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Ruthenium-Mediated Dual Catalytic Reactions of Isoquinoline *via* C–H Activation and Dearomatization for Isoquinolone

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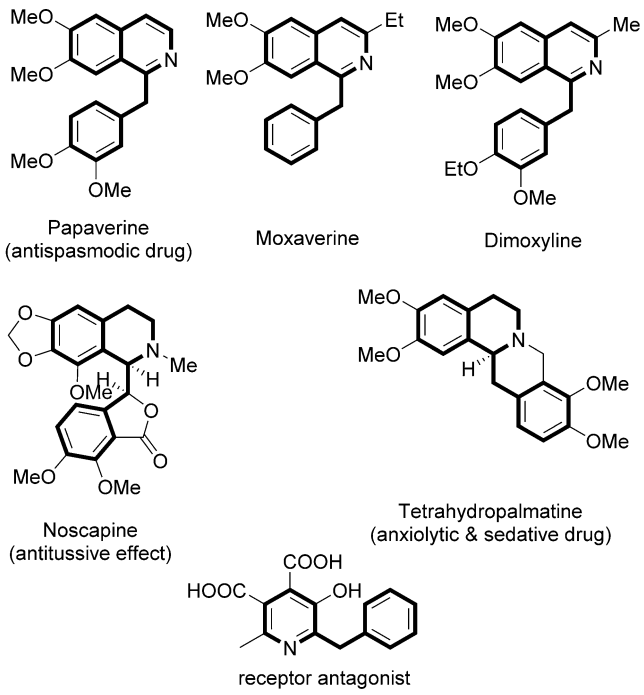
Abstract: We have unraveled the ruthenium-promoted prototype reaction based on C(sp^2)–C(sp^3) bond formation through the reigoselective C–H activation of isoquinoline and pyridine derivatives with various alkyl halides, leading to 1-substituted isoquinoline products in good yield. This C–H catalytic reaction did not rely on chelation assistance of the directing group of the substrates. The dimer $[RuCl_2(p\text{-cymene})]_2$ in combination with an N-heterocyclic carbene ligand, adamantanecarboxylic acid and K_2CO_3 base in *N*-methyl-2-pyrrolidone solution at 150 °C are the best conditions. Simultaneously, we are also able to chemically tune the reaction mode to dearomatization by adding water, leading to isoquinolone products. This reaction methodology is not suitable for other nitrogen-containing heteroarenes such as pyridazines and pyrimidines.

Keywords: C–H bond activation; dearomatization; isoquinolines; isoquinolones; ruthenium

Ruthenium-promoted synthetic methodology based on C–H activation has increasingly emerged as an attractive paradigm for the step-economical formation of C–C bonds.[1] Despite the milestone progress in the ruthenium catalysis, most Ru-mediated C–H reactivity relied on chelation assistance of the directing group embedded in the targeted substrate,[2,3] where the C–H transformation is in close proximity to the directing group. However, the widespread application for synthetic utility based on the directing group method might be limited by (i) the feasibility of removing directing group and (ii) the post-synthesis step problem arisen from functional intolerance with the directing group.

Isoquinoline motifs are considered as an essential component in biologically active molecular structures and possible drug precursors.[4] However, their industrial value is also exhibited in ligands for metallic catalysis[5] and organic light-emitting diodes in material science.[6] Traditional synthetic manipulations to synthesize isoquinolines based on Bischler–Napieralski, Pomeranz–Fritsch and Pictet–Spengler reactions involve intramolecular cyclization of substrates under unfriendly reaction conditions and exhibited poor functional group tolerance.[7] Quite recently, several groups have skillfully overcome these problems in the synthesis of isoquinolines by using transition metal-mediated C–H bond activation annulation of aromatic imines, amines, oximes and hydrazones with unsaturated substrates like alkynes.[8] Nevertheless, all these protocols depend on appropriate directing groups. In stark contrast, a general approach for C–H manipulations of the parent isoquinoline structure is less developed in this respect[9] as its C–H bond is less reactive and positional selectivity would always pose an issue. Therefore, a complementary method of functionalizing the C–H bond of isoquinoline in a selective manner will be desirable.

