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One-pot synthesis of 4-methylisoquinolines *via* a sequential Pd-catalyzed Heck reaction and intramolecular cyclization†

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An efficient, one-pot synthesis of 4-methylisoquinolines *via* a cascade Pd-catalyzed Heck reaction, intramolecular cyclization and isomerization has been developed. This reaction has a wide range of substrates with various functional groups, and the corresponding products have been obtained in good yields.

Functionalized isoquinolines are widely considered to be important structural motifs that are found in a vast array of natural products, endogenous substances and medicinal chemistry lead compounds (Fig. 1).[1] As the substituents on the isoquinolines have a great influence on their properties, efficient methods for the preparation of this valuable structural unit are highly desirable.

Traditional methods to synthesize isoquinoline analogues such as the Bischeler–Napieralski,[2] Pictet–Spengler[3] or Pomeranz–Fritsch[4] reactions normally have considerable drawbacks, including the use of strong acids and elevated temperatures, which are not suitable for sensitive substrates. In recent years, Larock and co-workers have reported a series of palladium-catalyzed methods for the preparation of substituted isoquinolines using the *tert*-butylimine of 2-iodobenzaldehydes and alkynes as annulation substrates.[5] Despite their high efficiency in the synthesis of isoquinolines, these methods still showed limitations such as a lack of regioselectivity and the requirement of lengthy synthesis of suitable starting materials. Rhodium-catalyzed C–H bond activation has also been reported for synthesizing substituted isoquinolines from aryl aldimines and alkynes.[6] However, the use of rhodium catalysts may involve a high cost.

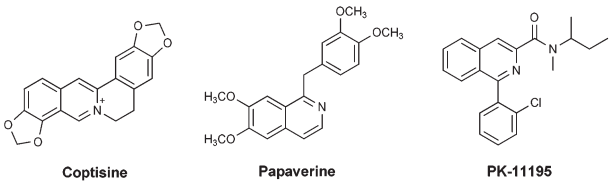
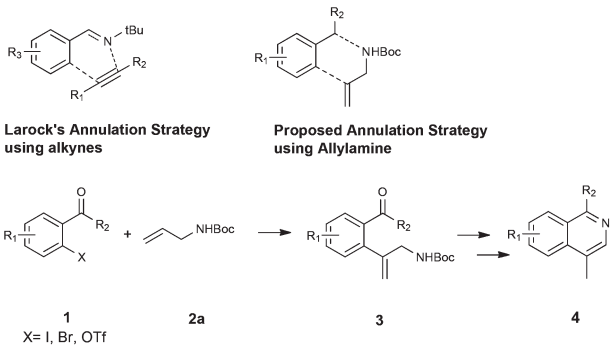


Fig. 1 Representative examples of isoquinoline derivatives.



Scheme 1 Strategy for the synthesis of 4-methylisoquinoline.

As part of our ongoing program on development of heterocycle oriented methods,[7] we envisioned a synthetic strategy to construct the 4-methylisoquinoline scaffold from commercially available building blocks. In our hypothesis, a regioselective Heck reaction developed by Hallberg between 2-acylphenyl triflates/halides (**1**) and *N*-Boc allylamine (**2a**) was conducted to give the corresponding 2-aryl-substituted allylcarbamates (**3**),[8] which was followed by deprotection, intramolecular cyclization and double bond isomerization to give the desired 4-methylisoquinoline (**4**) (Scheme 1). To our delight, these procedures were effectively conducted in a one pot condition, thereby offering a general and efficient approach to generate 4-methylisoquinolines in good yields. Herein, we disclose these results.

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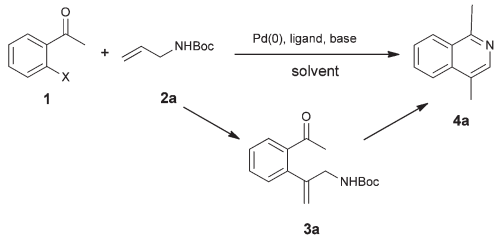
Table 1 Screening of the reaction conditions[a]



