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Enantioselective conjugate addition of stabilized arylzinc iodide to enones: an improved protocol of the Hayashi reaction

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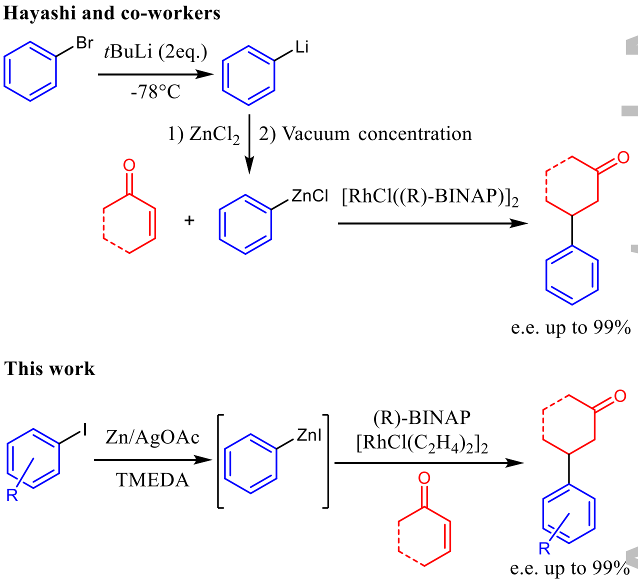
Abstract. Stabilised arylzinc iodide, prepared by direct insertion of zinc into aryl iodides, were used as nucleophiles in the Hayashi Rh-catalysed enantioselective conjugate addition to enones. The reaction conditions were optimized in the addition of phenylzinc iodide to 2-cyclohexen-1-one, obtaining good yields and 99% ee of the addition product. The general applicability of the protocol was checked using different arylzinc iodides and enones. Organometallic reagents endowed with both halogen and electrophilic groups were also successfully used.

Keywords: Asymmetric catalysis; Conjugate addition; Michael addition; Rhodium; Zinc

Introduction

The transition metal catalysed asymmetric conjugate addition of organometallic reagents to electron-poor alkenes represents one of the most straightforward methods for the C-C bond formation in an enantioselective way. The most used organometallic reagents to perform the reaction are arylboronic acids, in the presence of chiral Rh-catalysts,[1–3] and dialkylzinc reagents combined with chiral copper catalysts.[4,5] In this scenario less attention has been paid to the use of organozinc halides, although they are unreactive towards carbonyl groups and can transmetalate both with Rh and Cu, giving species able to perform conjugate additions.[6–10] So far only Hayashi and co-workers have used these organometallic reagents in combination with chiral rhodium catalysts to achieve successfully enantioselective conjugate addition to 2-aryl-4-pyperidones,[8] unsaturated ketones,[11] lactones and aldehydes (Scheme 1).[9] The organozinc halides were obtained by transmetalation of the corresponding organolithium reagents, a procedure entailing not only the need for cryogenic temperatures, pyrophoric substances and the use of two different organometallic reagents but also the preparation of a highly reactive organolithium species, which does not tolerate the presence of electrophilic groups. It is a pity, given that the mild character of organozinc halides, which tolerate the presence of several electrophilic functional groups,[12] should allow the preparation of organometallic nucleophiles endowed with electrophilic groups and hence the access to a wider choice of conjugate addition products. In addition, the search for more efficient and greener protocols of transition metal catalysed enantioselective conjugate additions prompts scientists to develop straightforward methods for the synthesis of the organometallic reagents.[13] To reach these goals the direct insertion of zinc metal to organic halides appears an appealing procedure, provided it can be performed under mild conditions.



Scheme 1. Comparison with literature.

To this purpose, we have recently developed a mild and efficient protocol for the preparation of organozinc iodide by silver catalysed zinc insertion into aryl iodide in the presence of TMEDA, which allowed to obtain in short times arylzinc iodides, also endowed with electron-rich substituent groups.[14] In addition, arylzinc iodides bearing electrophilic groups were obtained. These organometallic reagents were successfully used in Negishi cross-coupling reactions.[14] Encouraged by these results and given the great practical advantage of this strategy, we became interested in performing the Hayashi Rh-catalysed enantioselective conjugate additions to electron poor alkenes with organozinc halides made by direct insertion of zinc metal (Scheme 1). By avoiding the use of highly reactive organometallic reagents, these organozinc halides, obtained under mild reaction conditions, might result even more practical and convenient than the most commonly used arylboronic acids, which require extra effort for their preparation and purification. Herein a highly effective and step-economic protocol for the enantioselective Rh-catalysed conjugate addition of arylzinc iodides to enones is presented, which allowed to react organozinc species having different structures, also those endowed with electrophilic functional groups.