In an effort to advance the field of ruthenium catalysis we envisioned that alkyl cross-coupling reactions with isoquinoline might be possible *via* non-directing C–H bond cleavage to afford 1-substituted isoquinolines, considering that C-1 substituted isoquinolines present essential molecular motifs found in numerous biologically active products and pharmaceutical drugs as shown in Scheme 1.[4a–e] During the course of this investigation, we also found that the ruthenium complex could catalyze the dearomatization of isoquinolines to generate isoquinolones upon slightly altering

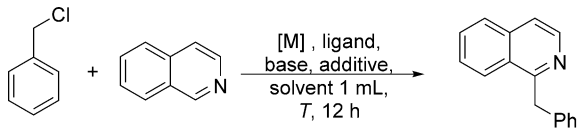


Scheme 1. Biologically active C-1 substituted isoquinolines.

the reaction conditions by the addition of water. Obviously, this new chemical synthesis involving transformation of isoquinoline to isoquinolone should serve as an attractive complementary method to annulation processes.[10] Herein, we unravel the Ru-promoted prototype reaction based on C–C bond formation through the C–H activation of isoquinoline and other nitrogen-based heteroarenes with alkyl halide, leading to the 1-substituted isoquinoline products. Simultaneously, we are also able to chemically tune the reaction mode towards producing isoquinolones just by adding water.

To examine the viability of the C–H bond functionalization of isoquinoline (**2a**) (Table 1), we attempted the reaction using benzyl chloride (**1a**) at 130 °C in toluene with 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$ in the presence of K_2CO_3 (2 equiv.) and *N*-acetylglycine (0.3 equiv.) as an additive. To our delight, the expected benzylated product (**3a**) was obtained in 48% yield (entry 1). The efficacy of the reaction could be further improved to a higher yield of 60% by changing the additive to 1-adamantanecarboxylic acid and increasing the reaction temperature to 150 °C (entry 3). Subsequently, we looked into the possibility

Table 1. Selected optimization parameters.[a]



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

Entry	[M][b]	Ligand	Base (equiv.)	Additive (equiv.)	Solvent	T [°C]	Yield [%][c]
1	Ru	---	K_2CO_3 (2)	*N*-acetylglycine (0.3)	toluene	130	48
2	Ru	---	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	130	58
3	Ru	---	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	150	60
4	Ru	PPh_3 (0.4 equiv.)	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	150	56
5	Ru	IMes (0.1 equiv.)	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	150	64
6	Ru	IPr (0.1 equiv.)	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	150	60
7	Ru	1,10-Phen (0.2 equiv.)[d]	K_2CO_3 (2)	1-AdCO_2H (0.3)	toluene	150	5
8	Ru	IMes (0.1 equiv.)[e]	K_2CO_3 (2)	1-AdCO_2H (0.3)	NMP[g]	150	90
9	Ru	IPr (0.1 equiv.)[f]	K_2CO_3 (2)	1-AdCO_2H (0.3)	NMP[g]	150	92
10	Ru	IPr (0.1 equiv.)[f]	---	1-AdCO_2H (0.3)	NMP[g]	150	trace
11	Ru	IPr (0.1 equiv.)[f]	K_2CO_3 (2)	---	NMP[g]	150	54
12	---	IPr (0.1 equiv.)[f]	K_2CO_3 (2)	1-AdCO_2H (0.3)	NMP[g]	150	0

[a] **1a** 1.5 mmol, **2a** 0.5 mmol.
[b] $[RuCl_2(p\text{-cymene})]_2$ 2.5 mol%.
[c] Isolated yield.
[d] 1,10-Phen = 1,10-phenanthroline.
[e] IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.
[f] IPr = 1,3-bis(2,6-diisopropyl-phenyl) imidazol-2-ylidene.
[g] 1.5 mL.

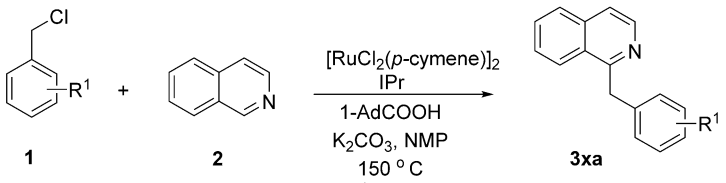
of a ligand-promoted reaction. It was found that strong σ-donating ligands like IPr[11] (92%) and IMes[12] (90%) with NMP solvent had beneficial effects on the yields of the reaction (entries 8 and 9). A series of control experiments established that the Ru complex, the acid additive and base are all essential (entries 10–12). Finally, benzyl bromide and iodide were also examined and found to be less effective reactants compared to the chloride analogues, furnishing only coupling product **3aa** in ~40% yield.

With the optimized conditions in hand (entry 1, Table 2), we examined the reaction scope with various benzyl chlorides **1** with isoquinoline (**2a**) (entries 2–14). Excellent yields were observed for methyl-substituted benzyl chlorides **1b** and **1c**. Commercially available benzyl chlorides bearing chloro functional groups at *para* (66%) and *meta* (60%) positions afforded the corresponding 2-benzylisoquinoline products **3da** and **3fa** in good yields in contrast to the *ortho* chloro substituent **1e** (30%). Similarly, **1g** (fluoride) was suitable in this catalytic reaction (~60%). Other electron-withdrawing entities like nitro (**1h**), ester (**1i**) and vinyl (**1j**) delivered rather inferior yields (entries 8–10). Encouragingly, other primary alkyl halides (**1k–m**) were possible in this reaction with good yields. But the secondary alkyl halide (**1n**) gave a lower yield of 35% (entry 14) than its primary counterparts, which could be attributed to the steric factor.

