Very Important Publication

DOI: 10.1002/adsc.201501056

Easy Access to 1-Amino and 1-Carbon Substituted Isoquinolines *via* Cobalt-Catalyzed C−H/N−O Bond Activation

Krishnamoorthy Muralirajan,[a] Ramajayam Kuppusamy,[a] Sekar Prakash,[a] and Chien-Hong Cheng[a,*]

[a] Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan
Fax: (+886)-3572-4698; e-mail: chcheng@mx.nthu.edu.tw

Received: November 17, 2015; Revised: December 18, 2015; Published online: February 11, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201501056.

Abstract: A green atom-economical method for the synthesis of highly functionalized 1-amino and 1-carbon substituted isoquinolines from the reaction of *N*′-hydroxybenzimidamides and aryl ketoximes, respectively, with alkynes *via* pentamethylcyclopentadienylcobalt(III)-catalyzed C−H/N−O bond activation is described. The external oxidant-free annulation reaction uses the =NOH moiety in *N*′-hydroxybenzimidamides or *N*-aromatic ketone oximes as the directing group and internal oxidant. This first row transition metal-catalyzed annulation serves as an efficient alternative for the synthesis of isoquinolines, as water is the only by-product and expensive noble metals such as rhodium(III), iridium(III), palladium(II), and ruthenium(II) are not required. The reaction proceeds *via* C−H activation, alkyne insertion, reductive elimination, and N−O activation.

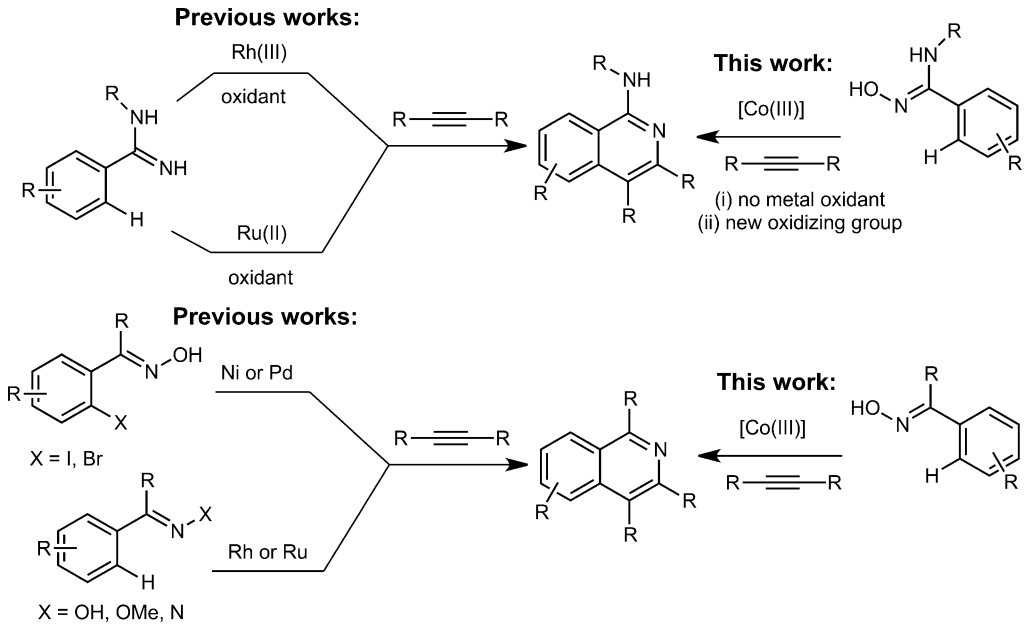
Keywords: alkynes; annulation; C−H activation; cobalt; isoquinolines; oximes

Introduction

Substituted isoquinolines are important N-heterocyclic compounds, which are often used in the synthesis of various alkaloids, inhibitors, pharmaceutically active salts, chiral ligands, and organic light-emitting diodes.[1] Their significance in pharmaceutical and heterocyclic chemistry as well as their unique structural features have attracted the attention of numerous synthetic organic chemists. In an effort to offer less expensive new routes towards isoquinoline frameworks, various synthetic routes have been developed (Scheme 1).[2,3] In this context, the Pd- and Ni-catalyzed annulation of *o*-halobenzimines with alkynes is a classical metal-catalyzed reaction that has been used to synthesize functionalized isoquinoline derivatives.[2] Transition metal-catalyzed, imine directed arene *ortho* C−H activations and oxidative annulations have also served as excellent approaches for the construction of isoquinolines.[3] However, conventional methods require the use of expensive metal complexes (Rh, Ru, and Pd), pre-functionalized starting materials, oxidants, and harsh reaction conditions. Furthermore, the cost and availability of second row metals and selection of starting materials are considered as drawbacks in industrial applications.

Transition metal-catalyzed, chelation-assisted C−H activation of arenes with subsequent alkyne insertion offers a regioselective and direct route for C−C/C−N bond construction.[4] In particular, metal-catalyzed, redox-neutral group-directed C−H bond activation and oxidative annulation reactions are known to be successful routes for the synthesis of N-heterocycles under a variety of conditions.[5] These methods often deliver atom economical paths in the absence of external metal oxidants. By utilizing this strategy, oxime and hydrazone directed C−H activation and incorporation of nitrogen may serve as leads towards a protocol for the synthesis of isoquinoline derivatives.[6] These reactions do not require an external oxidant; the N−O/N−N bond of the oxime/hydrazone acts as an internal oxidant.

To date, the majority of previous works have focused on synthesizing 1-carbon substituted isoquinolines using expensive metal catalysts *via* redox-neutral approaches. However, the synthesis of 1-amino-substituted isoquinolines is not well developed. It is known that 1-aminoisoquinolines play an important role in the initiation and propagation of thrombotic events and antithrombotic activities.[7a–d] Particularly, 1-isoquinolinylguanidines are used as the inhibitors of urokinase type plasminogen activator (uPA).[7b] Due to the biological significance of 1-aminoisoquino-



Scheme 1. Synthetic strategies for isoquinolines.