Results and Discussion

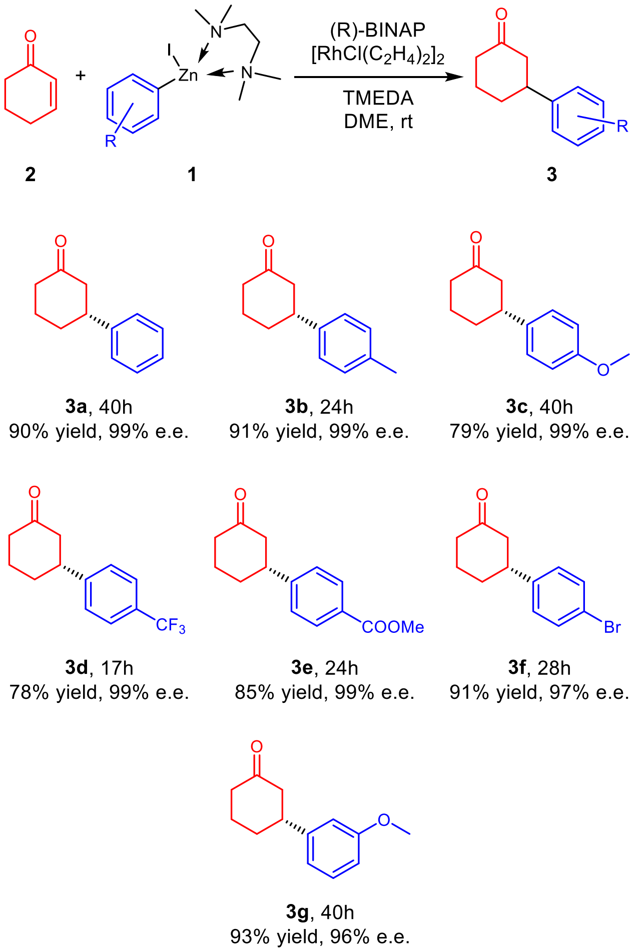
The conjugate addition of phenylzinc halide to 2-cyclohexen-1-one was chosen as a benchmark reaction to compare the effectiveness of organometallic reagents obtained according to different procedures: the results are collected in Table 1. The organometallic species were prepared, according to established protocols, in the same solvent used for the conjugate addition. All the enantioselective reactions were carried out at rT and stopped at complete substrate conversion or when it did not proceed further. The comparison of the results obtained with phenylzinc halides prepared via transmetalation, clearly shows that the effectiveness of the organozinc depended strongly on the organometallic precursor: using the phenylzinc halide obtained from the corresponding Grignard reagent only traces of the conjugated addition product were obtained after long reaction time (entry 1), whereas the organometallic reagent used by Hayashi[8] had given an almost quantitative yield of a nearly enantiomerically pure product after one hour (entry 2). The direct insertion of zinc into iodobenzene promoted by LiCl, according to the Knochel's protocol,[15] gave an organozinc halide that produced undesired reactions on the enone substrates,[16] resulting in the achievement of a negligible amount of addition product (entry 3). By contrast, using the phenylzinc iodide prepared through direct insertion, promoted by silver acetate in the presence of TMEDA,[14] the addition product was obtained with 99% ee, albeit in low yield (entry 4). Even in this case, the reason for the low yield was the formation of large amounts of by-products, likely due to undesired condensation and/or Michael reactions of the *in situ* formed zinc enolate. To improve the yield, trapping the enolate by addition of trimethylchlorosilane was attempted, but a worse result was obtained (entry 5). By contrast, the use of further TMEDA as additive was successful: a good yield of nearly enantiomerically pure addition product was obtained, even if a long reaction time was required to react the substrate (entry 6). Probably, TMEDA produced an extra-stabilisation of the organozinc, which resulted less reactive, and a stabilisation of the *in situ* formed enolate, so that side reactions were removed, but, at the same time, the addition slowed down. By contrast, the use of TMEDA with organozinc prepared according to the Knochel's method was unsuccessful (entry 7).

Table 1. Enantioselective conjugate addition of phenylzinc halide to 2-cyclohexen-1-one.