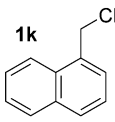
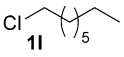
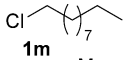
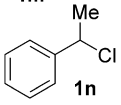
To further expand the utility of this methodology, we explored the generality of the transformation with various isoquinolines and pyridines as well (Table 3). Excellent-to-moderate yields were realized with 5-arylisoquinolines (**2b–g**) containing various electron-donating and electron-withdrawing groups (entries 2–6). Our protocol was effective for pyridine (**2i**) and fused cyclopentylpyridine derivatives like **2h** in good yield. Good reactivities are seen with bulkier pyridines like *p*-phenylpyridine (**2j**) and *o,p*-dimethylpyridine (**2k**) (~60%) to effect a highly selective *ortho*-benzylation with respect to the N atoms of **3aj** and **3ak**, respectively. In spite of the success in this methodology, other nitrogen-based heteroarenes such as pyridazines and pyrimidines are not viable in this reaction.

During the course of this investigation, we also discovered that the ruthenium complex could catalyze a dearomatization process of isoquinolines to generate *N*-benzylated isoquinolones by slightly altering the reaction conditions through addition of water. In the screening process for maximizing the ruthenium selectivity for dearomatization of **1a** with **2a**, we found that the reaction conditions of 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$ in the presence of 4 equiv. of K_2CO_3 and water under air, afforded a 92% yield of 1-benzylisoquinolinone adduct **4aa** (Table 4, entry 1).[13] High yields with complete chemoselectivity for isoquinolinones were observed for benzyl chlorides containing methyl, chloro and fluoro groups (**1b–**

Table 2. Scope of reactions with various alkyl halides.[a]

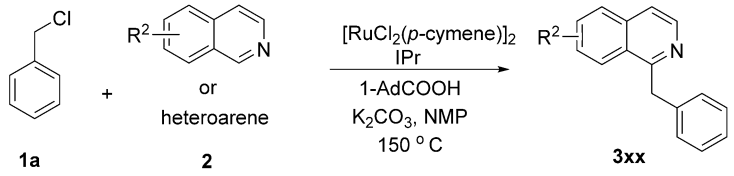


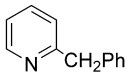
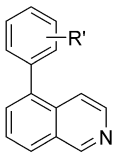
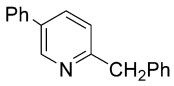
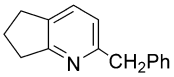
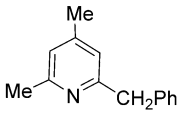
1 **2** **3xa**

Entry	Substrate	Product	Yield[b]	Entry	Substrate	Product	Yield[b]
1	**1a**	**3aa**	92%				
2	**1b** R^1= 2-Me	**3ba**	80%	11	 **1k**	**3ka**	80%
3	**1c** R^1= 4-Me	**3ca**	70%				
4	**1d** R^1= 4-Cl	**3da**	66%				
5	**1e** R^1= 2-Cl	**3ea**	30%	12[c]	 **1l**	**3la**	59%
6	**1f** R^1= 3-Cl	**3fa**	60%				
7	**1g** R^1= 4-F	**3ga**	60%	13[c]	 **1m**	**3ma**	50%
8	**1h** R^1= 4-NO_2	**3ha**	49%				
9	**1i** R^1= 4-COOMe	**3ia**	48%	14	 **1n**	**3na**	35%
10	**1j** R^1= 4-vinyl	**3ja**	31%				

[a] *Conditions:* **1** (1.5 mmol), **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), IPr (0.05 mmol), 1-$AdCO_2H$ (0.15 mmol) and K_2CO_3 (2.0 mmol) in NMP (1.5 mL) at 150 °C for 12 h unless otherwise noted.
[b] Isolated yield.
[c] 24 h.