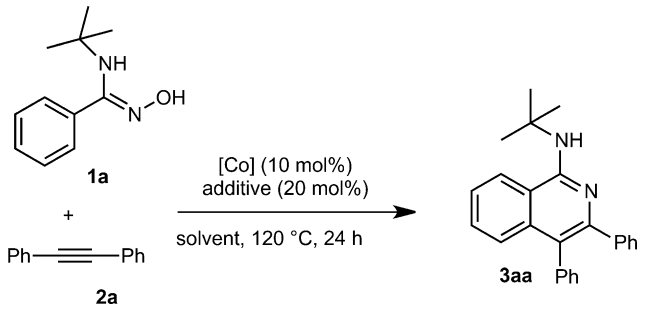
lines,[7a–c] Li[7d] and Ackermann[7e] independently reported Rh(III)- and Ru(II)-catalyzed oxidative coupling reactions of *N*-arylbenzamidines and *N*-alkylbenzamidines with alkynes to give the corresponding 1-aminoisoquinloines. These methods required stoichiometric amounts of an external Cu(II) metal oxidant. Therefore, to avoid the use of external metal oxidants, an atom-economical approach using a functional group that acts as a directing group as well as oxidant is required. Our interest in developing new metal-catalyzed C–H activation reactions[8] prompted us to explore the synthesis of highly substituted 1-aminoisoquinolines in a redox-neutral fashion. Until now, no first row transition metal-catalyzed method for the synthesis of 1-aminoisoquinolines through a redox-neutral group-assisted C–H activation has been reported. Recently, we reported the reaction of *N*′-hydroxybenzimidamides and alkynes for the synthesis of various 1-aminoisoquinolines and poly-N-heteroaromatic compounds using rhodium as the catalyst and copper(II) acetate as the oxidant.[6m] Directing group-assisted, Co-catalyzed arene C–H functionalizations have garnered considerable attention because Co is less expensive, more abundant, and less toxic than noble metal catalysts.[9] Particularly, some Co(III) complexes were found to show catalytic activities similar to Rh and Ru catalysts.[10] Herein, we report a Co-catalyzed redox-neutral group-assisted annulation of *N*′-hydroxybenzimidamides with alkynes to synthesize diverse 1-aminoisoquinolines *via* C–H activation as a key step. The method offers not only an alternative approach to 1-aminoisoquinline synthesis, but may also serve as a new route to synthesizing various N-heterocycles and as a replacement for metal catalysts such as Rh, Ru, Ir, and Pd in C–H activation reactions.

Results and Discussion

The reaction of *N*-*tert*-butyl-*N*′-hydroxybenzimidamide **1a** (0.20 mmol) with alkyne **2a** (0.26 mmol) in the presence of 10 mol% of $[CoCp^*(CO)I_2]$ and 20 mol% of CsOAc in TFE (2,2,2-trifluoroethanol) at 120 °C under N_2 for 24 h gave *N*-*tert*-butyl-3,4-diphenylisoquinolin-1-amine **3aa** in 86% isolated yield (Table 1, entry 4). The compound was carefully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data. The effects of the reaction conditions are summarized in Table 1. In the absence of the cobalt complex, product **3aa** was not observed. The presence of additive played an important role in the redox-neutral reaction. Use of CsOAc gave **3aa** in 89% (86% isolated) yield. Other additives such as NaOAc, KOAc, AgOAc, $Mn(OAc)_2$, and $Cu(OAc)_2$ gave only moderate yields. The solvent was also crucial to attain a high yield. Among the solvents examined, TFE afforded the highest yield, whereas DCE and CH_3CN were less effective. Other solvents including MeOH, EtOH, *t*-AmylOH, THF, and 1,4-dioxane are totally ineffective (Table 1, entries 8–10, 13 and 14). Similarly, we tested various cobalt complexes including CoI_2, $CoBr_2$, $Co(OAc)_2$, and $Co(acac)_3$, but only $[CoCp^*(CO)I_2]$ was active (entries 15–18).

With suitable reaction conditions in hand, we next explored the scope of the Co(III)-catalyzed redox-neutral protocol with a variety of *N*′-hydroxybenzimidamides **1** (Table 2). In general, all reactions pro-

Table 1. Screening the reaction conditions.[a,b]



Entry	[Co]	Solvent	Additive	Yield [%]
1	$[CoCp^*(CO)I_2]$	TFE	–	20
2	$[CoCp^*(CO)I_2]$	TFE	NaOAc	38
3	$[CoCp^*(CO)I_2]$	TFE	KOAc	55
4	***$[CoCp^*(CO)I_2]$***	***TFE***	***CsOAc***	89 ***(86)***
5	$[CoCp^*(CO)I_2]$	TFE	AgOAc	13
6	$[CoCp^*(CO)I_2]$	TFE	$Mn(OAc)_2$	78
7	$[CoCp^*(CO)I_2]$	TFE	$Cu(OAc)_2$	15
8	$[CoCp^*(CO)I_2]$	MeOH	CsOAc	–
9	$[CoCp^*(CO)I_2]$	EtOH	CsOAc	–
10	$[CoCp^*(CO)I_2]$	*t*-amylOH	CsOAc	–
11	$[CoCp^*(CO)I_2]$	DCE	CsOAc	28
12	$[CoCp^*(CO)I_2]$	CH_3CN	CsOAc	25
13	$[CoCp^*(CO)I_2]$	THF	CsOAc	–
14	$[CoCp^*(CO)I_2]$	1,4-dioxane	CsOAc	–
15	CoI_2	TFE	CsOAc	–
16	$CoBr_2$	TFE	CsOAc	–
17	$Co(OAc)_2$	TFE	CsOAc	–
18	$Co(acac)_3$	TFE	CsOAc	–

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.20 mmol), **2a** (0.26 mmol), [Co] (10 mol%), additive (20 mol%), and solvent (3.0 mL) at 120 °C for 24 h under N_2.

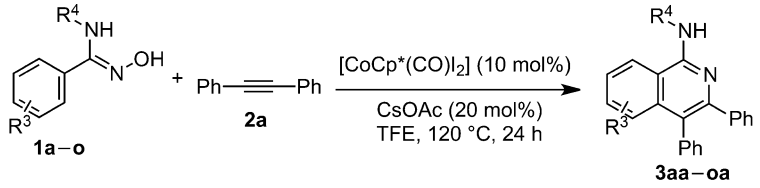
[b] Yields were determined by the ^1H NMR integration method; the value in parenthesis indicates isolated yield.

