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Rhodium/copper-cocatalyzed annulation of benzylamines with diazo compounds: access to fused isoquinolines†

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Benzylamine has been applied as an arene source in C–H activation and coupling with different types of diazo compounds, leading to the synthesis of fused isoquinolines. This occurs *via* a mild synergistic rhodium- and copper-catalyzed process. Moreover, ecofriendly O_2 has been used as a terminal oxidant with high efficiency.

Isoquinolines are a ubiquitous structural motif in numerous pharmaceuticals and biologically active compounds.[1] Recently, substantial progress has been made in the Rh(III)- and Ru(II)-catalyzed C–H bond functionalization of aromatic imines or oximes, which has streamlined access to synthetically important isoquinolines in an atom- and step-economical fashion without pre-activation of the substrates.[2] In this process, the lone pair of the nitrogen offers sufficient chelation-assistance which leads to metalation of an *ortho*-C–H bond. Nevertheless, these reports are limited by the demonstrated scope of imine or oxime substrates, which are simple and relatively stable aromatic ketimines or ketoximes. Thus, it is difficult to develop practical methods to construct 1-unsubstituted isoquinolines, in spite of the vast prevalence of these scaffolds in pharmaceutical molecules and natural products (Fig. 1).[3] One of the reasons is that aldimines are prone to hydrolysis under the catalytic conditions.[4] To steer around this intrinsic obstacle, Miura and co-workers developed a practical method in which readily available benzylamines are transferred to related aldimines *in situ* which then coupled with alkynes to form isoquinolines *via* a Rh/Cu-catalyzed oxidative cyclization (Scheme 1).[5]

The use of diazo compounds for coupling with arenes *via* transition-metal-catalyzed C–H activation has recently received much attention. The pioneering work by Yu indicated that an oxime group could induce *ortho*-C–H activation and coupling with diazomalonates in the presence of a Rh(III) catalyst.[6] Afterwards many groups further took advantage of the versatile reactivity of diazo compounds to assemble various nitrogen-containing heterocycles.[7] Inspired by these results, we envisioned the feasibility of C–H activation and annulation of benzylamines with diazocarbonyl compounds under rhodium catalysis.

In Miura's work, the benzylic amine was oxidized to an imine by using a stoichiometric amount of $Cu(OAc)_2{\cdot}H_2O$

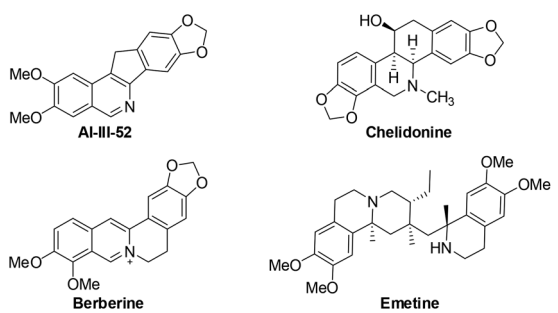
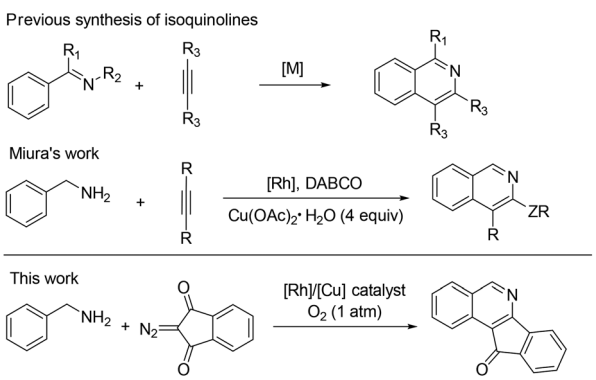


Fig. 1 Bioactive compounds containing 1-unsubstituted isoquinoline moieties.



Scheme 1 Strategies for the synthesis of isoquinolines.