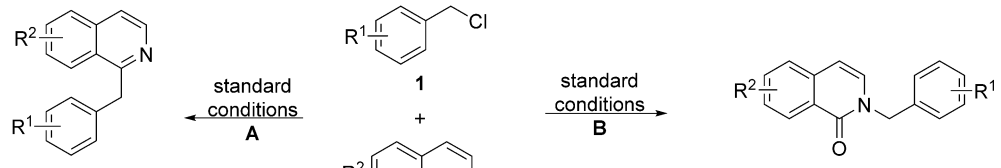
Table 3. Scope of various heteroarenes.[a]



Entry	Substrate		Product	Yield[b]	Entry	Substrate	Product	Yield[b]
1	**2b-2g**	R' = H	**3ab**	85%	8[c,d]	**2i**	 **3ai**	61%
2		R' = 2-Me	**3ac**	95%				
3		R' = 3-Me	**3ad**	73%				
4		R' = 4-Me	**3ae**	80%	9[c]	**2j**	 **3aj**	58%
5		R' = 4-OMe	**3af**	80%				
6		R' = 4-CN	**3ag**	68%				
7[c]	**2h**	 **3ah**		51%	10[c]	**2k**	 **3ak**	64%

[a] *Conditions:* **1** (1.5 mmol), **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), IPr (0.05 mmol), 1-$AdCO_2H$ (0.15 mmol) and K_2CO_3 (2.0 mmol) in NMP (1.5 mL) at 150 °C for 12 h unless otherwise noted.
[b] Isolated yield.
[c] 24 hours.
[d] DCPE = 1,2-bis(dicyclohexylphosphino)ethane (0.025 mmol) instead of IPr.

g) at different positions. Several electron-withdrawing benzyl chlorides such as nitro (**1h**, 64%), methyl ester (**1i**, 75%) and nitrile (**1o**, 82%) afforded amide products in good yields with the exception that vinyl group **1j** gave no reaction, which could perhaps be attributed to the poor solubility of **1j** in the aqueous conditions. Beside benzyl chloride, a variety of primary alkyl chlorides **(1k–p)** were also suitable in this catalytic reaction with the reaction efficiency ranging from good to moderate yields. Next, we systematically examined the effects of the isoquinoline derivatives and other heteroarenes on this reaction (entries 17–25, Table 4). A general observation is that electronic or electronic perturbations invoked by different substituents (**2b–g**, entries 17–22) at the aryl ring of the 5-arylisoquinoline did not have any adverse effect on



5aa 64%
R^1 = 3,4-$(OMe)_2$, R^2 = H

5ab 61%
R^1 = H, R^2 = 6,7-$(OMe)_2$

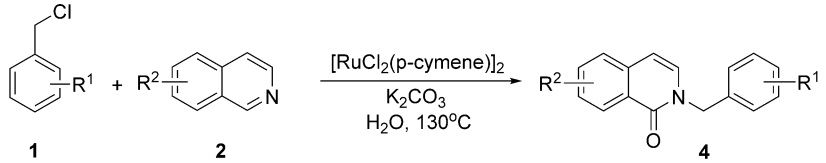
5ac (papaverine) 58%
R^1 = 3,4-$(OMe)_2$, R^2 = 6,7-$(OMe)_2$

5ba 48%
R^1 = 3,4-$(OMe)_2$, R^2 = H

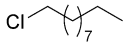
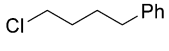
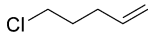
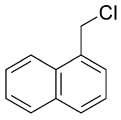
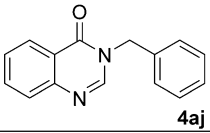
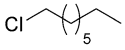
5bb 34%
R^1 = H, R^2 = 6,7-$(OMe)_2$

Figure 1. Preparation of papaverine and related compounds. *Standard conditions **A**:* **1** (1.5 mmol), **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), IPr (0.05 mmol), 1-$AdCO_2H$ (0.15 mmol) and K_2CO_3 (2.0 mmol) in NMP (1.5 mL) at 150 °C for 12 h. *Standard conditions **B**:* **1** (2.0 mmol), **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol) and K_2CO_3 (4.0 mmol) in H_2O (1.0 mL) at 130 °C in air for 12 h.

Table 4. Scope of the dearomatization process.[a]