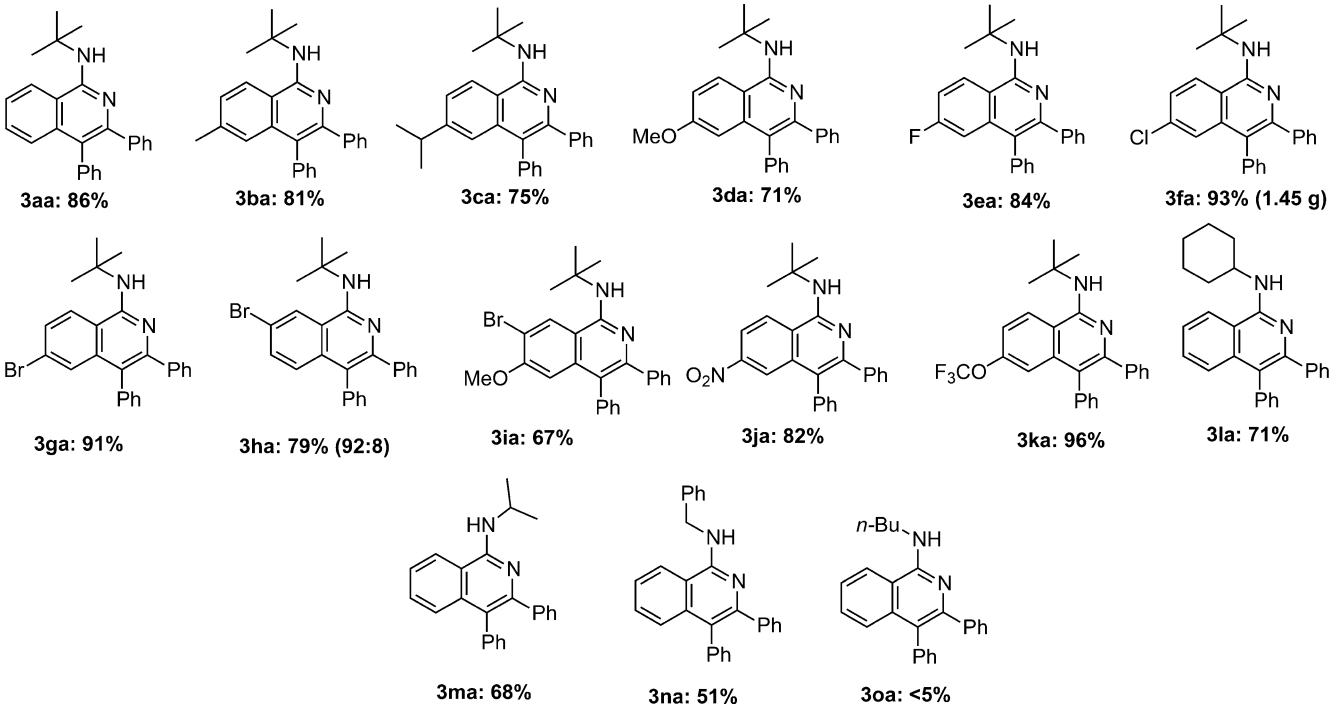
ceeded smoothly, and resulted in moderate to high yields of the corresponding 1-aminoisoquinolines. Reactions of substrates with electron-donating groups such as 4-methyl, 4-isopropyl, and 4-methoxy (**1b–d**) with **2a** furnished the corresponding products in 81, 75, and 71% yields (**3ba–da**), respectively. Similarly, halogen-containing substrates such as 4-F, 4-Cl, and 4-Br (**1e–g**) arenes reacted efficiently and gave the products in 84, 93, and 91% (**3ea–ga**) yields, respectively. Notably, the reaction of 3-bromo-substituted *N*′-hydroxybenzimidamide **1h** with **2a** under the standard reaction conditions gave regioisomeric products **3ha** (92:8) in 79% yield. With **1i**, the reaction proceed selectively at the least hindered position (C-6) and afforded a slightly lower yield (**3ia**). Here, electron-rich arenes such as **1d** and **1i** slightly suppressed the annulation product, but the annulation reaction with electron-deficient arenes such as **1j** and **1k** proceeded very effectively. Next, we tested the effects of different amino protecting groups (**1l–o**) under the same reaction conditions. The reaction between *N*-cyclohexyl and isopropyl substituted *N*′-hydroxybenzimidamides and **2a** afforded expected products **3la** and **3ma** in 71 and 68% yields, respectively. However, treatment of (*Z*)-*N*-benzyl-*N*′-hydroxybenzimidamide (**1n**) with **2a** gave **3na** in a lower yield (51%). Unfortunately, (*Z*)-*N*-butyl-*N*′-hydroxybenzimidamide (**1o**) afforded less than 5% yield, perhaps due to the coordination of the free NH group with the cobalt complex which cannot lead to C–H activation. The above results clearly revealed that sterically hindered amino groups at the 1-position were necessary for the reaction to proceed efficiently.[7e] Additionally, this Co-catalyzed redox-neutral reaction is more convenient for industrial applications and it is strengthened by the scale-up experiment for the synthesis of **3fa** in 85% (1.45 g) isolated yield.

Next, we studied the reactions of various aryl, symmetrical alkyl, and unsymmetrical alkynes with **1a** under the standard reaction conditions. The results are shown in Table 3. Electron-rich 4-Me, 4-MeO (**2b** and **2c**) and halo 4-F, 4-Br (**2d** and **2e**) substituted diarylacetylenes reacted smoothly with **1a** to give the desired isoquinolines **3ab–ae** in 79–86% yields. Similarly, thiophene-substituted alkyne **2f** resulted in the expected isoquinoline, **3af**, in 70% yield. We also tested the reactivity of dialkylalkynes; treatment of hex-3-yne (**2g**) and oct-4-yne (**2h**) with **1a** proceeded smoothly and afforded **3ag** and **3ah** in 61% and 73% yields, respectively. Furthermore, a selection of unsymmetrical alkynes, including 1-phenyl-1-propyne (**2i**), 1-phenyl-1-butyne (**2j**), and 1-(hex-1-ynyl)-4-methoxybenzene (**2k**) underwent oxidative annulations effectively with moderate regioselectivity. Interestingly, the reaction of trimethyl(phenylethynyl)silane (**2l**), afforded a trimethylsilyl-cleaved mixture of two separable regioisomeric products (**3al′** and **3am**) in 27% and 46% yields, respectively. Notably, terminal alkynes such as phenylacetylene also reacted nicely under the optimized conditions to give regioselective product **3am** in 61% yield.[9j,k] The latter result is intriguing because for most rhodium- and ruthenium-catalyzed C–H activation reactions, terminal alkynes cannot be used as the substrates for insertion and annulation.[6a–k]

The high catalytic efficiency in the redox-neutral assisted direct C–H activation and annulation of *N*-substituted *N*′-hydroxybenzimidamides with alkynes sparked our interest in expanding the strategy to include other directing groups such as aryl ketoximes to facilitate the synthesis of 1-carbon substituted isoquinolines. Notably, 5 mol% $[CoCp^*(CO)I_2]$ with 10 mol% KOAc at 100 °C for 18 h is highly suitable for this external metal oxidant-free oxidative annulation reaction (see the Supporting Information for detailed optimization studies). The treatment of acetophenone oxime (**4a**) with diphenylacetylene (**2a**)

Table 2. Synthesis of 1-aminoisoquinolines from various *N*-substituted *N′*-hydroxyimidamides.[a,b]



