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Nickel N-heterocyclic carbene-catalyzed cross-coupling reaction of aryl aldehydes with organozinc reagents to produce aryl ketones†

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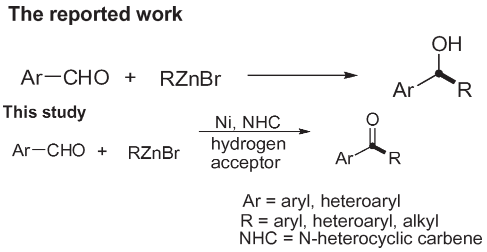
The transformation of aromatic aldehydes into aryl ketones by nickel-catalyzed cross-coupling has been developed. This transformation represents an efficient and attractive synthetic utilization of organozinc reagents. The reaction provides a mild, practical method toward the synthesis of aryl ketones which are versatile intermediates and building blocks in organic synthesis.

Aryl ketones are multifaceted compounds that function as components of pharmacophores, photolabels and photosensitizers, organic electronics, and polymers.[1] Furthermore, manipulation of the carbonyl group provides a generic entry into molecules containing benzylic functionality. As a consequence, their preparation has received considerable attention in organic chemistry. Classical methods for the formation of these important structural motifs include the addition of aryl-metal species to carbonyl compounds and Friedel–Crafts acylation reactions.[2] However, the presence of aromatic heterocycles can limit these strategies, as organometallic reagents can be incompatible with heteroaromatic nuclei and Friedel–Crafts acylations usually work best with π-rich arenes and sometimes result in isomeric mixtures. An alternative approach is the reaction of diazo compounds with aldehydes,[3] but the use of structurally diverse diazo compounds is hampered by preparation and safety issues. In recent years, significant progress has been achieved in carbonylative Suzuki–Miyaura cross-coupling reaction. Various substituted aryl ketones have been successfully synthesized.[4] However, because of the high toxicity, and odorless and flammable character of CO gas, transformations using CO gas must be operated with special care. More recently, metal-catalyzed C–H arylation of aldehydes has provided new pathways for the construction of these molecules.[5] Related to this strategy, aryl ketone formation from aldehydes has been realized using NHC catalysis through reactions with aromatic electrophiles or benzynes.[6] The carbon–carbon bond is the most widespread and fundamental bond existing in organic compounds. Very recently, the preparation of aryl ketones by activation of C–C bonds has received much attention.[7] Despite these advances,[8] versatile and efficient methods for the direct construction of aryl ketones that are compatible with various functional groups and use readily available starting materials remain highly desirable.

Organozinc reagents have been known for more than 150 years. These reagents are known as unique nucleophiles compared to other common organometallic reagents because the softer nucleophilicity of organozinc reagents shows higher functional group tolerance.[9] They have been increasingly applied in bond construction reactions such as Negishi coupling,[10] Fukuyama coupling,[11] oxidative cross-coupling,[12] aldol reaction, *etc.*[9] Notably, the formation of alcohols from aldehydes and organozinc reagents has been particularly successful, whereas the synthesis of ketones from the above two substrates has still rarely been reported. As part of our ongoing efforts to develop transition-metal-catalyzed organic reactions,[13] we herein report an unprecedented nickel N-heterocyclic carbene (NHC)-catalyzed cross-coupling reaction of aryl aldehydes with organozinc reagents that



Scheme 1 Reaction of aryl aldehydes and organozinc reagents.

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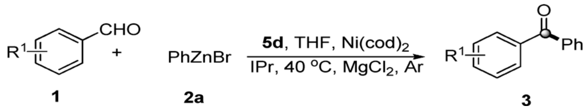
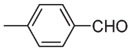
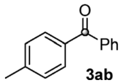
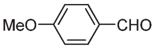
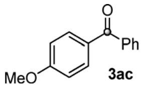
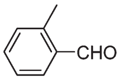
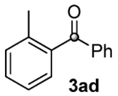
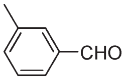
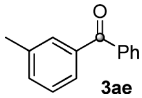
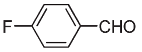
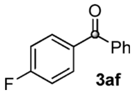
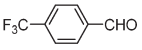
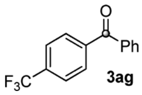
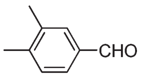
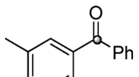
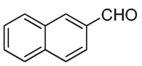
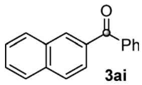
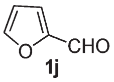
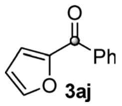
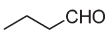
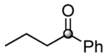
chemoselectively yields aryl ketones as the desired product.[14,15] This reaction constitutes a novel transformation from organozinc reagents into aryl ketones. The method advantageously enriches and complements the existing toolbox used by synthetic chemists, and allows a straightforward access to a wide range of functionalized products (Scheme 1).