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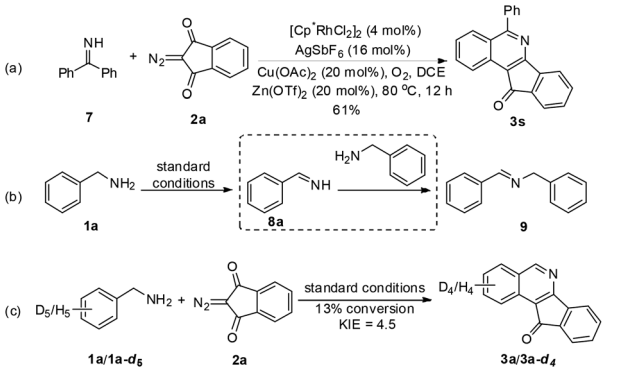
under rather harsh conditions. Given the importance of 1-unsubstituted and fused isoquinolines and the limitations of previous methods, we aim to adopt a clean oxidation of primary amines to imines and directly use the imine as an intermediate for further C–H functionalization under mild conditions. The oxidative transformation of amines using a green oxidant such as oxygen attracted our attention.[2s,5] We now report an efficient aerobic synthesis of isoquinolines starting from readily available benzylamines and diazo compounds *via* synergistic rhodium/copper catalysis. More importantly, access to such fused isoquinolines through traditional methods is a great challenge.[8]

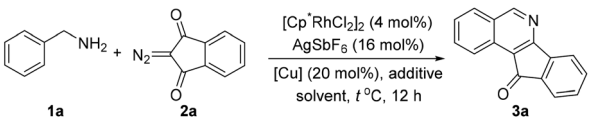
We selected the coupling of benzylamine **1a** with 2-diazo-1*H*-indene-1,3(2*H*)-dione **2a** as the model reaction (Table 1). Initially, the reaction of **1a** and **2a** catalyzed by $[Cp^*RhCl_2]_2$/$AgSbF_6$ in the presence of a stoichiometric amount of $Cu(OAc)_2$ afforded isoquinoline **3a** in 30% yield (entry 1). The reaction proceeded giving a similar yield when conducted under an O_2 atmosphere with 20 mol% of $Cu(OAc)_2$ (entry 2). A further increase of the reaction temperature to 80 °C gave rise to an improved yield of 75% (entry 3). However, a further increase of the temperature led to a lower yield (entry 4). Switching to other solvents such as THF and TFE gave no desired reaction (entries 5 and 6). Employment of other copper salts such as $CuCl_2$ and $CuSO_4$ also resulted in poor efficiency (entries 7 and 8). Further improvement was attained when $Zn(OTf)_2$ (20 mol%) was introduced as an additive (entry 9). Control experiments confirmed that essentially no desired product was detected when either the Rh catalyst or the Cu additive was omitted. Moreover, air was not an efficient oxidant for this transformation (entry 14). Consequently, the following reaction conditions have been identified: $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), $Cu(OAc)_2$ (20 mol%) and $Zn(OTf)_2$ (20 mol%) in DCE at 80 °C under O_2 (1 atm).

With the optimal conditions in hand, we scrutinized the scope of the aryl amines in the coupling with 2-diazo-1*H*-indene-1,3(2*H*)-dione (**2a**). Amines bearing electron-donating and -withdrawing groups in the aryl ring were well-tolerated, and the corresponding products were isolated in good to excellent yields (Scheme 2). The same observation applied to benzylamines bearing different *ortho* substituents (**3n–q**). Completely regioselective annulation occurred at the less hindered position for most *meta*-substituted substrates (**3k–l**), except that the *meta*-fluoro-substituted benzylamine **1m** showed a considerable secondary directing group effect,[9] thus leading to C–H functionalization at the sterically more hindered site (**3m**). Moreover, α-methyl and α-phenyl benzylamines also exhibited good reactivity (**3r** and **3s**), where no



Scheme 2 Mechanistic studies.