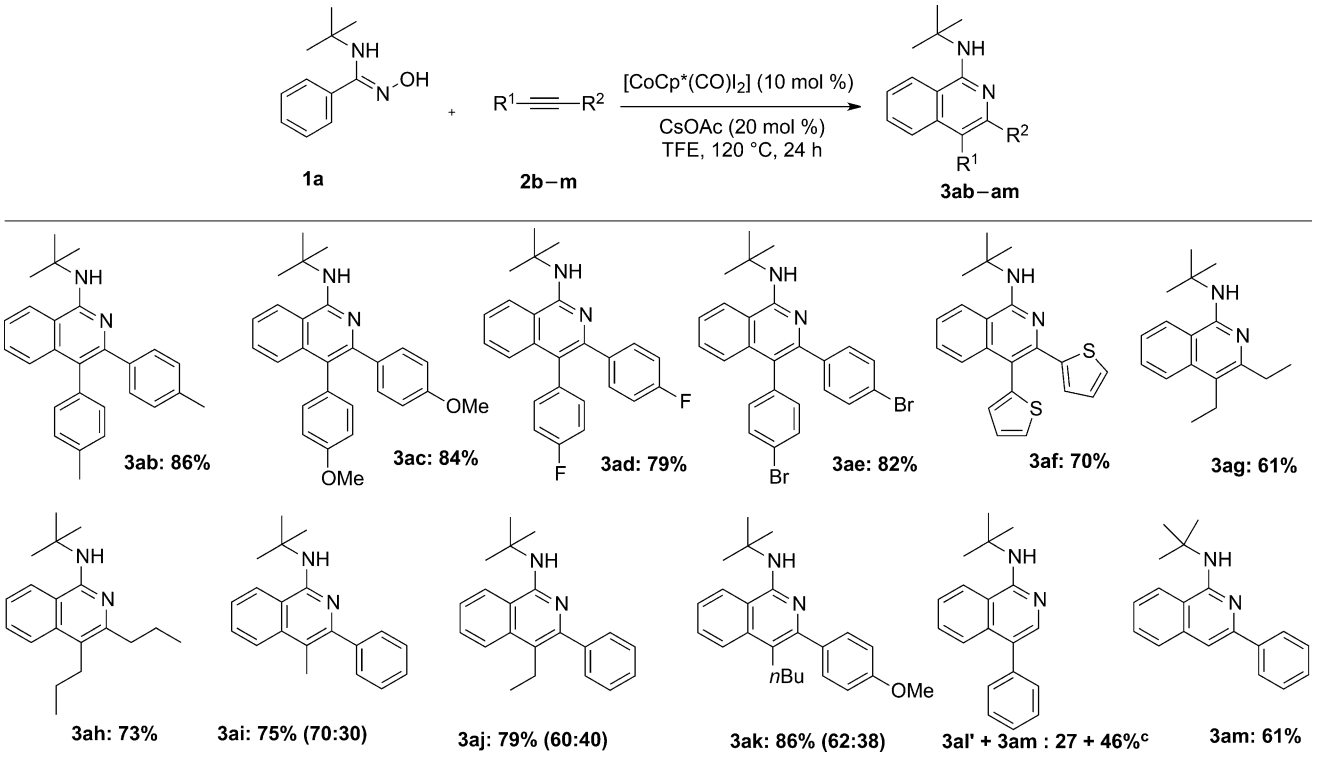


[a] Unless otherwise mentioned, all reactions were carried out using **1a–o** (0.20 mmol), **2a** (0.26 mmol), [CoCp*(CO)I_2] (10 mol%), CsOAc (20 mol%), and TFE (3.0 mL) at 120 °C for 24 h.
[b] Isolated yield.

under the mentioned reaction conditions gave 1-methyl-3,4-diphenylisoquinoline **5aa** in 90% isolated yield [95% isolated yield was observed in the presence of 15 mol% $Mn(OAc)_2$ as the additive]. During our preparation of this manuscript, three reports have been appeared on the synthesis of isoquinolines. The Kanai/Matsunaga[11a] and Ackermann[11b] groups independently showed the isoquinolines synthesis by using *o*-acylacetophenone oximes and alkynes in the presence of 10 mol% [CoCp*(CO)I_2] as the catalyst. It is important to mention here that, to attain high efficiency, these reactions required $AgSbF_6$ (20 mol%), NaOAc or KOAc (20 mol%) and a high temperature (120 °C). Similarly, Sundararaju et al also reported the synthesis of isoquinolines in the presence of 10 mol% [CoCp*(CO)I_2] and 20 mol% NaOAc.[11c] We had independently found the reaction conditions for the annulation of aryl ketoximes with alkynes. The reaction conditions are similar to those reported, but we used a lower amount of cobalt complex (5% *vs.* 10% reported) and TFE as the solvent (the same as that used by Sundararaju[11c]). In addition, we did not use a silver salt in the solutions to promote the reactions.

Then, we tested the reaction with various acetophenone oximes under the developed catalytic conditions and the results are presented in Table 4. The presence of electron-donating and halogen groups in the *para* position in acetophenone oximes **4b–h** did not affect the reaction and increased the yield to 92%. However, the presence of substituents in various positions in acetophenone oximes (**4i–l**) provided highly regioselective C–H functionalized isoquinoline derivatives in 75–85% yields. The reaction of 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanone oxime (**4m**) gave separable, regioisomeric products **5ma** and **5ma′** in 33% and 59% yields, respectively. In a similar manner, the effect of changing the methyl group (1 position) in acetophenone oxime **1a** to other substituents was also evaluated. Various 1-carbon substituted alkyl and aryl acetophenone oximes underwent C–H activation effectively and afforded the corresponding isoquinolines in 77 to 97% yields. Similarly, the reaction of hetero-

Table 3. Synthesis of 1-aminoisoquinolines from various alkynes.[a,b]



[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.20 mmol), **2b–m** (0.26 mmol), [CoCp*(CO)I_2] (10 mol%), CsOAc (20 mol%), and TFE (3.0 mL) at 120 °C for 24 h.
[b] Isolated yield.
[c] **2l** = $Me_3SiC{\equiv}CPh$.

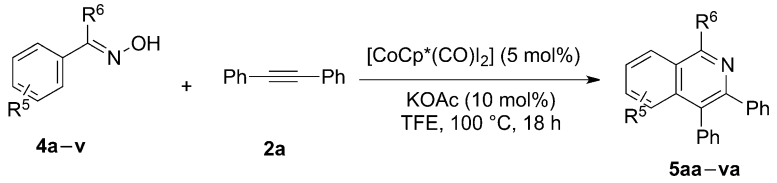
aromatic substrates such as 1-(pyridin-4-yl)ethanone oxime (**4t**), 1-(1*H*-indol-3-yl)ethanone oxime (**4u**), and 1-(thiophen-3-yl)ethanone oxime (**4v**) with **2a** gave the expected heterocyclic ring-containing isoquinolines **5ta**, **5ua**, and **5va** in 75%, 91%, and 73% yields, respectively.