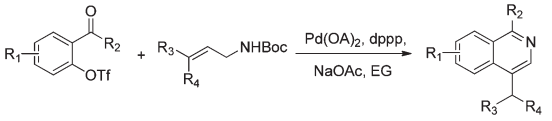
Entry	X	Pd	Lig	Base	Solv	Product[c] (%)
1	I	$Pd_2(dba)_3$	dppp	Et_3N	EG	**3a** (62)[b]
2	I	$Pd_2(dba)_3$	dppp	Et_3N	EG	**4a** (41)
3	I	$Pd_2(dba)_3$	dppp	Et_3N	DMF	**4a** (0)
4	I	$Pd_2(dba)_3$	dppp	Et_3N	NMP	**4a** (0)
5	I	$PdCl_2$	dppp	Et_3N	EG	**4a** (28)
6	I	$Pd(PPh_3)_4$	dppp	Et_3N	EG	**4a** (12)
7	I	$Pd(OAc)_2$	dppp	Et_3N	EG	**4a** (50)
8	I	$Pd(OAc)_2$	dppf	Et_3N	EG	**4a** (10)
9	I	$Pd(OAc)_2$	pph_3	Et_3N	EG	**4a** (0)
10	I	$Pd(OAc)_2$	dppp	DIPEA	EG	**4a** (20)
11	I	$Pd(OAc)_2$	dppp	NaOAc	EG	**4a** (70)
12	I	$Pd(OAc)_2$	dppp	Cs_2CO_3	EG	**4a** (12)
13	Br	$Pd(OAc)_2$	dppp	NaOAc	EG	**4a** (60)
14	OTf	$Pd(OAc)_2$	dppp	NaOAc	EG	**4a** (62)

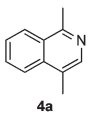
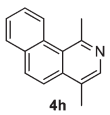
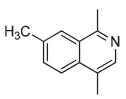
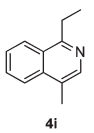
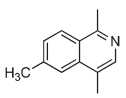
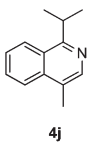
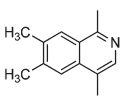
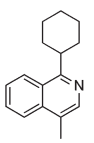
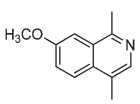
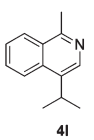
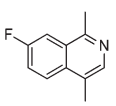
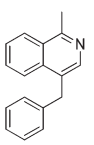
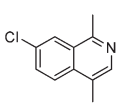
[a] The reaction was conducted under argon at 120 °C for 12 h. Used 0.05 equiv. of Pd catalyst, 0.1 equiv. of ligand, 2.0 equiv. of base. [b] The reaction was conducted under argon at 100 °C for 10 h. [c] Isolated yield.

We initiated our studies by choosing 2-iodoacetophenone (**1**) and *N*-Boc allylamine (**2a**) as the model substrates. The Heck reaction between **1** and **2a** was catalyzed by $Pd_2(dba)_3$ (5%) and dppp (10%) in the presence of Et_3N (2.0 equiv.) as the base in ethylene glycol (EG) at 100 °C, affording 2-aryl-substituted allylcarbamates (**3a**) in 62% yield after 10 hours, which was in accordance with our planned reaction sequence (Table 1, entry 1). The reaction mixture was subsequently heated at 120 °C to increase the yield of **3a**. To our delight, the desired product 1,4-dimethylisoquinoline **4a** was observed and isolated in 41% yield (Table 1, entry 2), which indicated that a one-pot reaction including sequential Heck reaction and cyclization has taken place. Promoted by this result, optimal conditions were examined to obtain more satisfactory results (Table 1). It was found that the reaction failed to proceed when it was performed in DMF or NMP (Table 1, entries 3 and 4), indicating that EG as a solvent plays an important role in this cascade reaction process. Screening of catalysts indicated that $Pd(OAc)_2$ displayed the highest catalytic activity toward the formation of **4a** (Table 1, entries 2 and 5–7). Different ligands were tested and dppp was found to be superior (Table 1, entries 7–9). Various bases such as Et_3N, DIPEA, Cs_2CO_3 and NaOAc were examined subsequently, which showed that NaOAc was the best choice (Table 1, entries 7 and 10–12). The effect of reactive group X in substrates was also investigated, giving the order of reactivity as follows: I > OTf ~ Br (Table 1, entries 11 and 13–14).

With the optimal conditions in hand, we examined the scope of our cascade reaction using different substituted

Table 2 Synthesis of isoquinolines[a]



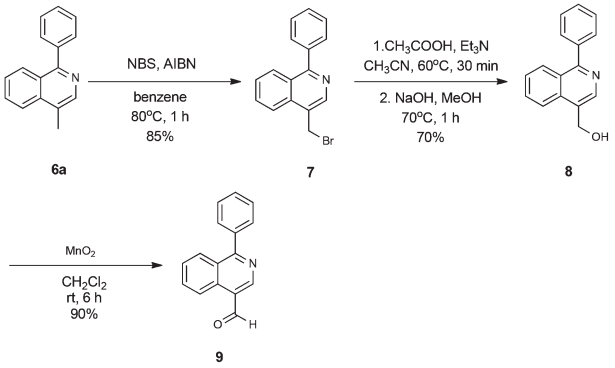
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **4a**	62	8	 **4h**	65
2	 **4b**	65	9	 **4i**	64
3	 **4c**	65	10	 **4j**	63
4	 **4d**	70	11	 **4k**	66
5	 **4e**	72	12	 **4l**	0
6	 **4f**	63	13	 **4m**	0
7	 **4g**	60			