Table 1 Optimization of the reaction conditions[a]



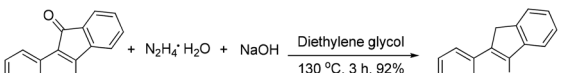
Entry	[Cu]	Additive	Solvent	Atmosphere	*T* (°C)	**3a** (%)
1	$Cu(OAc)_2$ [b]	—	DCE	N_2	60	30
2	$Cu(OAc)_2$	—	DCE	O_2	60	33
3	$Cu(OAc)_2$	—	DCE	O_2	80	75
4	$Cu(OAc)_2$	—	DCE	O_2	100	66
5	$Cu(OAc)_2$	—	TFE	O_2	80	—
6	$Cu(OAc)_2$	—	THF	O_2	80	—
7	$CuCl_2$	—	DCE	O_2	80	16
8	$CuSO_4$	—	DCE	O_2	80	21
9	**$Cu(OAc)_2$**	**$Zn(OTf)_2$ (20 mol%)**	**DCE**	**O_2**	**80**	**93**
10[c]	$Cu(OAc)_2$	$Zn(OTf)_2$ (20 mol%)	DCE	O_2	80	—
11	—	$Zn(OTf)_2$ (20 mol%)	DCE	O_2	80	—
12	—	$Fe(acac)_2$ (20 mol%)	DCE	O_2	80	—
13	—	MnO_2 (20 mol%)	DCE	O_2	80	—
14	$Cu(OAc)_2$	$Zn(OTf)_2$ (20 mol%)	DCE	Air	80	57

[a] Reaction conditions: **1a** (0.10 mmol) and diazo compound **2a** (0.11 mmol) with $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), [Cu] (20 mol%) and additive (20 mol%), DCE (3 mL), 80 °C, 12 h, yield was isolated. [b] 2 equiv. of $Cu(OAc)_2$ were added. [c] In the absence of Rh(III).

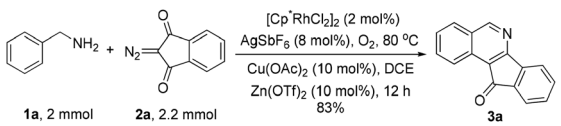
significant effect of the steric hindrance of the α-substituent was observed (Table 2).

We next explored the applicability of other diazo compounds under the standard conditions. A variety of α-diazo esters reacted smoothly with the benzylamines to afford the corresponding isoquinolines in moderate to good yields (Table 3).

The obtained products could be readily derivatized. The carbonyl group was reduced to a methylene group *via* a Wolff–Kishner reduction (eqn (1)),[10] and the final product **6** has the same scaffold with the TOP1 inhibitor **AI-III-52**.[3a] Moreover, the reaction can be successfully scaled up to 2 mmol without much loss of yield even with a reduced loading of the catalyst and the additive (eqn (2)).



(1)

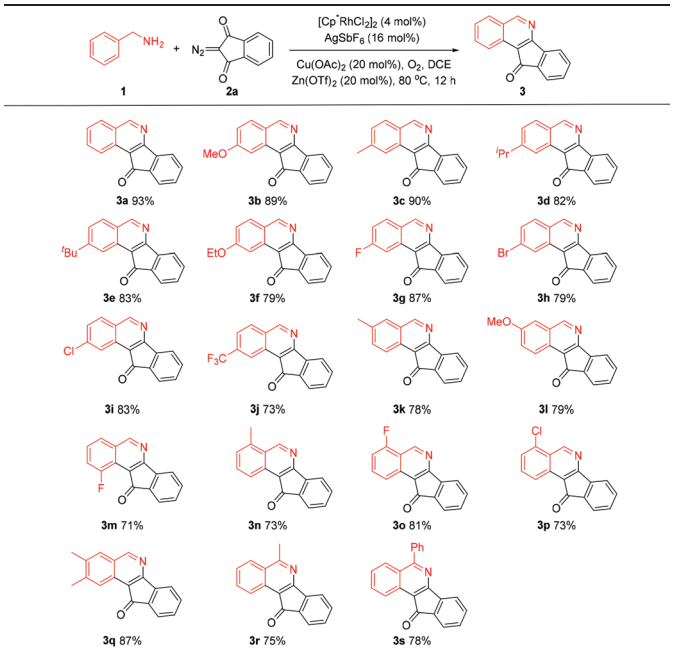


(2)