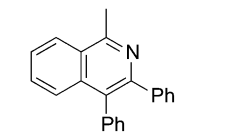
To develop the scope of the reaction and determine the regioselectivity, we also investigated the reaction of acetophenone oxime (**4a**) with various aryl, symmetrical alkyl, and unsymmetrical alkynes under the optimized conditions. The results are displayed in Table 5. The reaction conditions were highly compatible with *p*-Me, *p*-MeO, *p*-F, and *p*-Br-containing arylalkynes, and afforded the relevant isoquinolines in good to excellent yields. Similarly, heteroaromatic (**2f**) and dialkyl (**2g** and **2h**) alkynes reacted smoothly to give corresponding isoquinolines in 68–79% yields. Unsymmetrical alkynes such as 1-phenyl-1-propyne (**2i**), 1-phenyl-1-butyne (**2j**), 1-(hex-1-ynyl)-4-methoxybenzene (**2k**), and trimethyl(phenylethynyl)-silane (**2l**), underwent annulations and afforded fully separable regioisomeric isoquinolines in good yields with excellent regioselectivities. Notably, **5al** contains a trimethylsilyl group, which might be useful for further transformations. Interestingly, the reaction of phenylacetylene (**2m**) with **4a** gave highly regioselective product **5am** in 65% yield. The results with unsymmetrical alkynes are similar to those reported previously involving annulation reactions.[6]

Finally, we conducted intramolecular competition experiments using various electronically distinct arenes (Scheme 2). The reaction of phenyl(*p*-tolyl)-methanone oxime (**6a**) with **2a** gave fully separable isomers **7aa** and **7aa′** in 41% and 50% yields, respectively. Here, 4-Me-substituted arenes underwent C–H activation more quickly than unsubstituted arenes. A similar result was observed when **6b** was used as the substrate instead of **6a**. These results were supported by the intramolecular competition reaction using NO_2-substituted arene **6c** as the substrate. The selectivity was notable, and the results strongly suggested that electron-rich arenes could preferentially undergo C–H activation to the cobalt complex.

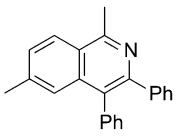
To elucidate the reaction mechanism, we conducted several kinetic experiments using [D_5]-**4a**, **4a**, and **2a** as model substrates (Scheme 3). First, we analyzed the reversibility of the reaction under the standard reaction conditions at different time intervals. For up to 10 min, no D/H exchange was observed in the *ortho* position. After 15 min, 3% D/H exchange was observed. Similarly, after 30 min and 1 h time intervals 8% and 10% D/H exchange products were observed,

Table 4. Synthesis of isoquinolines from various acetophenone oximes.[a,b]

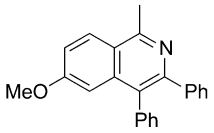




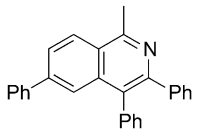
5aa: 90% [@ KOAc]
5aa: 95% [@ $Mn(OAc)_2$]



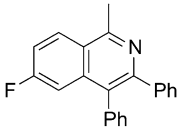
5ba: 89%



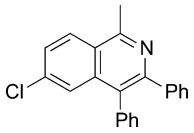
5ca: 87%



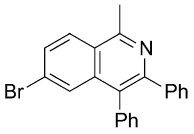
5da: 89%



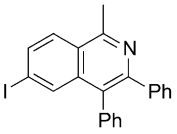
5ea: 88%



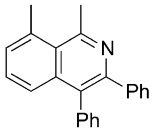
5fa: 90%



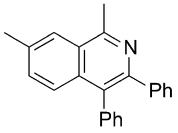
5ga: 92%



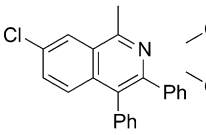
5ha: 91%



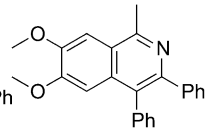
5ia: 75%



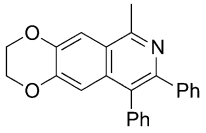
5ja: 81%



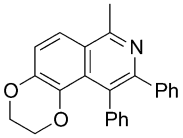
5ka: 79%



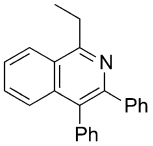
5la: 85%



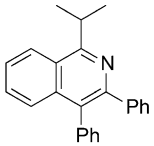
5ma: 33%



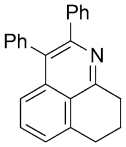
5ma': 59%



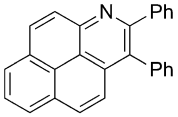
5na: 94%



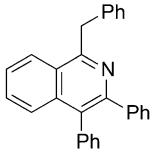
5oa: 88%



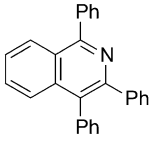
5pa: 83%



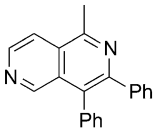
5qa: 77%



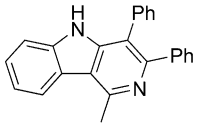
5ra: 78%



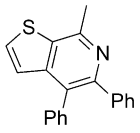
5sa: 97%



5ta: 75%



5ua: 91%



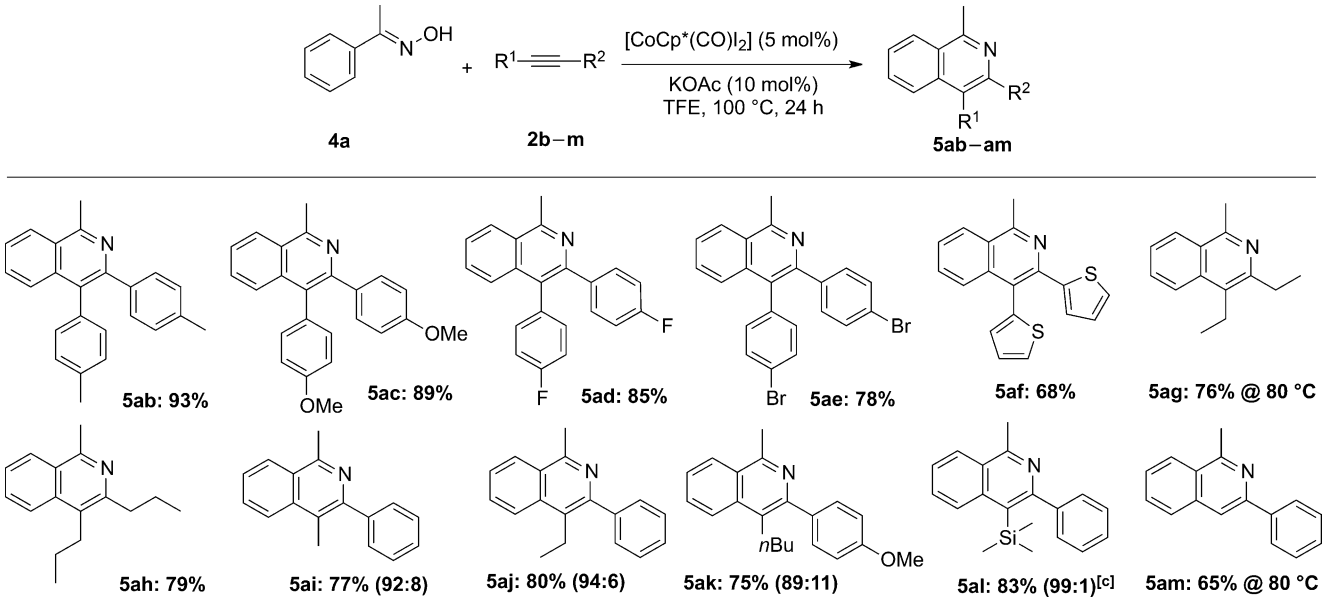
5va: 73% [@ $Mn(OAc)_2$]