Inspired by the pioneering works from the groups of Molander,[16] Cheng,[17] Matsubara[18] and Dong,[15f] we initially chose benzaldehyde **1a** and PhZnBr **2a** as standard substrates to test the feasibility of cross-coupling reaction to form ketones. To our delight, when **1a** and **2a** were treated with a catalytic system consisting of **5a** (hydrogen acceptor, 1.5 equiv.), $MgCl_2$ (1.0 equiv), $Ni(cod)_2$ (8 mol%), and IPr (ligand, 10 mol%) in THF at 30 °C, the desired benzophenone **3aa** was formed in 31% yield (Table S1,† entry 1). Tishchenko homodimer **4a** was obtained in 38% yield (Table S1,† entry 1). Further explorations showed that hydrogen acceptor **5d** [2,2,2-trifluoro-1-(4-methoxy- phenyl)ethanone] gave good results.[19] Next, different solvents were screened to enhance the efficiency of this reaction. It was found that a cosolvent system of 1,4-dioxane and THF was appropriate. Different nickel catalysts were screened, and $Ni(cod)_2$ turned out to be the most effective catalyst (entries 6–9). Other ligands, including ItBu, PCy_3, and SIPr, were tested and found to be less effective than IPr (Table S1,† entries 10–12). However, the absence of nickel catalyst resulted in no detectable amounts of **3aa** (Table S1,† entry 16). Without $MgCl_2$, the reaction gave the cross-coupling product in 46% yield after 10 h (Table S1,† entry 17). These results indicate that the structures of organozinc reagents are possibly not as simple as RZnX.[9b] The coordination of THF and $MgCl_2$ to RZnX may significantly affect the transmetalation step.

Table 1 Scope of aldehydes **1**[a]



1 **2a** **3**

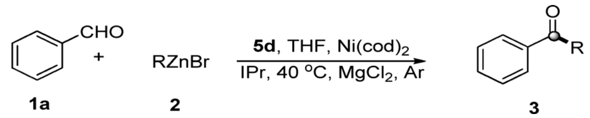
Entry	Aldehydes 1	Aryl ketones 3	Yield[b] (%)
1	 **1b**	 **3ab**	74
2	 **1c**	 **3ac**	74
3	 **1d**	 **3ad**	56
4	 **1e**	 **3ae**	54
5	 **1f**	 **3af**	61
6	 **1g**	 **3ag**	67
7	 **1h**	 **3ah**	69
8	 **1i**	 **3ai**	58
9	 **1j**	 **3aj**	52
10	 **1k**	 **3ak**	0

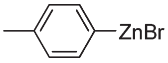
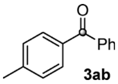
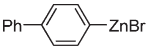
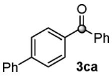
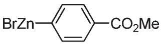
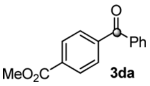
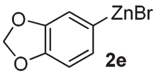
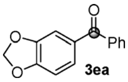
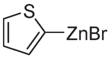
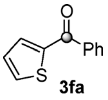
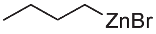
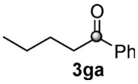
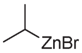
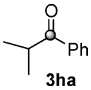
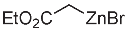
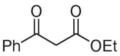
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.3 mmol), **5d** (1.5 equiv.), $MgCl_2$ (1.0 equiv.), $Ni(cod)_2$ (8 mol%), IPr (10 mol%), THF/1,4-dioxane (3 mL, 1 : 1), 30 °C, in Ar atmosphere for 8 h. [b] Isolated yield.

With a set of optimized conditions in hand, we then investigated a series of aldehydes to extend the substrate scope. As summarized in Table 1, the standard reaction conditions were found to be compatible with a wide range of aldehydes **1**. As summarized in Table 1, both electron-donating and -withdrawing aryl aldehydes could be successfully converted to the corresponding aryl ketones in moderate to good yields. Several aromatic substituents, including Me, MeO, F and CF_3, were well-tolerated under standard conditions (Table 1, entries 1–6); substituents at the *ortho*-, *meta*-, or *para*- positions had no distinct influence on the reaction (Table 1, entries 1, 3 and 4). It is noteworthy that trifluoromethyl-substituted aromatic aldehydes were tolerated well (Table 1, entry 6), thus leading to a trifluoromethyl-substituted product which has better membrane permeability and increased bioavailability.[20] The reaction of substrate **1h** with the polysubstituted aromatic aldehyde delivered the desired product **3ah** in good yield (Table 1, entry 7). An aromatic aldehyde with a naphthyl group also participated in this Ni-catalyzed cross-coupling reaction, affording the cross-coupling product in 58% yield (Table 1, entry 8). We also considered the reaction of **2a** with **1j** bearing a furanyl moiety and obtained heteroaryl ketone **3aj** in 52% yield (Table 1, entry 9), further extending the scope of this methodology. Application of an aliphatic aldehyde did not deliver the corresponding ketone under the same reaction conditions (Table 1, entry 10).[21]