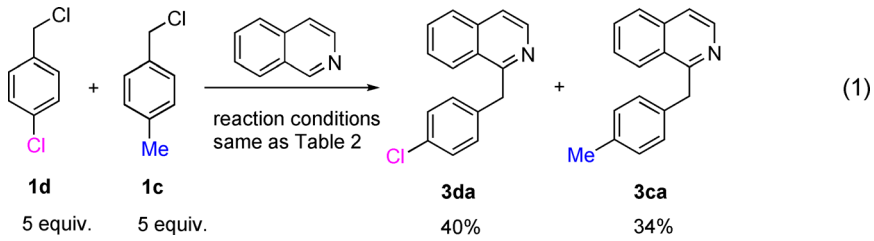
1 2 4

Entry	Substrate	Product	Yield[b]	Entry	Substrate	Product	Yield[b]
1	**1a** R^1= H	**4aa**	92%	14[d]	**1m** 	**4na**	46%
2	**1b** R^1= 2-Me	**4ba**	88%	15	**1p** 	**4oa**	58%
3	**1c** R^1= 4-Me	**4ca**	82%	16	**1q** 	**4pa**	65%
4	**1d** R^1= 4-Cl	**4da**	82%	17	**2b-g** R' = H	**4ab**	87%
5	**1e** R^1= 2-Cl	**4ea**	71%	18	R' = 2-Me	**4ac**	61%
6	**1f** R^1= 3-Cl	**4fa**	72%	19	R' = 3-Me	**4ad**	83%
7	**1g** R^1= 4-F	**4ga**	74%	20	R' = 4-Me	**4ae**	71%
8	**1h** R^1= 4-NO_2	**4ha**	80%	21	R' = 4-OMe	**4af**	64%
9[c]	**1i** R^1= 4-COOMe	**4ia**	75%	22	R' = 4-CN	**4ag**	36%
10	**1j** R^1= 4-vinyl	**4ja**	0%	23	**2m** R^2 = 5-Br	**4ah**	72%
11	**1o** R^1= 4-CN	**4ka**	82%	24	**2n** R^2 = 5-NO_2	**4ai**	80%
12	**1k** 	**4la**	88%	25[d]	**2o** 	**4aj**	47%
13[d]	**1l** 	**4ma**	52%				

[a] *Conditions:* **1** (2.0 mmol), **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol) and K_2CO_3 (4.0 mmol) in H_2O (1.0 mL) at 130 °C in air for 12 h unless otherwise noted.
[b] Isolated yield.
[c] Addition of 0.2 mL DME.
[d] 24 h.

the reaction yield or chemoselectivity. We also tested isoquinolines with election-withdrawing groups (**2m**, **n**) at the C-5 position, and found that they readily provided the expected dearomatized amidation products with good yields of 72–90%. Interestingly, a bioactive heterocyclic quinazolinone (**4aj**) could also be realized in a moderate yield from quinazoline (**2o**), illustrating the viability of this method for heteroarenes other than isoquinolines.

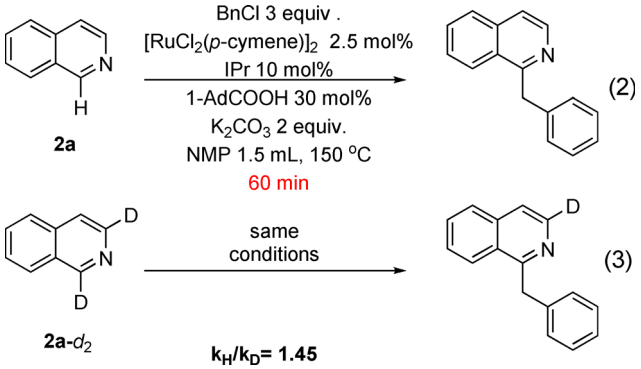
Finally, the utility of this methodology could be further applied to the preparation of compounds related to bioactive papaverine, which is used as a non-narcotic antispasmodic agent. Figure 1 shows that the synthesis of papaverine and its derivatives could be achieved in one step with acceptable yields of 50–60% (**5aa–5ac**) starting from isoquinoline. Somewhat surprisingly, a 4-methoxy-substituted benzyl chloride lacking one of the methoxy groups at the *meta* positions failed to give any product. Alternatively, dearomatization compounds bearing methoxy groups (**5ba**, **5bb**) have also been successfully prepared with reasonable yields.



