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Nickel-catalyzed regioselective carbocyclization of *ortho*-halophenyl ketones with propiolates: an efficient route to disubstituted indenols†

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Carbocylization of *o*-halophenyl ketones with propiolates in the presence of Ni(dppe)Br$_2$ and Zn powder in acetonitrile at 80 °C afforded the corresponding 2,3-disubstituted indenols.

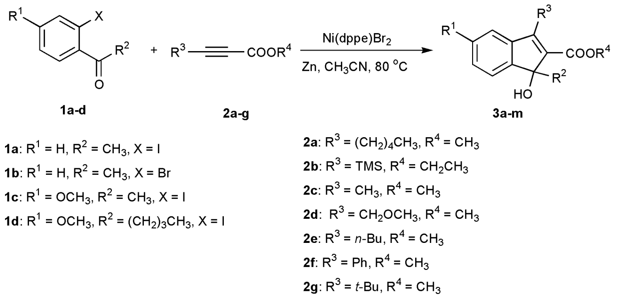
Transition metal-catalyzed carbocyclization has become a very powerful tool for the construction of carbocycles with various ring size.[1] Recently, cyclization of *o*-iodobenzene derivatives with unsaturated chemical bonds to give 5- or 6-membered ring carbocycles[2,3] or heterocycles[4] catalyzed by palladium complexes has attracted great attention. Indenols are an important class of organic compounds that show various bioactivities.[5,6] Despite their utility, few methods are known for the synthesis of these compounds.[7] Vicente and his coworkers reported the stoichiometric and catalytic synthesis of indenols from mono- and di-substituted alkynes and organomercuric compounds using palladium reagents,[8] while Yamamoto *et al.* described a palladium-catalyzed carbocyclization of *o*-halophenyl ketones with disubstituted alkynes to give indenols.[9] No other metal complex is known to catalyze the indenol formation reaction. Our interest in nickel-catalyzed carbon–carbon bond formation[10,11] and the observation of nickel complexes to promote arylation of aldehydes by aryl halides[12] led us to explore the possibility of nickel complexes as catalysts for the carbocyclization. Herein, we report that a nickel complex/zinc system is able to catalyze the carbocyclization of *o*-iodophenyl ketones with various alkynes under mild conditions to give the corresponding indenols with remarkably high regioselectivity. In addition, the alkynes that are effective in this nickel-catalyzed carbocyclization are considerably different from those in the palladium-catalyzed reaction reported previously.[9a]

The reaction of 2-iodoacetophenone **1a** (0.50 mmol) with methyl 2-octynoate **2a** (1.5 equiv) in the presence of Ni(dppe)Br$_2$ (dppe = bis(diphenylphosphino)ethane) and zinc metal powder in acetonitrile at 80 °C for 13 h gave a 2,3-disubstituted indenol **3a** in 94% yield. The reaction is completely regioselective and only a single regioisomer was detected by ^{1}H NMR in the crude product mixture. Under similar reaction conditions, **1a** underwent carbocyclization with a variety of substituted propiolates ($R^3C{\equiv}CCO_2R^4$) to give the corresponding indenols. Thus, treatment of **1a** with **2b–e**, where R^3 = –(CH$_3$)$_3$Si, –CH$_3$, –CH$_2$OCH$_3$, and –(CH$_2$)$_3$CH$_3$ (Scheme 1 and Table 1), provided the corresponding indenols **3b–e** in 86, 74, 68, and 87% yields, respectively (entries 3, 5, 7 and 8). There was no homo-trimerization product of these propiolates observed except methyl 2-butynoate. The latter gave the corresponding homo-trimerization product in 7% yield. The reaction of **1a** with methyl phenylpropiolate **2f** also proceeds smoothly to afford the desired carbocycle **3f** in 52% isolated yield. The regiochemical assignment of the propiolate moiety was carefully established based on NOE experiments.