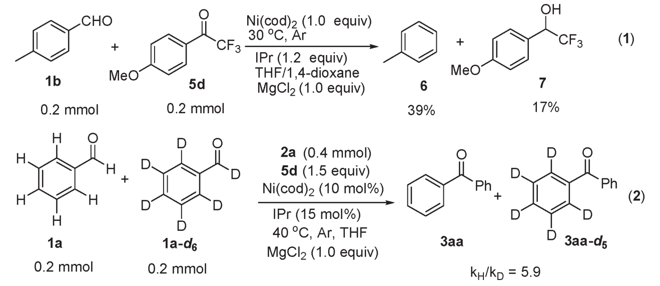
To further highlight the synthetic usefulness of our strategy, we turned our attention to the scope of organozinc reagents (Table 2). Aryl zinc reagents bearing electron-donating groups at the *para* position of the phenyl ring, such as methyl, proceeded smoothly in the reaction to give the corresponding aryl ketone **3ab** in good yield (Table 2, entry 1). Substrates substituted with electron-withdrawing groups, such as Ph and ester, also worked well and afforded the desired products **3ca**–**3da** in 49% and 73% yields, respectively (Table 2, entries 2–3). These results indicate that the electronic nature of the aryl-zinc reagents has little influence on the cross-coupling process. Heteroaryl-substituted substrates could also be converted into the desired products. For example, substrates **2e** and **2f** were transformed into products **3ea** and **3fa** in 70% and 47% yields, respectively (Table 2, entries 4–5). Efforts were made to apply this methodology for the synthesis of aryl alkyl ketones. It was found that reactions with **2g**–**2i** proceeded smoothly to give the aryl alkyl ketones in good yields (Table 2, entries 6–8).

Table 2 Scope of organozinc reagents **2**[a]

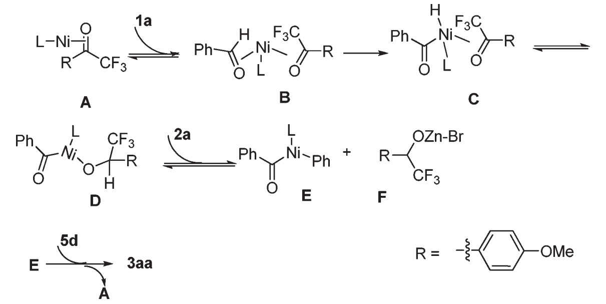


Entry	Organozinc reagents 2	Aryl ketone 3	Yield[b] (%)
1	 **2b**	 **3ab**	69
2	 **2c**	 **3ca**	49
3	 **2d**	 **3da**	73
4	 **2e**	 **3ea**	70
5	 **2f**	 **3fa**	47
6	 **2g**	 **3ga**	62
7	 **2h**	 **3ha**	66
8	 **2i**	 **3ia**	77

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.3 mmol), **5d** (1.5 equiv.), $MgCl_2$ (1.0 equiv.), $Ni(cod)_2$ (8 mol%), IPr (10 mol%), THF/1,4-dioxane (3 mL, 1 : 1), 30 °C, in Ar atmosphere for 8 h. [b] Isolated yield.



Scheme 2 Control experiment.



Scheme 3 Plausible mechanism.

To further probe the mechanism, control experiments with possible intermediates were designed and investigated. In the absence of organozinc reagents, we observed decarbonylation of *p*-tolualdehyde **1b** to produce toluene and reduction of hydrogen acceptor **5a** (Scheme 2, 1).[15f] This result supports the intermediacy of an acyl nickel hydride species, which can undergo decarbonylation in the absence of a organozinc reagent. When a 1 : 1 mixture of **1a** and **1a**-d_6 was subjected to the Ni-catalyzed cross-coupling reaction conditions, we obtained the cross-coupling products **3aa** and **3aa**-d_5 in a ratio of 5.9 : 1.[22] The result suggests that C–H bond activation is the rate-determining step (Scheme 2, 2). Computational studies by Fu and co-workers support the concept of electron-deficient π-ligands on nickel promoting oxidative addition to form aldehyde C–H bonds.[23]

On the basis of these preliminary results and those of previous studies, a plausible mechanism for the Ni-catalyzed cross-coupling reaction of aryl aldehydes with organozinc reagents yielding aryl ketones was proposed (Scheme 3). Ketone **5d** binds to nickel to form complex **A**. Subsequently, complex **A** can coordinate to benzaldehyde **1a** to form intermediate **B**. Oxidative addition to the aldehyde C–H bond gives **C**.[15f] Simultaneously, hydrogen acceptor **5d** is reduced by intermediate **C** to produce acyl nickel alkoxide **D**. Ligand exchange with organozinc reagent **2a** affords **E**, and reductive elimination provides the desired product **3aa**. Coordination of ketone **5d** may occur prior to or immediately after reductive elimination.[24] The coordination inhibits the formation of the undesired product **4a** by disrupting the formation of a cycloisomerization intermediate between two aryl aldehydes.

In summary, we have described a nickel N-heterocyclic carbene-catalyzed cross-coupling reaction of aryl aldehydes and organozinc reagents for the formation of complex aryl ketones. The process operates under mild conditions, involves simple experimental protocols, and uses a commercially available N-heterocyclic carbene catalyst. Further investigations of the mechanism of the reaction and its application are ongoing in our laboratory.

Acknowledgements

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