Entry	Source of the PhZnX	Additive	Solvent	Time	Yield[a]	Ee[b]
1	PhMgCl	-	THF	72 h	traces	n.d.
2[c]	PhLi	-	THF	1 h	98 %	99%
3	Insertion of Zn on PhI promoted by LiCl[d]	-	THF	24 h	traces	n.d.
4	Insertion of Zn on PhI promoted by AgOAc[e]	-	THF	6 h	24 %	99%
5	Insertion of Zn on PhI promoted by AgOAc[e]	TMSCl (1.6 eq.)	THF	7 h	traces	n.d.
6	Insertion of Zn on PhI promoted by AgOAc[e]	TMEDA (1.5 eq.)	THF	70 h	67%	99%
7	Insertion of Zn on PhI promoted by LiCl[d]	TMEDA (1.5 eq.)	THF	70 h	traces	n.d.
8[f]	Insertion of Zn on PhI promoted by AgOAc[e]	TMEDA (1.5 eq.)	THF	70 h	68 %	99%
9[f]	Insertion of Zn on PhI promoted by AgOAc[e]	TMEDA (1.5 eq.)	DME	48 h[g]	65 %	99%
10[f]	Insertion of Zn on PhI promoted by AgOAc[e]	TMEDA (0.75 eq.)	DME	40 h	90 %	99%

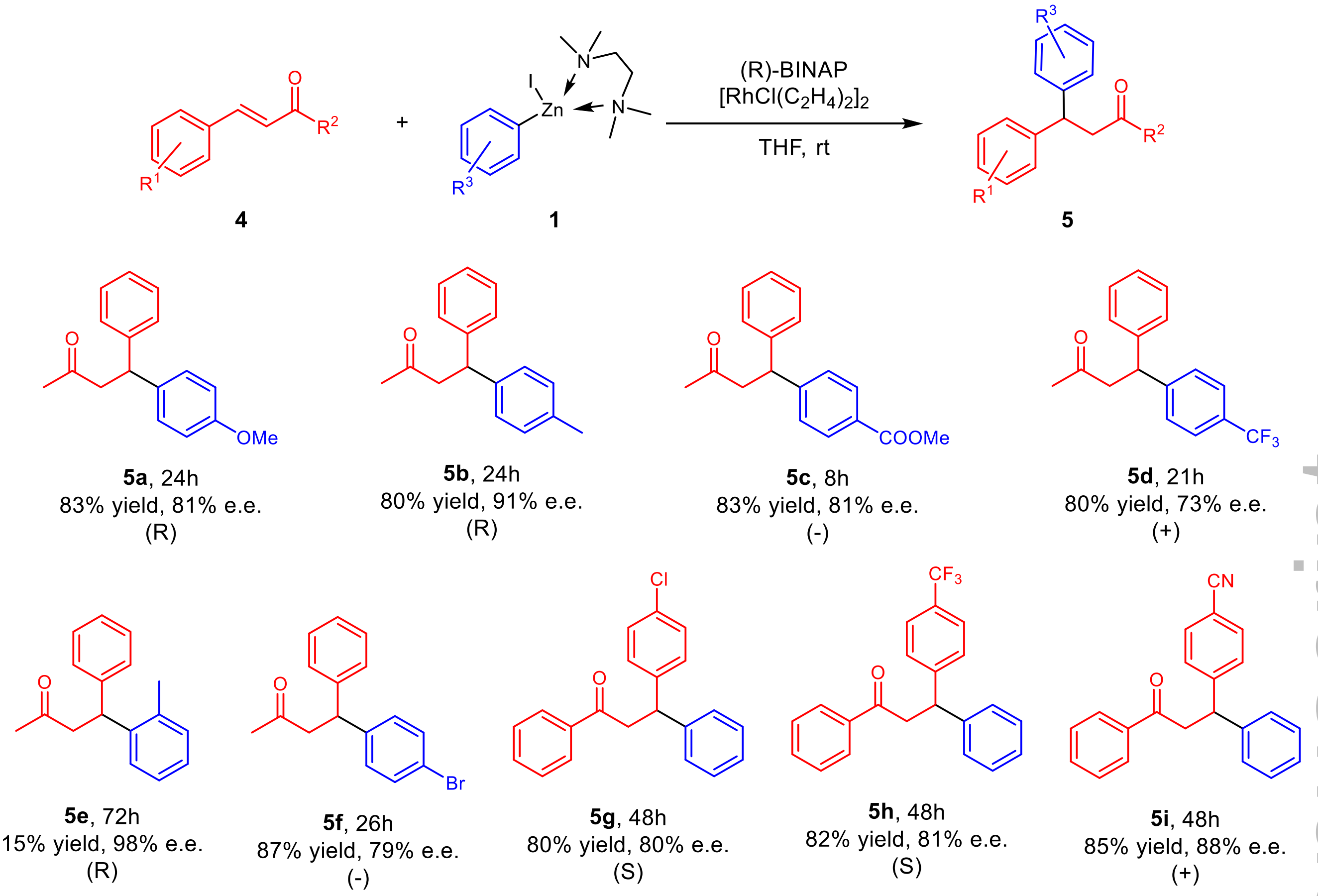
[a] Isolated yield. [b] Determined by HPLC analysis on chiral stationary phase (see Supporting Information). [c] Literature data.[8] [d] Prepared according to Knochel's protocol.[15] [e] Prepared according to our protocol.[14] [f] The chiral catalytic complex was prepared *in situ*.[17] [g] Incomplete conversion.