Similar to *o*-iodophenyl ketone, *o*-bromophenyl ketone (**1b**) cyclizes with propiolates **2a–c** to give corresponding indenols **3a–c**, but in slightly lower yields (Table 1, entries 2, 4 and 6). *o*-Iodophenyl ketone bearing a methoxy group on the aromatic ring was also tested for the cyclization reaction. Treatment of **1c** with propiolates **2a** and **2c** provided the corresponding substituted indenols **3g** and **3h** in 86 and 75% yields, respectively. The reaction of **1c** with *tert*-butylpropiolate **2g** afforded the expected indenol **3i** albeit in lower yield (entry 12). Carbocylization of *o*-iodophenyl butyl ketone (**1d**) with various propiolates **2a–c**, **f** also proceeded smoothly to give the desired indenol **3j–m** in excellent to moderate yields (entries 13–16).

The carbocyclization reaction can be further applied to simple alkynes. Thus, the reaction of **1d** with diphenylacetylene (**2h**) afforded the desired indenol **4** in 80% yield (Scheme 2).

The nature of the phosphine ligand drastically influences the yield of the product. Control experiments indicate that in the



Scheme 1

Table 1 Results of nickel-catalyzed carbocyclization of *o*-halophenyl ketones (**1**) with propiolates (**2**)

Entry	Ketone[a]	Propiolate	R^3	R^4	Product, Yield[b]
1	**1a**	**2a**	(CH$_2$)$_4$CH$_3$	CH$_3$	**3a**, 87 (94)
2	**1b**	**2a**	(CH$_2$)$_4$CH$_3$	CH$_3$	**3a**, (85)
3	**1a**	**2b**	TMS	CH$_2$CH$_3$	**3b**, 78 (86)
4	**1b**	**2b**	TMS	CH$_2$CH$_3$	**3b**, (76)
5	**1a**	**2c**	CH$_3$	CH$_3$	**3c**, 74
6	**1b**	**2c**	CH$_3$	CH$_3$	**3c**, (65)
7	**1a**	**2d**	CH$_2$OCH$_3$	CH$_3$	**3d**, 68
8	**1a**	**2e**	(CH$_3$)$_3$CH$_3$	CH$_3$	**3e**, (87)
9	**1a**	**2f**	Ph	CH$_3$	**3f**, 52
10	**1c**	**2a**	(CH$_2$)$_4$CH$_3$	CH$_3$	**3g**, 75 (86)
11	**1c**	**2c**	CH$_3$	CH$_3$	**3h**, 70 (75)
12	**1c**	**2g**	C(CH$_3$)$_3$	CH$_3$	**3i**, 46
13	**1d**	**2a**	(CH$_2$)$_4$CH$_3$	CH$_3$	**3j**, 85 (92)
14	**1d**	**2b**	TMS	CH$_2$CH$_3$	**3k**, 82 (86)
15	**1d**	**2c**	CH$_3$	CH$_3$	**3l**, 88
16	**1d**	**2f**	Ph	CH$_3$	**3m**, 48

[a] All reactions were carried out in a side-arm flask consisting of *o*-halophenyl ketone (0.50 mmol), propiolate (1.50 equiv), Ni(dppe)Br$_2$ (5.0 mol%) and Zn (2.75 equiv) in CH$_3$CN (3.0 mL) at 80 °C under N$_2$ (1 atm) for 13 h. The mixture was cooled, diluted with dichloromethane, stirred in the air for 15 min and then filtered through a Celite and silica gel pad. The filtrate was concentrated and the residue was purified on a silica gel column using hexane–ethyl acetate as eluent to afford the desired product **3**. [b] Isolated yields; yields in parentheses were determined by ^{1}H-NMR using mesitylene as an internal standard.