[a] All reactions were conducted under argon using **1** (1.0 equiv.), **2** (1.2 equiv.), $Pd(OAc)_2$ (0.05 equiv.), dppp (0.1 equiv.), NaOAc (2.0 equiv.) in EG at 120 °C for 12 h. [b] Isolated yield.

2-acylphenyl triflates to generate a series of 4-methylisoquinolines. As summarized in Table 2, it was found that a number of alkyl and alkoxyl substituted 2-acetylphenyl triflates worked well (Table 2, entries 2, 3 and 5). Of note, the fluoro and chloro groups in the phenyl ring of the substrates were tolerated in the current reaction system as well (Table 2, entries 6 and 7). Additionally, the condition was not only restricted to the use of monosubstituted substrates, but also allowed the

efficient synthesis of disubstituted 4-methylisoquinolines (Table 2, entry 4). Meanwhile, we have also successfully synthesized a phenanthrene-like benzoisoquinoline using this method (Table 2, entry 8), which was observed as the common structure in bioactive molecules.[9] Apart from the methyl group, the substituents in 1-position of the isoquinoline scaffold can also be other alkyl groups like ethyl, isopropyl and cyclohexyl (Table 2, entries 9–11). However, no target isoquinoline products were obtained when *N*-Boc 3-methylbut-2-en-1-amine and *N*-Boc 3-phenylprop-2-en-1-amine were used as substrates (Table 2, entries 12 and 13).

Encouraged by the above results, we extended our work to construct substituted 1-phenyl-4-methylisoquinolines, which is a common structure existing in the compounds with bioactive interest[10] (Table 3). The reaction was found to be tolerant to a variety of substitutions on either benzene ring including electron-donating groups (**6b–e**, **h–k**), electron-withdrawing groups (**6n–o**), as well as halogen substitution (**6f–g**, **l–m**), which generate the corresponding substituted 1-phenyl-4-methylisoquinolines in moderate to good yields. The pyridine ring was also introduced into the 4-methylisoquinoline scaffold under these conditions (**6p**). In general, substrates with electron-donating groups led to higher yields than those with electron-withdrawing groups. The results proved that the method is noteworthy for its utility in preparing 1-phenyl-4-methylisoquinolines in high efficiency and in one step, providing a new route to isoquinoline systems.



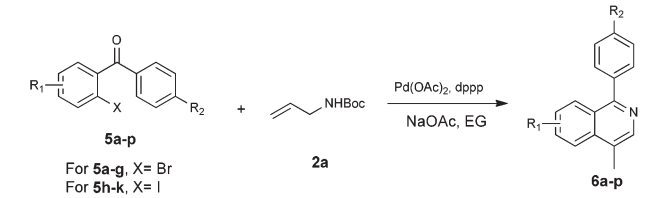
6a **7** **8** **9**

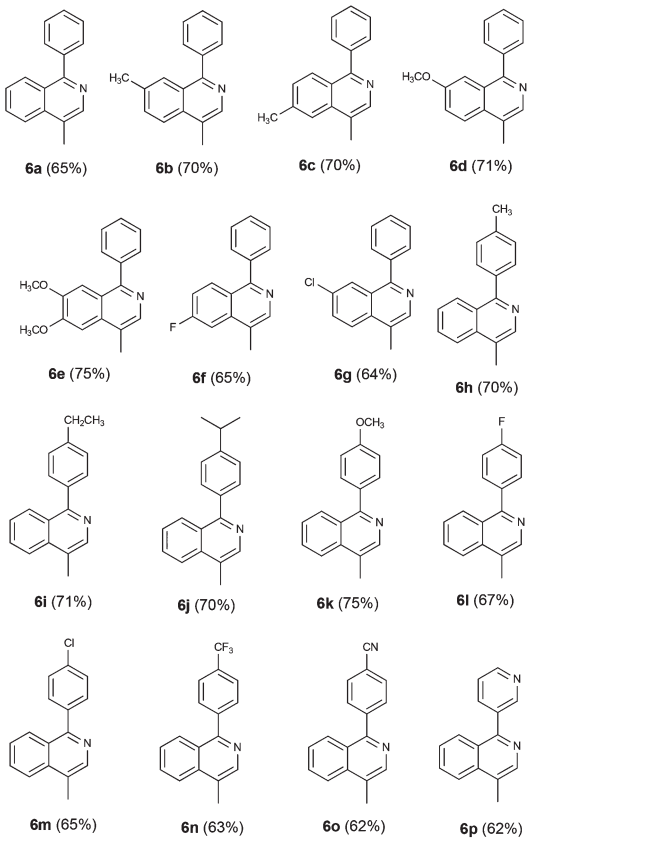
Scheme 2 Functional group transformations of **6a** to isoquinoline derivatives.