[a] Unless otherwise mentioned, all reactions were carried out using **4a–v** (0.25 mmol), **2a** (0.30 mmol), $[CoCp^*(CO)I_2]$ (5 mol%), KOAc (10 mol%) and TFE (2.0 mL) at 100 °C for 18 h. 15 mol% $Mn(OAc)_2$ was used for **5aa** and **5va**.
[b] Isolated yield.

respectively. Finally, 63% of D/H exchange in $[D_5]$-**4a** along with 9% of D/H exchange in ketone products were observed under standard reaction conditions. These results illustrated that the cobalt intermediate was stable for up to 10 min, after which it dissociated. We tried to isolate the five-membered cobaltacycle in a stoichiometric reaction before 10 min, but we were not able to isolate any intermediate. Additionally, we also conducted the reaction of $[D_5]$-**4a** with **2a** for 5 min under standard reaction conditions. The result shows the existence of 3% H/D exchange in product $[D_4]$-**5aa**. This indicates that the reaction is also reversible in the presence of alkyne [Scheme 3, Eq. (2)]. Finally, we measured inter- and intramolecular kinetic isotopic effects (KIEs). An intermolecular KIE of $k_H/k_D = 3.5$ was observed for the competitive reaction of $[D_5]$-**4a** and **4a** with **2a** to give **5aa**. An intramolecular competition experiment with $[D_1]$-**4a** and **2a** indicated that $k_H/k_D = 2.5$. The observed large KIE values indicate that the C–H bond cleavage step is possibly involved in the rate-determining step (see the Supporting Information for details on the deuterium labelling experiments).

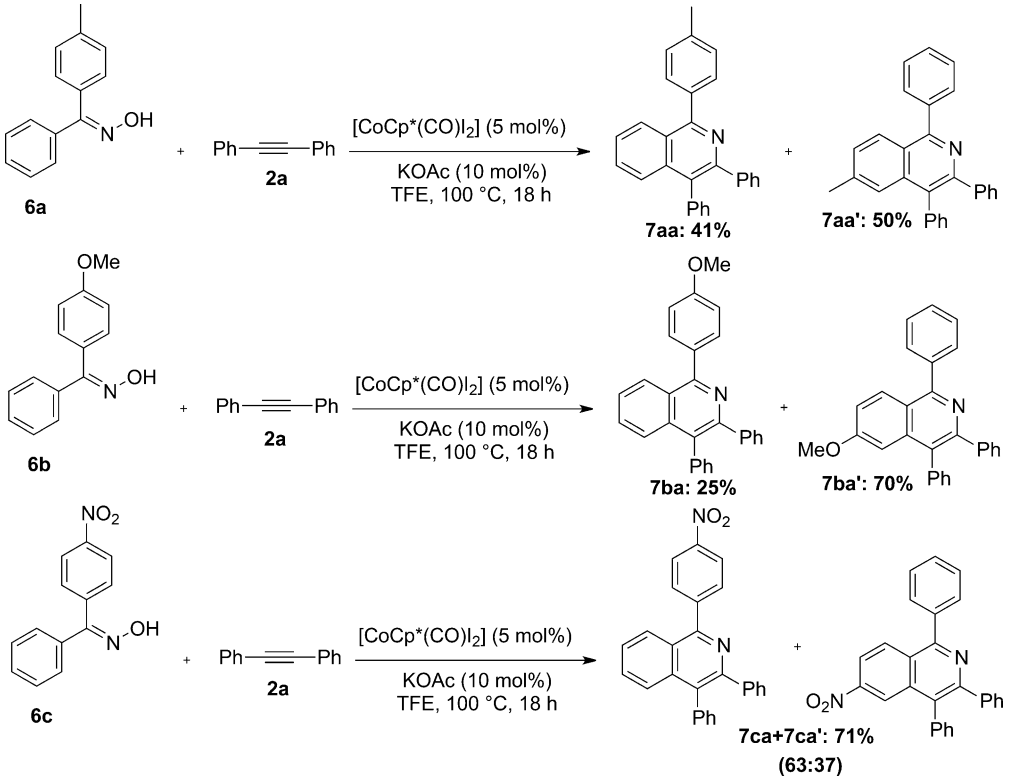
A surprising result in the present isotope labelling studies is that the intermolecular KIE of $k_H/k_D = 3.5$ is substantially larger than the intramolecular value of $k_H/k_D = 2.5$. We should note that in most transition metal-catalyzed C–H activation reactions, the intramolecular KIE of k_H/k_D is larger than the corresponding intermolecular value. This is likely due to the precoordination of the directing group prior to the C–H cleavage to form the metallacycle intermediate. While the reason for the observed contrast kinetic isotope effects is still not clear, one possibility is that cobalt-catalyzed intermediate (**C**, Scheme 4) in this intramolecular oxidative annulation also undergoes H/D exchange with the solvent leading to higher H content of substrate **4a**. For example, if the protonation of co-

Table 5. Synthesis of isoquinolines from various alkynes.[a,b]