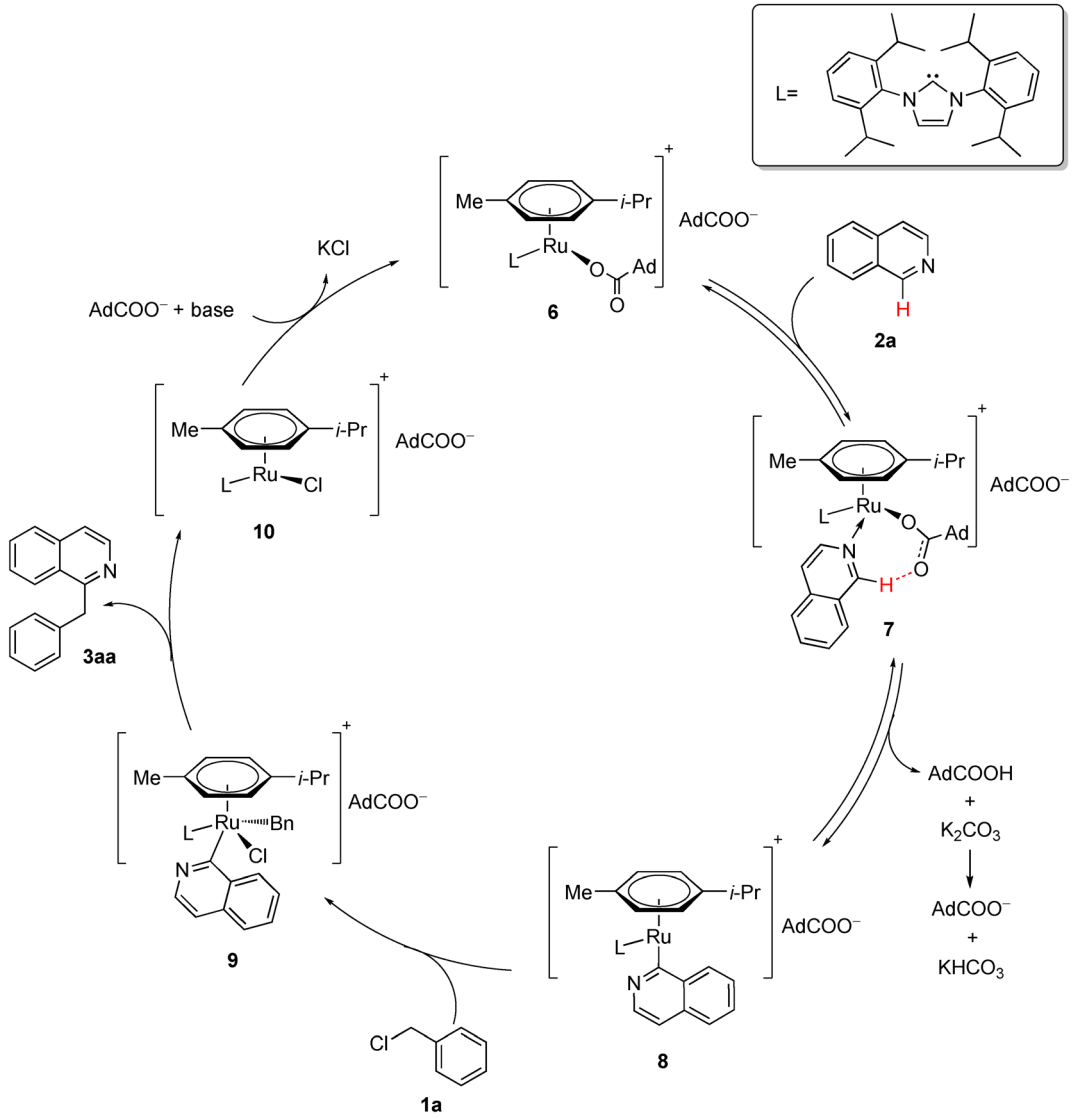
1d 5 equiv. **1c** 5 equiv. **3da** 40% **3ca** 34%

Scheme 2. Inter-molecular competition experiment.

To gain insights into the reaction mechanism, the following experiments were conducted. The catalytic reactions of isoquinoline with an equal amount of electronic-rich (**2c**) and electron-deficient (**2d**) benzyl chlorides were examined (Scheme 2). As revealed by ^{1}H NMR analysis, there is no significant difference between electron-withdrawing and electron-donating derivatives in intermolecular competition reactions. The result indicated that the oxidative addition of benzyl chloride may not be the slowest step in the reactivity profile. The kinetic isotope effect (KIE) was investigated by an intermolecular competition between **2a** and **2a**-d_2 (Scheme 3). The small KIE value of 1.45 obtained in C-1 alkylation suggested that C–H bond cleavage may not be significant with respect to the overall rate-determining step. [14] Based on these mechanistic studies, we propose the catalytic pathway described in Scheme 4. The initial step is slow C–H activation through cyclometallation–deprotonation (CMD) with **7** to afford **8**. Subsequently, a facile oxidative addition of benzyl chloride occurred to furnish



Scheme 3. Kinetic isotope experiment (KIE) study.



Scheme 4. Proposed mechanism for the catalytic reaction of C–H benzylation.

Ru(IV) complex **9**. Finally, reductive elimination of **9** occurred to afford the coupling product **3**. However, the mechanism of isoquinolone formation triggered by water may undergo a different operative mechanism and still remains elusive at this stage, which is the subject of our continuing study.

In summary, we have unraveled the Ru-promoted prototype reaction based on C(sp^2)–C(sp^3) bond formation through the C–H activation of isoquinoline and pyridine derivatives with alkyl halides, leading to the 1-substituted isoquinoline products. Simultaneously, we are able to chemically tune the reaction mode by adding water towards dearomatization, leading to isoquinolones. Ongoing work seeks to gain a detailed mechanistic understanding of the dual reaction modes of isoquinoline mediated by ruthenium.

