Highly enantioselective Cu-catalysed asymmetric 1,4-addition of diphenylzinc to cyclohexenone†

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Highly enantioselective Cu-catalysed 1,4-addition of diphenylzinc to cyclohexenone has been achieved for the first time using a monodentate phosphoramidite ligand.

The metal-catalysed enantioselective conjugate addition of organometallic reagents is a widely used method for C–C bond formation in asymmetric synthesis.[1] In particular, during the last decade considerable progress has been made in the copper-catalysed asymmetric 1,4-addition of organozinc compounds to enones.[2] This has led to well established protocols for the highly enantioselective addition of (functionalised) dialkylzinc reagents to a wide variety of unsaturated systems. As a common view in the field, only di*alkyl*zinc reagents can be effectively used in this enantioselective reaction. Despite the fact that diphenylzinc is known to undergo the non-asymmetric copper-catalysed conjugate addition,[3] to the best of our knowledge no highly enantioselective version of the arylzinc addition has been reported. This severe limitation has been compensated by the development of the Rh-catalysed asymmetric 1,4-addition of aryl boronic acids to enones.[4] This reaction allows the enantioselective transfer of aryl and vinyl groups, but not of alkyl groups, to the beta-position of an α,β-unsaturated carbonyl compound.[4,5] Nevertheless, the enantioselective copper-catalysed transfer of aryl groups remains an important goal, if only because of the difference in cost between copper and rhodium. Recently, Reiser *et al.* disclosed the first example of an asymmetric phenyl transfer to cyclohexenone using diphenylzinc as a reagent.[6] With a bisoxazoline-based copper catalyst no reaction was found using pure diphenylzinc, whereas a 1 : 3 mixture of diphenyl- and dimethylzinc afforded exclusively the 1,4-phenylated product with 74% ee.[7]

Encouraged by these findings we decided to use this approach for the phenyl transfer to enones using monodentate phosphoramidite ligands (Fig. 1). This class of ligands affords excellent enantioselection in the Cu-catalysed conjugate addition of dialkylzinc reagents to enones.[2] 3-Phenylcyclohexanone (**6**, Scheme 1) was selectively obtained in less than three hours with 36% ee from cyclohexenone and a mixture of diphenyl- and dimethylzinc (1 : 1),

using Cu(OTf)$_2$ (1 mol%) and ligand (*S,R,R*)-**1** (2 mol%) at −30 °C in toluene. Surprisingly, when the reaction was carried out under the same experimental conditions but with ZnPh$_2$ in the absence of ZnMe$_2$, a major improvement in the enantioselectivity was found, affording **6** with a promising 76% ee (entry 1, Table 1).

To our delight we found that by optimization of the reaction temperature (entries 1–3), we could obtain the corresponding 1,4-addition product (*S*)-**6** with an excellent 94% ee (entry 3) at −60 °C! As far as we know, this is the highest enantioselectivity ever reported for an asymmetric phenyl transfer in a Cu-catalyzed conjugate addition.

In order to study a possible matched–mismatched effect in ligand **1**, we performed the reaction using ligand (*R,R,R*)-**1**, which led to (*R*)-**6** with 83% ee (entry 4). Therefore, in analogy with the 1,4-addition of diethylzinc to cyclohexenone,[8] the matched–mismatched effect was found to be relatively small and the absolute configuration of the product depends on the configuration of the BINOL moiety (compare entries 3 and 4). The use of monophosphoramidites **2–4** as chiral ligands in this asymmetric conjugate addition led to a drastic decrease in both the conversion and the enantioselectivity (entries 5–7). Usually, biphenyl was detected as byproduct of the reaction and/or as result of the work-up and decomposition of the excess of ZnPh$_2$.[9] Moreover, at temperatures below 0 °C the conjugate addition turned out to be especially sensitive and in some cases the reaction did not run to completion.[10] Using ligand (*S,R,R*)-**1**, this undesirable early termination of the reaction was avoided by carefully performing the reaction under rigorous water and oxygen free conditions.[11]

In order to explore the reaction further and since pure diarylzinc reagents are not always easily available, we next studied the use of *in situ* prepared ZnPh$_2$ in this enantioselective conjugate addition of phenyl groups (Table 2). Remarkably, under the previously established experimental conditions, the use of diphenylzinc prepared from the corresponding lithium or Grignard reagent by

Fig. 1 Monodentate phosphoramidite ligands.
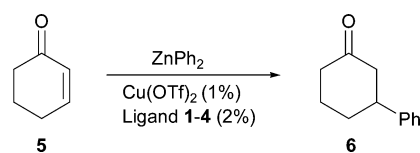
Scheme 1 Copper-catalysed asymmetric conjugate addition of diphenylzinc to cyclohexenone **5**.

Table 1 Ee's obtained with monophosphoramidite ligands **1–4**[a]

Entry	Ligand	Temp. (°C)	Time (h)	Conv. (%)[b]	ee (%)[b]	Conf- **6**[c]
1	(*S,R,R*)-**1**	−30	3	100	76	*S*
2	(*S,R,R*)-**1**	0	1	100	73	*S*
3	(*S,R,R*)-**1**	−60	16	**100**	**94**	*S*
4	(*R,R,R*)-**1**	−60	16	50	83	*R*
5	(*S,R*)-**2**	−60	16	5	2	*S*
6	(*S,R*)-**3**	−60	16	24	11	*R*
7	(*S*)-**4**	−60	16	13	24	*S*