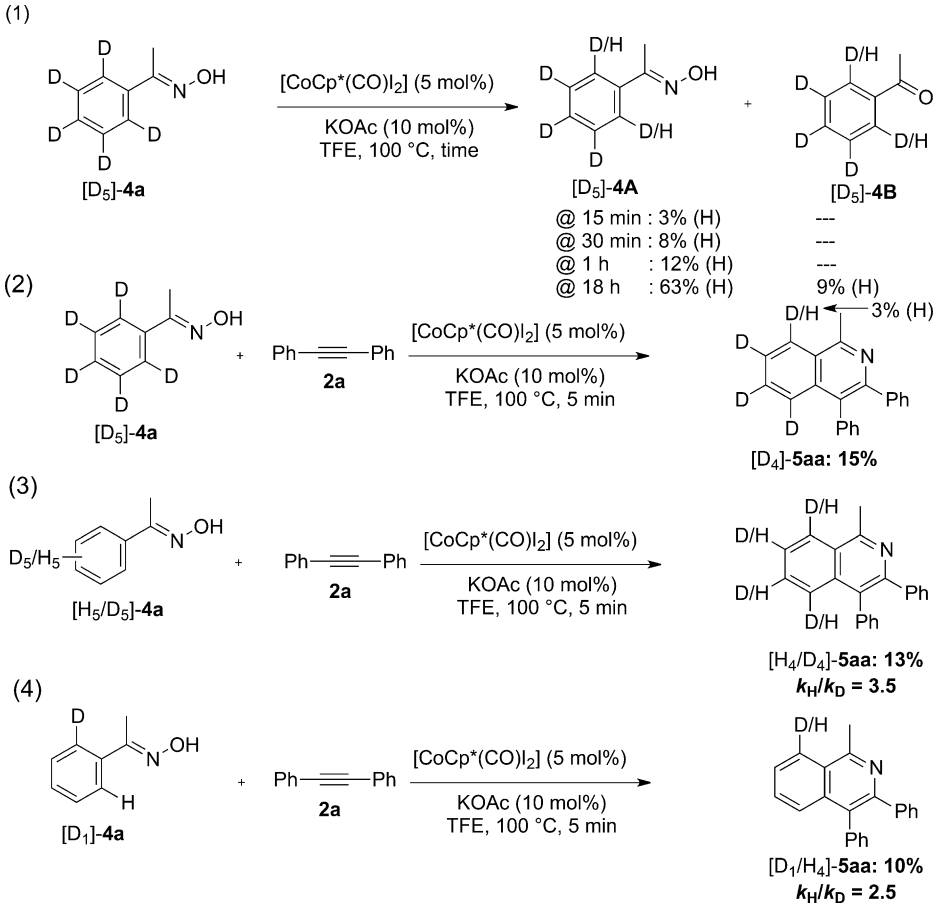


[a] Unless otherwise mentioned, all reactions were carried out using **4a** (0.25 mmol), **2b–m** (0.30 mmol), $[CoCp^*(CO)I_2]$ (5 mol%), KOAc (10 mol%), and TFE (2.0 mL) at 100 °C for 24 h.
[b] Isolated yield.
[c] < 5% **5am** was observed.

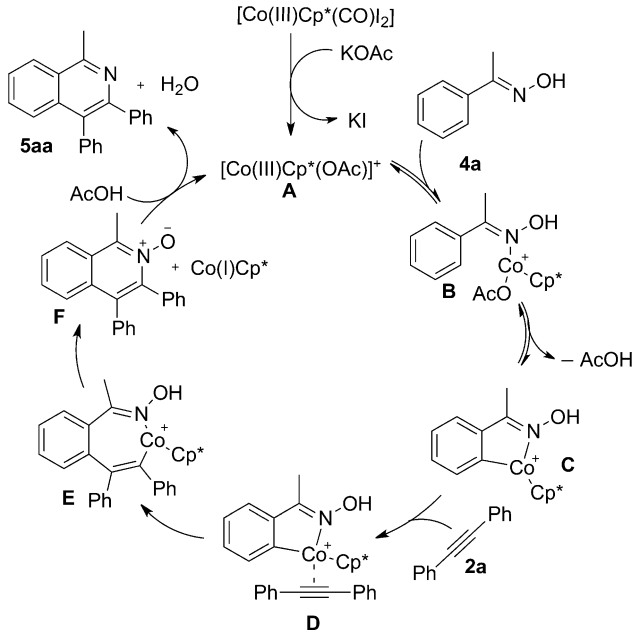
baltacycle of $[D_1]$-**4a** occurs to give back the intermediate **B**, the effective concentration of $[D_1]$-**4a** decreases and $[H_5]$-**4a** increases. In this case, the measured k_H/k_D value from the ratio of {$[D_1]$-**5aa**}/{$[H_4]$-**5aa**} is smaller than the real k_H/k_D without any H/D exchange.



Scheme 2. Intramolecular competition reactions.



Scheme 3. Kinetic experiments.



Scheme 4. A plausible reaction mechanism.

Based on our results and known metal-catalyzed redox-neutral reactions,[6] a plausible mechanism for the Co-catalyzed redox-neutral pathway is shown in Scheme 4 using **4a** and **2a** as model substrates. $[CoCp^*(OAc)]^+$[10] possibly initiated the reaction by the removal and exchange of the ligand from $[CoCp^*(CO)I_2]$ by KOAc. Then, coordination of the nitrogen atom to the Co(III) center, followed by arene *ortho* C–H bond cleavage afforded five-membered cobaltacycle **C**, which was reversible in nature. Further, coordination of the alkyne π-bond to cobaltacycle **C** and subsequent insertion of the alkyne into the Co–C bond of intermediate **D** affords a seven-membered cobaltacyclic intermediate **E**. The intermediate **E** possibly undergoes reductive elimination to give 1-methyl-3,4-diphenylisoquinoline 2-oxide (**F**) and a Co(I) species.[6,11] Finally, the cleavage of the N–O bond of salt **F** by the Co(I) species releases expected isoquinoline **5aa**, Co(III) species **A** and by-product H_2O.[3b,6e,i]

Conclusion

In summary, we have developed an efficient method for the synthesis of 1-amino- and 1-carbon-substituted isoquinolines using a more abundant first row transi-

tion metal as the catalyst and water is the only side product. Here, the *N*′-hydroxybenzimidamide-directed, cobalt-catalyzed *ortho* C–H addition to alkynes and regeneration of the active catalyst by a redox-neutral strategy were demonstrated. This Co-catalyzed method is similar to that with noble metal-containing catalysts, but the atom economy in this reaction is an addition advantage.

Experimental Section

General Procedure for the Synthesis of 1-Aminoisoquinolines

A sealed tube containing *N*-substituted *N*′-hydroxyimidamides **1** (0.20 mmol), alkynes **2** (0.26 mmol), $[CoCp^*(CO)I_2]$ (10 mol%) and CsOAc (20 mol%) was evacuated and purged with nitrogen gas three times. Then, TFE (3.0 mL) was added *via* syringe under a nitrogen atmosphere and the reaction mixture was allowed to stir at 120 °C for 24 h. After 24 h, the mixture was cooled and diluted with CH_2Cl_2 (10 mL). The mixture was filtered through a Celite pad and the Celite pad was washed with CH_2Cl_2 (3×10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford the desired pure product **3.**

Acknowledgements

We thank the Ministry of Science and Technology of the Republic of China (MOST-103-2633M-007-001) for support of this research.

References

[1] a) J. D. Phillipson, M. F. Roberts, M. H. Zenk, (Eds.), *The Chemistry and Biology of Isoquinoline Alkaloids*, Springer Verlag, Berlin, **1985**; b) K. Bhadra, G. S. Kumar, *Med. Res. Rev.* **2011**, *31*, 821; c) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; d) V. G. Kartsev, *Med. Chem. Res.* **2004**, *13*, 325; e) Y. Kashiwada, A. Aoshima, Y. Ikeshiro, Y. P. Chen, H. Furukawa, M. Itoigawa, T. Fujioka, K. Mihashi, L. M. Cosentino, S. L. Morris-Natschke, K. H. Lee, *Bioorg. Med. Chem.* **2005**, *13*, 443; f) 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; g) B. A. Sweetman, H. Muller-Bunz, P. J. Guiry, *Tetrahedron Lett.* **2005**, *46*, 4643; h) Q. Liu, S. Zhao, M. Shi, C. Wang, M. Yu, L. Li, F. Li, T. Yi, C. Huang, *Inorg. Chem.* **2006**, *45*, 6152.

[2] a) R. P. Korivi, C.-H. Cheng, *Org. Lett.* **2005**, *7*, 5179; b) R. P. Korivi, Y. C. Wu, C. H. Cheng, *Chem. Eur. J.* **2009**, *15*, 10727; c) W.-C. Shih, C. C. Teng, K. Parthasarathy, C.-H. Cheng, *Chem. Asian J.* **2012**, *7*, 306; d) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 5306; e) Q. Huang, J. A. Hunter, R. C. Larock, *Org. Lett.* **2001**, *3*, 2973; f) K. R. Roesch, H. Zhang, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 8042.

