrocene **1b** proved to be equally efficient and gave identical results (entry 5). Finally, the reaction temperature was lowered to −20 °C. Still, high conversion was achieved, but the increase in ee was only minor (entry 4). It is of note that the absolute configuration of the product is *R*, indicating that the face selectivity of the catalysis is unchanged with regard to the related alkylation reactions described before.[7] Such unchanged selectivity had also been reported by Fu,[3] but contrasts the findings by Soai observed in reactions with *in situ* formed diphenylzinc.[1d,5a]

Table 1 Asymmetric addition of diphenylzinc to 4-chlorobenzaldehyde (**2**) in the presence of catalytic amounts of ferrocene **1a** or **1b**



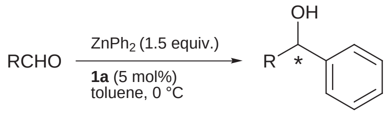
Entry	Ferrocene (mol %)	*t*/h	Yield[a] (%)	Ee of **3**[b] (%)	Configuration[c]
1	**1a** (3)	12	99	64	*R*
2	**1a** (5)	15	99	82	*R*
3	**1a** (10)	14	99	88	*R*
4[d]	**1a** (10)	11	92	90	*R*
5	**1b** (10)	13	99	88	*R*

[a] Isolated yield after column chromatography. [b] Determined by HPLC using a chiral stationary phase (Chiralcel OB, *n*-hexane–Pr^{i}OH = 4 : 1, 1.0 ml min^{-1}). [c] Determined by comparison of the optical rotation with literature values. [d] Reaction was carried out at −20 °C.

In order to guarantee a reasonable catalytic process, the catalysts loading was limited to 5 mol% and the reaction temperature was maintained at 0 °C in further studies. Under these conditions, several other aldehydes were submitted to the asymmetric arylation using ferrocene **1a** as catalyst precursor (Table 2).

Several conclusions can be drawn from these results: unsubstituted or *para*-substituted aromatic aldehydes give the highest enantioselectivities (entries 1, 2). *ortho*-Substituents at the aryl group lower the product ee of aromatic substrates (entries 3, 4). Aliphatic aldehydes give enantioselectivities up to a 75% ee as obtained for acetaldehyde (entries 5, 6). A sterically

Table 2 Asymmetric addition of diphenylzinc to various aldehydes in the presence of 5 mol% of ferrocene **1a**



Entry	R	*t*/h	Yield[a] (%)	Ee[b] (%)	Configuration[d]
1	4-ClC_6H_4	15	99	82	*R*
2	Ferrocenyl	11	89	⩾96[c]	*R*
3	2-BrC_6H_5	14	98	31	*R*
4	1-Naphthyl	14	99	28	*R*
5	Me	15	94	75	*S*
6	$Ph(CH_2)_2$	10	91	50	*S*
7	Bu^t	16	99	56	*S*
8	2-Pyridyl	12	98	3	*R*

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC on stationary phase. [c] Determined by ^1H NMR in the presence of Eu(tfc)$_3$. [d] Determined by comparison of the optical rotation with literature values.

demanding *tert*-butyl group does not allow a high ee (entry 7).

The low enantioselectivity in the arylation of 2-formylpyridine (entry 8) is due to a competitive uncatalysed nonselective reaction of diphenylzinc with the substrate itself.[11] Unlike all other arylations where a dark orange to red solution was obtained, in this case the reaction mixture turns light yellow immediately after the addition of the aldehyde. A control experiment in the absence of **1a** showed a solution of identical colour. From this reaction mixture the product alcohol was isolated in 97% yield. Thus, we assume that the arylation of this substrate is initiated by the pyridine itself leading to a product which then is able to catalyse its own formation in an non-stereoselective manner giving racemic pyridyl alcohol.[1d,12,13]

In order to reveal details of the nature of the active catalytic species, a catalysis with scalemic **1b** was performed: arylation of 4-chlorobenzaldehyde (**2**) in the presence of 10 mol% of **1b**, which had an enantiomeric excess of 57%, led to the formation of (*R*)-4-chlorophenyl(phenyl)methanol [(*R*)-**3**] with 48% ee. From this correlation between the enantiomeric excesses of the ferrocene and the product[13] we conclude that heterodimeric species are not involved in the catalytic conversion of the substrate. This is in accordance with our previous results for related alkylation reactions with non-enantiopure ferrocenyl oxazolines.[7–9,14]

In summary, we have described a novel catalytic system for asymmetric arylations of various differently substituted aldehydes employing diphenylzinc as organometallic aryl source.

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Notes and references

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