Experimental Section

Typical Procedure for the Synthesis of 3aa

Benzyl chloride **1a** (190 mg, 1.5 mmol) and isoquinoline **2a** (65 mg, 0.5 mmol) were added to a mixture of [$RuCl_2$(*p*-cymene)]$_2$ (7 mg, 0.00125 mmol), IPr (20 mg, 0.05 mmol), 1-AdCOOH (27 mg, 0.15 mmol) and K_2CO_3 (138 mg, 1 mmol) in NMP (1.5 mL) under N_2. After heating at 150 °C for 12 h, the resulting mixture was filtered through Celite, the residue washed with ethyl acetate. After concentration, the crude product was purified by flash chromatography (ethyl acetate/*n*-hexane 1:8).

Typical Procedure for the Synthesis of 4aa

Benzyl chloride **1a** (253 mg, 2 mmol) and isoquinoline **2a** (65 mg, 0.5 mmol) were added to a mixture of [$RuCl_2$(*p*-cymene)]$_2$ (7 mg, 0.00125 mmol) and K_2CO_3 (276 mg, 2 mmol) in H_2O (1 mL). The reaction mixture was heated at 130 °C for 12 h. After extraction with ethyl acetate (3 × 5 mL) and filtration over Celite, the collected organic layers were dried over $MgSO_4$. After concentration, the crude product was purified by flash chromatography (ethyl acetate/*n*-hexane 1:8).

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References

[1] a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; c) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260–269.

[2] a) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032–5035; b) I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157; c) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125; d) L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332–3335; e) C. Sollert, K. Devaraj, A. Orthaber, P. J. Gates, L. T. Pilarski, *Chem. Eur. J.* **2015**, *21*, 5380–5386; f) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem.* **2015**, *127*, 5604–5608; *Angew. Chem. Int. Ed.* **2015**, *54*, 5513–5517; g) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem.* **2009**, *121*, 6161–6164; *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048; h) F. Yang, L. Ackermann, *J. Org. Chem.* **2014**, *79*, 12070–12082; i) L. Ackermann, P. Novák, *Org. Lett.* **2009**, *11*, 4966–4969; j) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875–1877.

[3] Recent C–H functionalization work related to Ru catalysts: a) V. P. Mehta, J.- A. García-López, M. F. Greaney, *Angew. Chem.* **2014**, *126*, 1555–1559; *Angew. Chem. Int. Ed.* **2014**, *53*, 1529–1533; b) C. Suzuki, K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Adv. Synth. Catal.* **2014**, *356*, 1521–1526; c) H. Li, X. Xie, L. Wang, *Chem. Commun.* **2014**, *50*, 4218–4221; d) K. Padala, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 14573–14576; e) P. M. Liu, C. G. Frost, *Org. Lett.* **2013**, *15*, 5862–5865; f) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295; g) M. Schinkel, L. Wang, K. Bielefeld, L. Ackermann, *Org. Lett.* **2014**, *16*, 1876–1879; h) M. R. Yadav, M. Shankar, E. Ramesh, K. Ghosh, A. K. Sahoo, *Org. Lett.* **2015**, *17*, 1886–1889; i) H. Cheng, W. Dong, C. A. Dannenberg, S. Dong, Q. Guo, C. Bolm, *ACS Catal.* **2015**, *5*, 2770–2773; j) K. Kim, H. Choe, Y. Jeong, J. H. Lee, S. Hong, *Org. Lett.* **2015**, *17*, 2550–2553; k) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.* **2015**, *137*, 13894–13901; l) R. Prakash, K. Shekarrao, S. Gogoi, *Org. Lett.* **2015**, *17*, 5264–5267; m) R. Manikandan, P. Madasamy, M. Jeganmohan, *ACS Catal.* **2016**, *6*, 230–234; n) D. J. Paymode, C. V. Ramana, *J. Org. Chem.* **2015**, *80*, 11551–11558; o) M. K. Singh, H. K. Akula, S. Satishkumar, L. Stahl, M. K. Lakshman, *ACS Catal.* **2016**, *6*, 1921–1928; p) G. S. Kumar, M. Kapur, *Org. Lett.* **2016**, *18*, 1112–1115; q) J. A. Fernández-Salas, S. Manzini, L. Piola, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2014**, *50*, 6782–6784.

