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Highly enantioselective arylation of ketones

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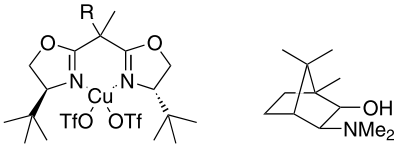
Abstract—The enantioselective arylation of different ketones was successfully performed using several arylzinc reagents, titanium tetraisopropoxide and substoichiometric amounts of *trans*-1,2-bis(hydroxycamphorsulfonylamino)cyclohexane as chiral C_2-symmetric ligand, the enantiomeric excess reaching up to 96%. © 2003 Elsevier Science Ltd. All rights reserved.

One of the most important challenges in organic synthesis is the enantioselective preparation of chiral compounds by forming quaternary substituted stereocenters.[1] Among the different strategies, the 1,2-nucleophilic addition to carbonyl compounds is probably the most straightforward and useful manner of achieving this goal.[2]

In contrast to the enantioselective nucleophilic alkyl transfer process to aldehydes, mainly through organozinc reagents,[3] the corresponding arylation process has not yet reached a high level of maturity.[4] When the electrophile is a prostereogenic ketone, the case is even more difficult. In fact, to our best knowledge, only two examples have been reported in the literature on the enantioselective addition of nucleophilic aryl reagents to ketones. The first example is the Friedel–Crafts reaction of electron-rich aromatic and heteroaromatic compounds to trifluoropyruvate derivatives catalysed by substoichiometric amounts of bisoxazolidine-copper(II) complex **1**, giving the corresponding tertiary alcohol with enantiomeric excesses up to 92%.[5]



1a: R=Me

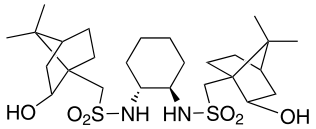
1b: R=$(CH_2)_{11}S(CH_2)_3Si(OMe)_2$-Si

2

The second example is the enantioselective addition of diphenylzinc to ketones catalysed by chiral aminoalcohol **2** in the presence of methanol, the enantioselection being always lower than 91%.[6] However, in both cases, the reactions are limited to only one substrate.

On the other hand, we have recently introduced several camphorsulfonamide derivatives as good chiral ligands for the enantioselective addition of dialkylzinc reagents to ketones.[7] Among the different ligands tested, the C_2-symmetry system **3** gave the best results for this process, with enantiomeric excesses up to 99%.[8]

Herein, we report the first enantioselective arylation of ketones catalysed by titanium[9] tetraisopropoxide and the chiral ligand **3**. This arylation process is not limited to only one reagent, it being possible to use different aryl reagents and ketones.



3

The study started with the addition of commercially available diphenylzinc to 4-methylacetophenone at room temperature in the presence of a substoichiometric amount of chiral ligand **3** (5 mol%) giving the expected tertiary alcohol with practically quantitative chemical yield, after column chromatography. In fact, the GC spectrum of the crude reaction mixture only showed two peaks: the product and the chiral ligand. Moreover, the enantiomeric excess was 92%, as high as previously reported results for similar aryl transfer processes.[5,6] This preliminary result encouraged us to extend this study to other ketones (see Table 1). In all

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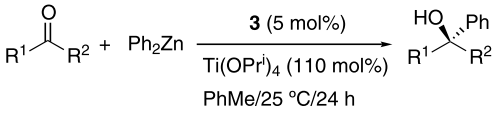
Table 1.



Entry	R^1	R^2	Yield (%)[a]	E.e. (%)[b]
1	Me	4-MeC_6H_4	98	92 (–)
2	Me	4-BrC_6H_4	98	96 (+)
3	Me	4-$CF_3C_6H_4$	97	91 (+)
4	Et	4-BrC_6H_4	95	80 (+)

[a] Isolated yields after column chromatography.
[b] Determined by HPLC (Chiracel AD), the sign of the predominant enantiomer is indicated in parentheses.

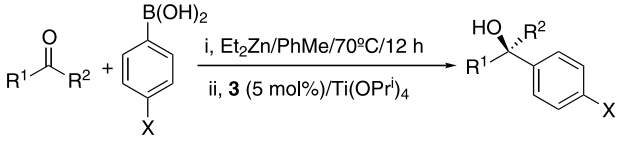
cases tested the chemical yield was nearly quantitative, the enantiomeric excess being independent of the *para*-substituent in the phenone, such as electron-donating or withdrawing groups. However, when the reaction was carried out using 4-bromopropiophenone, instead of 4-bromoacetophenone, the enantiomeric excess decreased to 80% (compared to 96% e.e. obtained for the corresponding acetophenone) what seems to indicate that the reaction is quite sensitive to the steric hindrance (Table 1, entries 2 and 4).