[3] a) S.-G. Lim, J. H. Lee, C. W. Moon, C. J.-B. Hong, C.-H. Jun, *Org. Lett.* **2003**, *5*, 2759; b) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645; d) R. M. Martin, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 2501; e) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141; f) Y.-F. Wang, K. K. Toh, J.-Y. Lee, S. Chiba, *Angew. Chem.* **2011**, *123*, 6049; *Angew. Chem. Int. Ed.* **2011**, *50*, 5927.

[4] For selected reviews: a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; b) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; c) J. W. Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; e) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5705; f) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; g) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; h) P. Gandeepan, C.-H. Cheng, *Chem. Asian J.* **2015**, *10*, 824; i) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; j) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; k) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; l) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 and references cited therein.

[5] a) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; b) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; c) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573; d) H. Wang, F. Glorius, *Angew. Chem.* **2012**, *124*, 7430; *Angew. Chem. Int. Ed.* **2012**, *51*, 7318; e) L. Xu, Q. Zhu, G. Huang, B. Cheng, Y. Xia, *J. Org. Chem.* **2012**, *77*, 3017; f) S. Prakash, K. Muralirajan, C.-H. Cheng, *Chem. Commun.* **2015**, *51*, 13362; g) K. Muralirajan, C.-H. Cheng, *Adv. Synth. Catal.* **2014**, *356*, 1571; h) K. Muralirajan, R. Haridharan, S. Prakash, C.-H. Cheng, *Adv. Synth. Catal.* **2015**, *357*, 761; i) R. B. Dateer, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4908; j) N. Kuhl, N. Schrçder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; k) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66.

[6] a) P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688; b) P. C. Too, S. H. Chua, S. H. Wong, S. Chiba, *J. Org. Chem.* **2011**, *76*, 6159; c) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449; d) T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846; e) S. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719; f) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3703; g) S.-C. Chuang, P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 5750; h) D. Zhao, F. Lied, F. Glorius, *Chem. Sci.* **2014**, *5*, 2869; i) C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190; j) X.-C. Huang, X.-H. Yang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 1025; k) L. Zheng, J. Ju, Y. Bin, R. Hua, *J. Org. Chem.* **2012**, *77*, 5794; l) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**,

14, 3032; m) J. Jayakumar, K. Parthasarathy, Y.-H. Chen, T.-H. Lee, S.-C. Chuang, C.-H. Cheng, *Angew. Chem.* **2014**, *126*, 10047; *Angew. Chem. Int. Ed.* **2014**, *53*, 9889.

[7] a) C. N. Hedge, J. Pierce, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1605; b) C. G. Barber, R. P. Dickinson, P. V. Fish, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3227; c) J. B. M. Rewinkel, H. Lucas, P. J. M. van Galen, A. B. J. Noach, T. G. van Dinther, A. M. M. Rood, A. J. S. Jenneboer, C. A. A. van Boeckel, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 685; d) D. B. Khadka, H. Woo, S. H. Yang, C. Zhao, Y. Jin, T. N. Le, Y. Kwon, W.-J. Cho, *Eur. J. Med. Chem.* **2015**, *92*, 583; e) X. Wei, M. Zhao, Z. Du, X. Li, *Org. Lett.* **2011**, *13*, 4636; f) J. Li, M. John, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 5403.

[8] a) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 4255; *Angew. Chem. Int. Ed.* **2011**, *50*, 4169; b) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 4262; c) J. Karthikeyan, R. Haridharan, C.-H. Cheng, *Angew. Chem.* **2012**, *124*, 12509; *Angew. Chem. Int. Ed.* **2012**, *51*, 12343; d) K. Muralirajan, C.-H. Cheng, *Chem. Eur. J.* **2013**, ***19***, 6198; e) C.-Z. Luo, P. Gandeepan, C.-H. Cheng, *Chem. Commun.* **2013**, *49*, 8528; f) R. Haridharan, K. Muralirajan, C.-H. Cheng, *Adv. Synth. Catal.* **2015**, *357*, 366.

[9] a) Q. Chen, L. Llies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428; b) W. Song, L. Ackermann, *Angew. Chem.* **2012**, *124*, 8376; *Angew. Chem. Int. Ed.* **2012**, *51*, 8251; c) K. Gao, P.-S. Lee, C. Long, N. Yoshikai, *Org. Lett.* **2012**, *14*, 4234; d) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279; e) W. Liu, H. Cao, J. Xin, L. Jin, A. Lei, *Chem. Eur. J.* **2011**, *17*, 3588; f) H. Li, C.-L. Sun, M. Yu, D.-G. Yu, B.-J. Li, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 3593; g) L. Grigorjeva, O. Daugulis, *Angew. Chem.* **2014**, *126*, 10373; *Angew. Chem. Int. Ed.* **2014**, *53*, 10209; h) R. Santhoshkumar, S. Mannathan, C.-H. Cheng, *Org. Lett.* **2014**, *16*, 4208; i) P. Gandeepan, C.-H. Cheng, *Acc. Chem. Res.* **2015**, *48*, 1194; j) L. Grigorjeva, O. Daugulis, *Angew. Chem.* **2014**, *126*, 10373; *Angew. Chem. Int. Ed.* **2014**, *53*, 10209; k) D. Kalsi, B. Sundararaju, *Org. Lett.* **2015**, *17*, 6118.

[10] a) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem.* **2013**, *125*, 2263; *Angew. Chem. Int. Ed.* **2013**, *52*, 2207; b) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142; c) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491; d) J. Li, L. Ackermann, *Angew. Chem.* **2015**, *127*, 3706; *Angew. Chem. Int. Ed.* **2015**, *54*, 3635; e) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *127*, 8671; *Angew. Chem. Int. Ed.* **2015**, *54*, 8551; f) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem.* **2015**, *127*, 4591–4594; *Angew. Chem. Int. Ed.* **2015**, *54*, 4508; g) D.-G. Yu, T. Gensch, F. Azambuja, S. Vasquez-Cespedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722; h) J. R. Hummel, J. A. Ellman, *Org. Lett.* **2015**, *17*, 2400; i) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490; j) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660; k) P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853; l) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424; m) Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem.* **2015**, *127*, 10082–10085; *Angew. Chem. Int. Ed.* **2015**, *54*, 9944; n) J. Park, S. Chang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14103.

[11] a) B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Angew. Chem.* **2015**, *127*, 13160; *Angew. Chem. Int. Ed.* **2015**, *54*, 12968; b) H. Wang, J. Koeller, W. Liu, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 15525; c) M. Sen, D. Kalsi, B. Sundararaju, *Chem. Eur. J.* **2015**, *21*, 15529; d) N. Barsu, M. Sen, J. R. Premkumar, B. Sundararaju, *Chem. Commun.* **2016**, *52*, 1338.