[4] a) K. Bhadra, G. S. Kumar, *Med. Res. Rev.* **2011**, *31*, 821–862; b) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444–463; c) K. C. Nicolaou, C. R. H. Hale, C. Nilewski, H. A. Ioannidou, *Chem. Soc. Rev.* **2012**, *41*, 5185–5238; d) A. Graulich, S. Dilly, A. Farce, J. Scuve-Moreau, O. Waroux, C. Lamy, P. Chavatte, V. Seutin, J. F. Ligeois, *J. Med. Chem.* **2007**, *50*, 5070–5075; e) M. Shamma, J. L. Moniot, *The Isoquinoline Alkaloids, Chemistry and Pharmacology,* Academic Press, New York, London, **1972**; f) Q. Wang, G. Han, Y. Liu, Q. Wang, *Nat. Prod. Rep.* **2010**, *27*, 1168–1185; g) M. Torres, S. Gil, M. Parra, *Curr. Org. Chem.* **2005**, *9*, 1757–1779; h) C. Ito, M. Itoigawa, T. Otsuka, H. Tokuda, H. Nishino, H. Furukawa, *J. Nat. Prod.* **2000**, *63*, 1344–1348; i) M. Daudon, H. Mehri, M. M. Plat, E. W. Hagaman,

F. M. Schell, E. Wenkert, *J. Org. Chem.* **1975**, *40*, 2838–2839.
[5] a) B. A. Sweetman, H. Müller-Bunz, P. J. Guiry, *Tetrahedron Lett.* **2005**, *46*, 4643–4646; b) F. Durola, J. P. Sauvage, O. S. Wenger, *Chem. Commun.* **2006**, 171–173; c) C. W. Lim, O. Tissot, A. Mattison, M. W. Hooper, J. M. Brown, A. R. Cowley, D. I. Hulmes, A. J. Blacker, *Org. Process Res. Dev.* **2003**, *7*, 379–384.
[6] a) K. H. Fang, L. L. Wu, Y. T. Huang, C. H. Yang, I. W. Sun, *Inorg. Chim. Acta* **2006**, *359*, 441–450; b) Q. Zhao, S. Liu, M. Shi, C. Wang, M. Yu, L. Li, F. Li, T. Yi, C. Huang, *Inorg. Chem.* **2006**, *45*, 6152–6160; c) A. Tsuboyama, H. Iwawaki, M. Furugori, T. Mukaide, J. Kamatani, S. Igawa, T. Moriyama, S. Miura, T. Takiguchi, S. Okada, M. Hoshino, K. Ueno, *J. Am. Chem. Soc.* **2003**, *125*, 12971–12979.
[7] For Bischler–Napieralski examples, see: a) X. Xu, S. Guo, Q. Dang, J. Chen, X. Bai, *J. Comb. Chem.* **2007**, *9*, 773–782; b) T. Ishikawa, K. Shimooka, T. Narioka, S. Noguchi, T. Saito, A. Ishikawa, E. Yamazaki, T. Harayama, H. Seki, K. Yamaguchi, *J. Org. Chem.* **2000**, *65*, 9143–9151; c) A. Bischler, B. Napieralski, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903–1908. For Pomeranz–Fritsch examples, see: d) E. V. Brown, *J. Org. Chem.* **1977**, *42*, 3208–3209; e) W. Herz, S. Tocker, *J. Am. Chem. Soc.* **1955**, *77*, 6353–6355; f) P. Fritsch, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 419–422; g) C. Pomeranz, *Monatsh. Chem.* **1893**, *14*, 116–119. For Pictet–Spengler examples, see: h) S. W. Youn, *J. Org. Chem.* **2006**, *71*, 2521–2523; i) A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036.
[8] a) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5705–5713; b) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051; c) Z. Zhu, X. Tang, X. Li, W. Wu, G. Deng, H. Jiang, *J. Org. Chem.* **2016**, *81*, 1401–1409; d) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204–12207; e) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Angew. Chem.* **2014**, *126*, 5050–5053; *Angew. Chem. Int. Ed.* **2014**, *53*, 4950–4953.
[9] C. S. Yeung, T. H. H. Hsieh, V. M. Dong, *Chem. Sci.* **2011**, *2*, 544–551.
[10] a) L. Shi, K. Yu, B. Wang, *Chem. Commun.* **2015**, *51*, 17277–17280; b) Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao, A. Lin, *J. Org. Chem.* **2016**, *81*, 2166–2173.
[11] 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.
[12] 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene.
[13] For further details of the optimization, see the Supporting Information.
[14] The KIE value is based on the rate constant derived from a plot of the first order reaction of **2a** and **2a**-*d*. See the Supporting Information for details.

Ruthenium-Mediated Dual Catalytic Reactions of Isoquinoline *via* C–H Activation and Dearomatization for Isoquinolone

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