Once it was proved that the enantioselective addition of diphenylzinc to ketones was possible,[10] we turned our attention to the standard procedures to obtain diarylzinc reagents. In principle, the most used methods use the corresponding aryllithium or arylmagnesium reagents, which, after a transmetallation process, give organozinc reagents.[11] However, this procedure has an intrinsic problem in the field of enantioselective reactions: the achiral metal salts, which are formed during the transmetallation process, also catalyse the addition leading to racemic products.[12] In order to avoid this undesired reaction, tedious and difficult procedures have been introduced. In this context, the metal exchange between organoboron[13] or organoboronic[14] derivatives with diethylzinc has been proposed as an alternative for the synthesis of salt-free organozinc reagents.

We chose the last alternative for the in situ preparation of arylzinc reagents. Thus, the transmetallation of phenylboronic acid with a solution of commercially available diethylzinc led to the corresponding phenylzinc reagent, which was used as a phenyl source in the enantioselective addition to 4-bromoacetophenone using the aforementioned procedure (Table 2).

The aforementioned result (Table 2, entry 1) was slightly worse than using pure diphenylzinc. After 24 h, the chemical yield was only 79%, various by-products being detected resulting from ethyl addition and ketone auto-aldol condensation processes. The lower enantioselection, as well as the chemical yield, might be attributed to the presence of organobononate salts and therefore to side-reactions promoted by them. In order to minimise these side-reactions several reaction conditions were tested (Table 2, entries 2–5). The reactions performed at lower or higher temperature did not

Table 2. Enantioselective addition of in situ generate arylzinc reagents to ketones



Entry	R^1	R^2	X	T (°C)	Yield (%)[a]	E.e. (%)[b]
1	Me	4-BrC_6H_4	H	25	79	81 (+)
2	Me	4-BrC_6H_4	H	0	45[c]	73 (+)
3	Me	4-BrC_6H_4	H	60	2	N.d.
4	Me	4-BrC_6H_4	H	25[d]	40	72 (+)
5	Me	4-BrC_6H_4	H	25[e]	35	75 (+)
6	Me	Et	H	25	25	6 (*R*)
7	Me	Bu^n	H	25	65	30[f] (*R*)
8	Me	Ph	Me	25	58	84 (+)
9	Me	Ph	Br	25	65	93 (–)
10	Me	Ph	CF_3	25	31[g] (52)[h]	64 (–)
11	Et	4-BrC_6H_4	H	25	41[g] (91)[h]	68 (+)

[a] Isolated yields after column chromatography.
[b] Determined by HPLC (Chiracel AD), the sign or absolute configuration of the predominant enantiomer is indicated in parentheses.
[c] Isolated yield after 10 days.
[d] 10 mol% of $Ti(OPr^i)_4$ was added.
[e] CH_2Cl_2 was used as solvent.
[f] Determined by HPLC (Chiracel AS).
[g] Isolated yield after 3 days.
[h] In parenthesis yield based on the starting ketone consumed.

improve the previous results and the change of solvent did not have any positive consequence. In addition, a decrease of the titanium alkoxide amount, in order to diminish its possible catalysed auto-aldol reaction, did not have the desired result.

Once the best reaction conditions were established (Table 2, entry 1), other ketones and some arylboronic acids were submitted to this procedure (see Table 2). The reaction with butanone gave a discouraging result, the tertiary alcohol being obtained as a nearly racemic mixture (Table 2, entry 6). However, with slightly different alkyl groups, such as the case of 2-hexanone, the result was better for both the chemical yield and the enantioselection.

Then, keeping acetophenone as electrophile, the effect of different arylboronic acids on the reaction was studied. The enantioselection obtained for the system bearing a weak electron-donating group (*para*-methylpenylboronic acid) was 84%, while for slightly electron-withdrawing group (*para*-bromophenylboronic acid) was as high as 93%, in the range of those obtained using pure diphenylzinc. However, when the reaction was performed using *para*-trifluoromethylphenylboronic acid, as starting material, the enantioselection dropped and the time required for obtaining only 31% chemical yield was 3 days, the starting ketone being recovered in 40% (Table 2, entry 10). A similar result in the enantioselection, reaction time and chemical yield was obtained when 4-bromopropiophenone was used as electrophile (Table 2, entry 11), in this last case the lower result being due probably to the steric hindrance.

The reaction performed using 3-pyridylboronic acid or diethyl(3-pyridyl)borane merits a separate comment. In both cases, the expected tertiary alcohol could not be detected, the starting acetophenone being consumed in reduction and auto-aldol processes.

All the present results seem to indicate that the success of the enantioselective addition is a complicated balance of different equilibria between, on one hand, the formation and reactivity of arylzinc reagents and their asymmetric addition and, on the other hand, the reactions catalysed by all achiral Lewis acids present in the reaction mixture, as well as the reduction process due to the organozinc reagent.

In conclusion, we have reported here the first highly and general enantioselective nucleophilic addition of aryl moieties to ketones catalysed by chiral C_2-symmetry *trans*-1,2-bis(hydroxycamphor-sulfonylamino)cyclohexane ligand **3**. The enantioselection found is as high as that found for similar alkyl transfer processes and the highest for the arylation of prostereogenic ketones.

Acknowledgements

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