[a] See Scheme 1. Reactions were performed in toluene, using 1.5 equiv of ZnPh$_2$. [b] Determined by GC analysis with Chiraldex A-TA column. [c] Determined by comparison of the optical rotation with literature values.
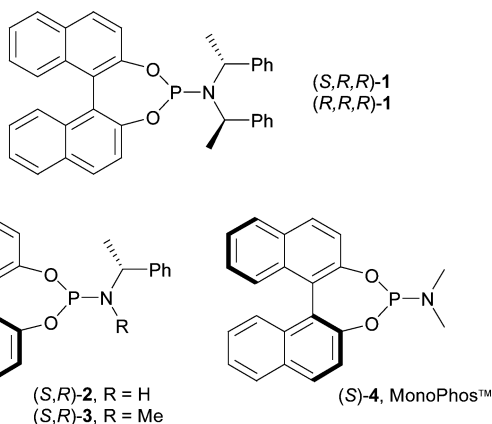
† Electronic supplementary information (ESI) available: experimental and chromatographic details. See http://www.rsc.org/suppdata/cc/b4/b402868f/

Table 2 Ee's obtained of (*S*)-**6** using *in situ* prepared ZnPh$_2$^{a}

| Entry	*in situ* "ZnPh$_2$"	Temp. (°C)	Conv. (%)^b	ee (%)^b
1	PhLi + ZnCl$_2$	−60	44	< 2
2^c	PhLi + ZnCl$_2$	−60	25	42
3	PhMgBr + ZnCl$_2$	−60	18	< 2
4^c	PhMgBr + ZnCl$_2$	−60	12	78
5	Ph$_3$B + ZnEt$_2$	0	**100**	**71**
6	PhB(OH)$_2$ + ZnEt$_2$	0	**100**	**65**

^{a} See Scheme 1. Reactions were performed using 1.5 equiv of "ZnPh$_2$", 1 mol% of Cu(OTf)$_2$ and 2 mol% of ligand (*S,R,R*)-**1** in toluene for 16 h. ^{b} Determined by GC analysis with Chiraldex A-TA column. ^{c} LiCl and MgX$_2$ were partially removed by filtration. See ESI for details.

transmetallation with ZnCl$_2$ afforded the 1,4-addition product **6** as a racemic mixture (entries 1 and 3). The presence of inorganic salts (LiCl or MgX$_2$) is presumed to be the cause of this lack of enantioselection. In fact, moderate enantioselectivities (42–78% ee) were obtained when the corresponding salts were partially removed by filtration after the transmetallation process (entries 2 and 4).

In order to circumvent this problem we examined methods for preparing salt-free diphenylzinc. Among those, boron-to-zinc exchange procedures are promising since byproducts can frequently be removed by evaporation. In particular, we prepared diphenylzinc *in situ* by reaction of triphenylborane and diethylzinc.[12] This transmetallation proceeded at room temperature in less than 1 h, and the subsequently formed BEt$_3$ was easily removed from the reaction mixture under vacuum. The use of ZnPh$_2$ generated in this way led to full conversion and 71% ee in the Cu-catalysed 1,4-addition to cyclohexenone using (*S,R,R*)-**1** at 0 °C (entry 5). Remarkably, this promising enantioselectivity is similar to the one obtained using pure diphenylzinc at that temperature (73% ee, entry 2, Table 1). Unfortunately, it was not possible to enhance the enantioselectivity with the boron-to-zinc exchange methodology since reactions tested at lower temperatures led to poor conversions.

A similar version of this transmetallation, based on the use of readily available phenylboronic acid instead of triphenylborane has been reported recently by Bolm and Rudolph in the asymmetric aryl transfer reaction to aldehydes.[13] Therefore, we tested this protocol in the Cu-catalyzed enantioselective conjugate addition. Although the transmetallation was performed under more drastic conditions (60 °C, 12 h in toluene) we obtained full conversion and a reasonable enantioselectivity in the subsequent asymmetric conjugate addition to cyclohexenone (65% ee, entry 6). Finally, the conjugate addition of phenylmagnesium bromide was studied, as the use of readily accessible aryl Grignard reagents provides a highly attractive alternative to the zinc- or boron-based reagents. Unfortunately, the phosphoramidite based copper catalyst did not yield significant ee's in the conjugate addition of PhMgBr to **5** (Scheme 1). On the contrary, satisfactory results were found employing the recently introduced ferrocenyldiphosphine-copper catalyst.[14] Using JosiPhos **7** as the ligand in Et$_2$O a regioselectivity of 77 : 23 and ee of 44% could be reached (Scheme 2). Changing the solvent to ^{t}BuOMe an excellent regioselectivity 90 : 10 and high ee of 70% were found. Although ee's have to be optimized further, this promising methodology opens the possibility of replacing precious Rh catalysts with cheap Cu complexes in the asymmetric aryl transfer to enones.[4]

In conclusion, highly enantioselective copper-catalysed conjugate addition to enones is no longer limited to the use of dialkylzinc reagents, since a phenyl group can also be transferred to

Solvent	1,4:1,2	ee (%)
Et$_2$O	77:23	44
^{t}BuOMe	90:10	70
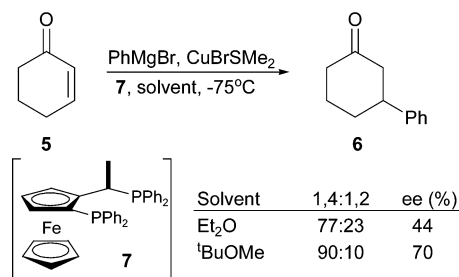
Scheme 2 Cu-catalysed asymmetric conjugate addition of PhMgBr to **5**.

cyclohexenone with 94% ee and full conversion, using a monodentate phosphoramidite ligand. This copper-catalysed asymmetric arylation provides the basis for an important alternative to current rhodium-catalysed arylations. The possibility of using aryl boronic acids as reagents followed by a boron-to-zinc exchange protocol considerably adds to the value of this asymmetric conjugate addition.

Notes and references

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