To further simplify the procedure, the chiral catalytic complex was prepared *in situ*, by stirring for 30 min a solution of $[Rh(C_2H_4)_2Cl]_2$ and (R)-BINAP (1: 2 ratio) in the reaction solvent,[17] then adding the enone and the solution of the organometallic reagent: the same results, both in terms of yield and ee, were obtained (entry 8). The use of DME as reaction solvent resulted in a slower reaction, giving incomplete conversion after 48h, which did not improve further: however, the isolated yield was similar to that obtained using THF (entry 9). This result suggested that also DME contribute to the stabilisation of both organozinc and enolate so that the substrate was cleanly converted to the addition product, but its conversion was incomplete.The best result was obtained by lowering the amount of TMEDA and using DME as the reaction solvent: complete conversion of the enone in 40h was observed and the addition product was obtained in 90% isolated yield (entry 10). It is to note that an (R)-configurated addition product in 99% ee was always obtained, suggesting that the different source of the phenylzinc halide, as well as the different preparation of the catalytic complex, did not alter the asymmetric induction mechanism.



Scheme 2. Enantioselective conjugate addition of arylzinc iodides to 2-cyclohexen-1-one.

With the optimized conditions in hand, we checked the effect of the structure of the stabilized arylzinc iodides on the outcome of the reaction. To this purpose, the enantioselective conjugate addition of different arylzinc iodides on 2-cyclohexen-1-one was performed (Scheme 2). The obtained results suggest that there is small or no effect of the presence of a substituent on the phenyl ring of the organozinc reagent on the stereochemical outcome of the reaction. An (R)-configurated product was always obtained in 99% ee. By contrast, the reaction rate was in general positively affected by the presence of the substituent: slightly higher isolated yields of products **3b**, **3e** and **3f** were obtained in shorter reaction times. The reaction was faster when a strong electron-withdrawing group was present on the phenyl ring (**3d**), whereas a strong electron-donating group slowed down the reaction (**3c** and **3g**). It is worthy of note to have obtained products **3e** and **3f**, which could not be prepared starting from the organozinc halide obtained by transmetalation, because of the presence of groups undergoing nucleophilic attack or metal-halogen exchange with organolithium reagents. It is particularly interesting to note the possibility of further functionalization of products like **3f**, for example, with well-established palladium-catalyzed cross-coupling reactions.[18] This can be achieved thanks to both the high selectivities of the zinc-insertion protocol and the conjugate addition reaction. The generality of this protocol was checked by reacting acyclic enones, both benzalacetone and substituted chalcones, with different stabilized arylzinc iodides: the results are shown in Scheme 3. These substrates were less reactive than 2-cycloehexen-1-one towards stabilised arylzinc halides to the point that the reaction conducted in DME without any additive did not give a decent conversion, even after prolonged reaction time. Therefore THF was used as the reaction solvent and no TMEDA was added: under these conditions the reactions proceeded smoothly, affording good yields of isolated addition products. The reaction rate depended both on the substrate and the arylzinc structure. As far as the structure of the substrate is concerned, chalcones were less reactive than benzalacetone, so that longer reaction times were needed to obtain good yields of products **5g-i**. The most reactive arylzinc halides were again those bearing electron-withdrawing groups: **5c** and **5d** were obtained in less time with respect to the other products. The presence of an ortho substituent on the arylzinc iodide was detrimental for the reaction: only poor yield of **5e** was obtained after long reaction time. The conjugate addition was less enantioselective with these acyclic enones, the ees ranging from 80 to 91% for the majority of the products. A lower ee was obtained in the case of **5d**, whereas **5e** was obtained in very high ee, suggesting that although the steric hindrance on the arylzinc iodide slows down the reaction, however, it makes highly enantioselective the conjugate addition.