It was well acknowledged that the methyl group in the 4-position of isoquinoline is an active reaction site that could be converted into various functional groups to link other moieties or side chains. The bromination of **6a** gave **7** in 85% yield. Subsequently, hydrolysis and additional oxidation afforded **8** and **9**, respectively (Scheme 2). All three 1-phenyl-4-methylisoquinoline derivatives might be used as intermediates for the synthesis of complicated structures.

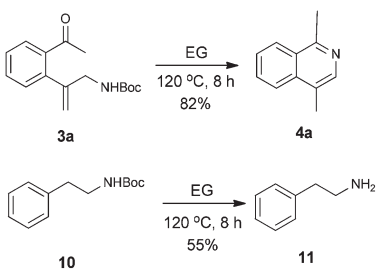
To investigate the factor that promoted intramolecular cyclization, the intermediate 2-aryl-substituted allylcarbamate (**3a**) was heated in EG from low to high temperature. It was found that the target 4-methylisoquinoline was directly formed in EG at 120 °C without any other additional reagents (Scheme 3). However, changing EG to other solvents (DMF, DMSO, NMP, xylene) failed to give the desired product at 120 °C. A simple reaction of *N*-Boc phenylethylamine (**10**) was conducted in

Table 3 Synthesis of 1-phenyl-4-methylisoquinolines[a,b]

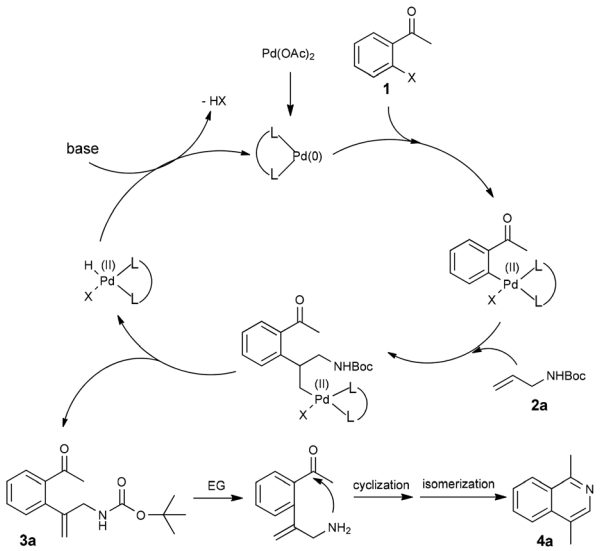




[a] All reactions were conducted under argon using **5** (1.0 equiv.), **2a** (1.2 equiv.), $Pd(OAc)_2$ (0.05 equiv.), dppp (0.1 equiv.), NaOAc (2.0 equiv.) in EG at 120 °C for 12 h. [b] Isolated yield.



Scheme 3 Formation of 4-methylisoquinoline from **3a**.



Scheme 4 A plausible reaction mechanism.

EG at 120 °C to verify the Boc removal effect of EG, and phenylethylamine (**11**) was obtained in 55% yield after 8 hours, which indicated that EG was essential for the deprotection of the Boc group to promote intramolecular cyclization.

On the basis of these results, a plausible mechanism is presented in Scheme 4. Initially, a Pd-catalyzed regioselective Heck reaction was performed through oxidative addition, migratory insertion, and the β-H elimination process to provide **3a**.[8a,11] Then the Boc group of **3a** was removed by an attack of EG at a high enough temperature. Subsequently, intramolecular cyclization and double bond isomerization gave the product **4a**.

In conclusion, we have developed a new approach for constructing 1-substituted-4-methylisoquinolines, starting from 2-acylphenyl triflates/halide and *N*-Boc allylamine, based on a one-pot Pd-catalyzed Heck reaction and intramolecular cyclization. The efficiency and substituent tolerance of this procedure have been fully demonstrated by synthesizing a wide range of functionalized 4-methylisoquinolines. Moreover, three isoquinoline derivatives from 1-phenyl-4-methylisoquinoline have been synthesized, which can be used in the further synthesis of complicated structures. The high efficiency and simple manipulation render this one-pot reaction an attractive method in organic synthesis.