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† Electronic supplementary information (ESI) available: synthesis and characterization of compounds **3**. See http://www.rsc.org/suppdata/cc/b2/b201473d/

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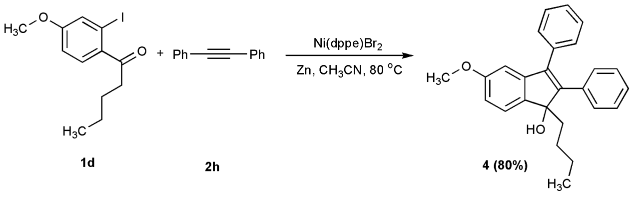
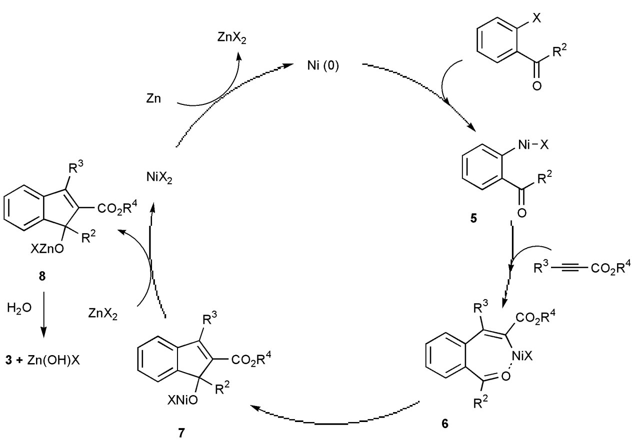


Scheme 2

absence of either nickel catalyst or zinc powder, no reaction proceeded. The activities of several nickel catalyst $Ni(PPh_3)_2Br_2$, $Ni(dppm)Br_2$, $Ni(dppe)Br_2$ and $Ni(dppb)Br_2$ were examined for the cyclization of **1c** with **2a**. The yields of indenol **3g** were 26, 57, 86 and 21% respectively suggesting that $Ni(dppe)Br_2$ is most active among the nickel complexes tested. Solvent also plays a crucial role in the present carbocyclization reaction. DMF and THF afforded low to moderate yields of the indenol product, while in toluene, no indenol **3g** was produced. The best solvent for the carbocyclization using $Ni(dppe)Br_2$ as the catalyst is acetonotrile giving **3g** in 86% yield.

It is interesting to compare the difference between the current nickel-catalyzed carbocyclization and the palladium-catalyzed reaction.[9a] First, in the nickel-catalyzed reaction, the reducing agent which is required for the indenol formation is zinc metal, but in the palladium-catalyzed reaction, KOAc–DMF is responsible for the reduction.[9a] The low reducing power of KOAc–DMF relative to zinc metal possibly accounts at least in part for the long reaction time and higher temperature in the palladium-catalyzed reaction. It is noteworthy that under the reaction conditions used by the palladium system, $Ni(dppe)Br_2$ does not catalyze the expected carbocyclization. Secondly, the present nickel catalyst is more effective for *ortho*-iodo- than for *ortho*-bromophenyl ketones, while the palladium system prefers *o*-bromophenyl ketones to the corresponding iodo substrates. Thirdly, the $Ni(dppe)Br_2$/Zn system is effective for the cyclization of *o*-halophenyl ketone with propiolates, but the cyclization by palladium complexes has not been explored previously.[9a]

Based on the above results and the known nickel chemistry, a catalytic cycle is proposed as shown in Scheme 3. Reduction of Ni(II) to Ni(0) by zinc powder[13] initiates the catalytic cycle. Oxidative addition of aryl iodide to nickel(0) species to yield nickel(II) intermediate **5** is followed. Regioselective insertion of a propiolate into the nickel–aryl bond generates a vinyl nickel intermediate **6**. Intramolecular nucleophilic addition of **6** to the keto group leads to a nickel alkoxide **7**. Subsequent transmetallation with zinc halide gives zinc alkoxide **8** and a Ni(II) species. Reduction of the latter by zinc metal regenerates the Ni(0) catalyst. **8** is converted to the final product **3** after protonation by water.



Scheme 3

In summary, we have demonstrated a facile $Ni(dppe)Br_2$-catalyzed carbocyclization of *o*-halophenyl ketones with propiolates using zinc metal powder as the reducing agent to afford indenol derivatives in moderate to excellent yields. The reaction is highly regioselective and proceeds under mild conditions. It appears that this nickel-catalyzed and the palladium-catalyzed carbocyclization reactions are complementary to each other. Further studies on its asymmetric version and application are underway.

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