Scheme 3. Enantioselective conjugate addition to acyclic enones

To check if the lower enantioselectivity could be produced by a possible background reaction of the organometallic reagent, as in other cases,[17] a blank experiment was performed, by reacting chalcone with phenylzinc iodide without Rh catalyst. No conversion of the substrate was observed after 48h, suggesting that the lower enantioselectivity is likely attributable only to the structural features of the acyclic enones.

Conclusion

An efficient protocol for the enantioselective Hayashi conjugate addition of arylzinc halides to enones was realized, based on the use of stabilized arylzinc iodide. The achievement of the organometallic nucleophiles by direct insertion of zinc into aryl iodides and the in situ preparation of the chiral catalytic complex make straightforward this protocol. The comparison of the results obtained in the conjugate addition of phenylzinc iodide to 2-cyclohexen-1-one with those obtained by Hayashi, demonstrate that the enantioselectivity of the reaction is not affected by the different source of the organozinc. The protocol demonstrated its effectiveness and versatility in particular in the addition of arylzinc iodides endowed with reactive groups under transmetalation conditions, allowing to obtain the conjugate addition products **3e**, **3f**, **5c** and **5f** in good yields and high ees.

Experimental Section

General information.

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. GC-FID analyses were performed on GC instrument with a Split/Splitless injector a FID detector. The melting points were measured using an instrument *Melting Point B-545*. Analytical TLC was performed on precoated silica gel *ALUGRAM Xtra G/UV$_{254}$* plates. Purifications were performed by flash chromatography on silica gel (40-63 µm). All reactions were performed in flame dried glassware under argon atmosphere. Ethereal solvents were dried twice over molecular sieves and distilled before the use. Zinc was flame dried under high vacuum before the use. All other solid reagents were dried under high vacuum before the use.

General procedure for the preparation of ArZnX[14]

In a typical procedure, zinc powder (490 mg, 7.5 mmol) was flame dried under vacuum and cooled under argon atmosphere in a round-bottomed flask equipped with a reflux condenser and magnetic stirrer; silver acetate (8.4 mg, 0.05 mmol) was then added under argon and the mixture dried again under vacuum; the flask was refilled with argon and anhydrous THF (5 mL) or anhydrous DME (5 mL) and chlorotrimethylsilane (15 µL, 0.075 mmol) were added. The mixture was stirred and heated at the reflux for 5 minutes. After cooling, anhydrous TMEDA (750 µL, 5 mmol) and the aromatic iodide (5 mmol) were added.

The mixture was heated at the reflux and stirred for the time needed for each substrate,[14] then was cooled, settled down and the supernatant was used in the following addition reaction. To verify full conversion, an aliquot of the supernatant solution was quenched with NH_4Cl and extracted with Et_2O and another aliquot was iodolyzed and extracted with Et_2O, both the samples were analysed by GLC.

General procedure for the conjugate addition of arylzinc halides to acyclic enones (A)

In a typical procedure, $[RhCl(C_2H_4)_2]_2$ (11.4 mg, 3 mol%) and (R)-BINAP (37.4 mg, 6 mol%) were placed under inert and dry atmosphere and then 1 mL of THF was added. The mixture was stirred for 45 minutes and then the enone (1 mmol) and the arylzinc halide solution in THF (1.5 mmol) were added. The reaction mixture was stirred at room temperature until the GC-FID analysis showed complete conversion of the substrate or when it did not proceed further. Water was added to the mixture and the aqueous phase was extracted with ethyl acetate (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and analysed by chiral HPLC.

For the preparation of the racemic products, the same procedure was followed using racemic BINAP instead of (R)-BINAP.

General procedure for the conjugate addition of arylzinc halides to 2-cyclohexen-1-one (B)

In a typical procedure, $[RhCl(C_2H_4)_2]_2$ (11.4 mg, 3 mol%) and (R)-BINAP (37.4 mg, 6 mol%) were placed under inert and dry atmosphere and then 1 mL of DME was added. The mixture was stirred for 45 minutes and then TMEDA (113 µL, 0.75 mmol), the enone (1 mmol) and the arylzinc halide solution in DME (1.5 mmol) were added. The reaction mixture was stirred at room temperature until the GC-FID analysis showed complete conversion of the substrate or when it did not proceed further. Water was added to the mixture and the aqueous phase was extracted with ethyl acetate (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and analysed by chiral HPLC.

For the preparation of the racemic products, the same procedure was followed using racemic BINAP instead of (R)-BINAP.

Acknowledgements

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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