To gain mechanistic insight into the reaction, benzophenone imine (7) was treated with **2a** under the standard reaction conditions, and the same annulation product **3s** was isolated in 61% yield (Scheme 2). Additionally, benzylamine **1a** was transformed to imine **9** (determined by GC-MS) in the absence of a coupling partner under the standard conditions, in which an unstable imine **8a** is proposed to undergo condensation with another molecule of **1a**,[11] which was consistent with Miura's work.[5] These results indicate that amine oxidation likely took place prior to the C–H bond activation. Subsequently, the intermolecular isotope effect (k_H/k_D = 4.5) indicated that C–H bond cleavage was possibly involved in the turnover-limiting step of this transformation.

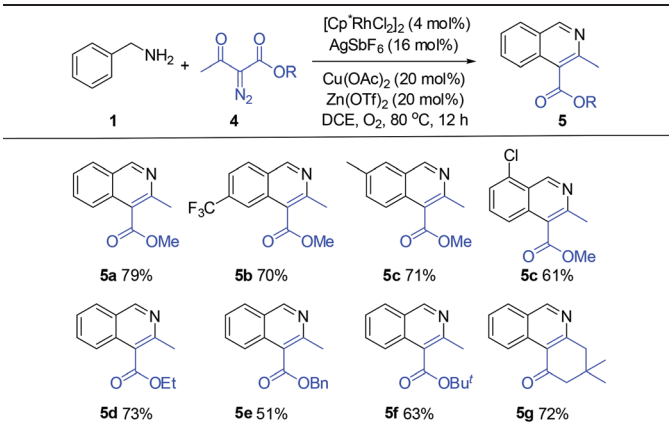
On the basis of above experimental results and the literature reports,[12] a plausible mechanism has been proposed (Scheme 3). Cyclometalation of aldimine **8a** generated *in situ* gives a rhodacyclic intermediate **II** *via* a proposed concerted metalation/deprotonation (CMD) process.[13] Interactions with an incoming diazo substrate then occur to form a rhodium–carbene intermediate **III** by dediazonization. Subsequently, the intermediate **III** underwent migratory insertion to afford a six-membered rhodacyclic intermediate **IV**. Proto-demetalation of **IV** gave an alkylated imine intermediate **V** and regenerated the active species **I**. Finally, nucleophilic cyclization–condensation of **V** produces the final product **3a**.

Table 2 The substrate scope of benzylamines[a,b]

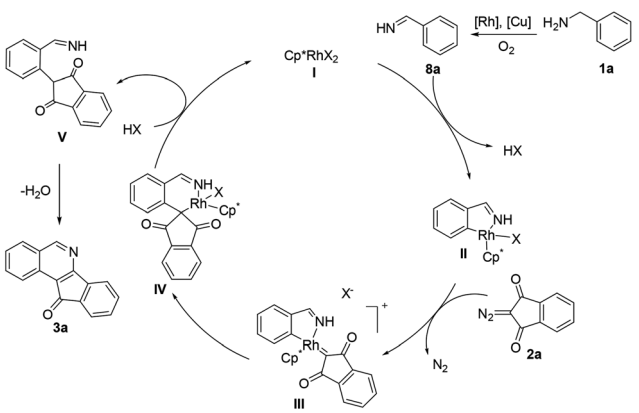


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), $Cu(OAc)_2$ (20 mol%) and $Zn(OTf)_2$ (20 mol%), DCE (3 mL), 80 °C, 12 h, under O_2 (1 atm). [b] Isolated yield.

Table 3 The substrate scope of diazo compounds[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **4** (0.22 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), $Cu(OAc)_2$ (20 mol%) and $Zn(OTf)_2$ (20 mol%) in DCE (3 mL) at 80 °C for 12 h under an O_2 (1 atm) atmosphere. [b] Isolated yields are reported.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have developed a novel system of Rh/Cu co-catalyzed synthesis of condensed isoquinolines in which readily accessible benzylamines serve as efficient building blocks *via* a dehydrogenation process and the ecologically friendly O_2 can be used as the terminal oxidant. Further synthetic applications to bioactive molecules are underway in our laboratory.

Acknowledgements

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