Acknowledgements

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Notes and references

1 (*a*) A. Cappelli, M. Anzini, S. Vomero, L. Mennuni, F. Makovec, E. Doucet, M. Hamon, G. Bruni, M. R. Romeo, M. C. Menziani, P. G. D. Benedetti, T. Langer and P. S. Rajender, *J. Med. Chem.*, 1998, **41**, 728; (*b*) B. A. Weissman and L. Raveh, *J. Neurochem.*, 2003, **84**, 432; (*c*) S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku and M. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 3148; (*d*) Y. Watanabe, S. Aoki, D. Tanabe, A. Setiawan and M. Kobayashi, *Tetrahedron*, 2007, **63**, 4074; (*e*) S. Aoki, Y. Watanabe, D. Tanabe, A. Setiawan, M. Arai and M. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 4485; (*f*) K. W. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 444.

2 (*a*) W. M. Whaley and T. R. Govindachari, in *Organic Reactions*, ed. R. Adams, Wiley, New York, 1951, vol. 6, p. 151; (*b*) N. Sotomayor, E. Domínguez and E. Lete, *J. Org. Chem.*, 1996, **61**, 4062; (*c*) T. Ishikawa, K. Shimooka, T. Narioka, S. Noguchi, T. Saito, A. Ishikawa, E. Yamazaki, T. Harayama, H. Seki and K. Yamaguchi, *J. Org. Chem.*, 2000, **65**, 9143.

3 (*a*) W. M. Whaley and T. R. Govindachari, in *Organic Reactions*, ed. R. Adams, Wiley, New York, 1951, vol. 6, p. 74; (*b*) E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797; (*c*) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (*d*) S. W. Youn, *J. Org. Chem.*, 2006, **71**, 2521.

4 (*a*) W. J. Gensler, in *Organic Reactions*, ed. R. Adams, Wiley, New York, 1951, vol. 6, p. 191; (*b*) M. Boudou and D. Enders, *J. Org. Chem.*, 2005, **70**, 9486.

5 (*a*) K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 1998, **63**, 5306; (*b*) K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 553; (*c*) G. Dai and R. C. Larock, *Org. Lett.*, 2001, **3**, 4035; (*d*) K. R. Roesch, H. Zhang and R. C. Larock, *J. Org. Chem.*, 2001, **66**, 8042; (*e*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7042; (*f*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920; (*g*) Q. Huang and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 980.

6 (*a*) N. Guimond and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 12050; (*b*) P. C. Too, Y.-F. Wang and S. Chiba, *Org. Lett.*, 2010, **12**, 5688; (*c*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (*d*) J. Jayakumar, K. Parthasarathy and C. H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 197.

7 (*a*) K. Liu and D. Yin, *Org. Lett.*, 2009, **11**, 637; (*b*) G. Li, Q. Xiao, C. Li, X. Wang and D. Yin, *Tetrahedron Lett.*, 2011, **52**, 6827.

8 (*a*) K. Olofsson, H. Sahlin, M. Larhed and A. Hallberg, *J. Org. Chem.*, 2001, **66**, 544; (*b*) Y. Deng, Z. Jiang, M. Yao, D. Xu, L. Zhang, H. Li, W. Tang and L. Xu, *Adv. Synth. Catal.*, 2012, **354**, 899; (*c*) C. A. Baxter, E. Cleator, M. Alam, A. J. Davies, A. Goodyear and M. O'Hagan, *Org. Lett.*, 2010, **12**, 668.

9 (*a*) M. A. Kerry, G. W. Boyd, S. P. Mackay, O. Meth-Cohn and L. Platt, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2315; (*b*) A. Cappelli, G. Giuliani, A. Gallelli, S. Valenti, M. Anzini, L. Mennuni, F. Makovec, A. Cupello and S. Vomero, *Bioorg.*

Med. Chem., 2005, **13**, 3455; (*c*) M. Shimazawa, K. Kondo, H. Hara, M. Nakashima and K. Umemura, *Eur. J. Pharmacol.*, 2005, **520**, 118; (*d*) N. Atatreh, C. Stojkoski, P. Smith, G. W. Booker, C. Dive, A. D. Frenkel, S. Freeman and R. A. Bryce, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1217.

10 D. A. Walsh, L. F. Sancilio and D. L. Reese, *J. Med. Chem.*, 1978, **21**, 582.

11 (*a*) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2; (*b*) G. T. Crisp, *Chem. Soc. Rev.*, 1998, **27**, 427; (*c*) J. Ruan and J. Xiao, *Acc. Chem. Res.*, 2011, **44**, 614.