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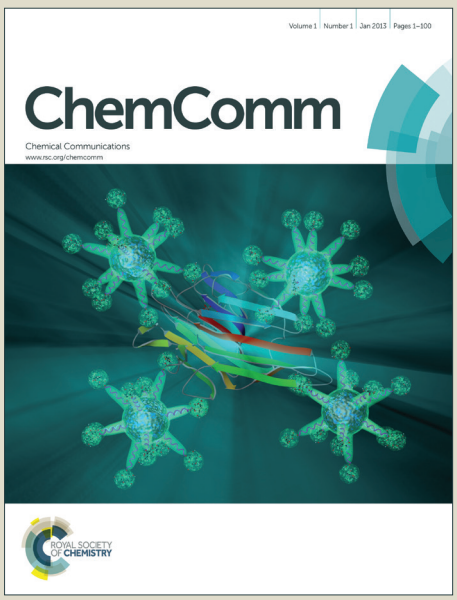

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ARTICLE TYPE

Rh(III)-catalyzed synthesis of 1-aminoindole derivatives from 2-acetyl-1-arylhydrazines and diazo compounds in water

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A novel and direct approach to synthesize 1-aminoindole derivatives by Rh(III)-catalyzed cyclization of 2-acetyl-1-arylhydrazines with diazo compounds via aryl C-H activation has been developed. This intermolecular annulation involving tandem C-H activation, cyclization and condensation steps proceeds efficiently in water, obviates the need of external oxidant, and displays a broad substituent scope.

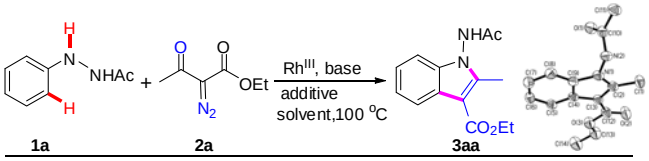
The indole unit is without doubt a privileged structure in medicinal chemistry, and also very ubiquitous in natural products.[1] 1-aminoindole derivatives display important pharmacological properties. For example, some of them exhibit psychotropic,[2a] anticonvulsant,[2b] analgesic,[2c] antioxidant effect[2d] and they have been extensively studied as potential therapeutic reagents for treatment of Alzheimer's disease.[2e] Despite 1-aminoindoles derivatives hold great potential in organic synthesis, to date, only limited synthetic methods have been reported.[3] Therefore, the development of a direct and efficient synthetic protocol for accessing 1-aminoindole derivatives remains an important goal.

$[Cp^*RhCl_2]_2$ is a promising catalyst, which plays a very important role in C-H bond activation. Many unsaturated compounds, like alkenes, alkynes, allenes, imines, isonitriles, and isocyanates, have been successfully employed in Rh(III)-catalyzed system.[4-5] Interestingly, Glorius and coworkers recently reported a Rh(III)-catalyzed hydrazine-directed C-H activation to synthesize indole using N-N functionality as an internal oxidant.[6] Very recently, a new metal carbene reaction pattern has emerged as a powerful tool to functionalize aryl C-H bond. In contrast to traditional mode,[7] this pattern is believed to follow a pathway involving C-H metalation, metal carbene formation, and migratory insertion.[8] Notably, direct carbene functionalization of aryl C-H bond has limited precedent in the literature. Recently, Wang, Satoh, and Miura independently reported the metal-catalyzed C-H bond cross-coupling of 1, 3-azoles with N-tosylhydrazones.[9] Unfortunately, these methods are limited to heteroarene C-H bonds, and require harsh conditions. In 2012, Yu elegantly developed the first example of chelation-assisted Rh(III)-catalyzed intermolecular cross-couping of diazomalonates and aryl C-H activation.[10] The group of Rovis,[11] Glorius,[12] Li,[13] Cui,[14] and Wang[15] have also successfully demonstrated their exploration in Rh(III)-catalyzed aryl C-H activation using diazo compounds as coupling partners. Although some progress has been made, we believe, such interesting area is worthy further exploration. Herein, we report a Rh(III)-catalyzed synthesis of 1-aminoindole derivatives from 2-acetyl-1-arylhydrazines and diazo compounds in water (Scheme 1, eq 3).

We initiated our studies by using 2-acetyl-1-phenylhydrazine and ethyl diazoacetoacetate as model substrates. Gratifyingly, the desired ethyl 1-acetamido-2-methyl-1H-indole-3-carboxylate (**3aa**) was isolated in 60% yield by treating 2-acetyl-1-phenylhydrazine (**1a)** (0.5 mmol) with ethyl diazoacetoacetate (**2a**) (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (15 mol%), and CsOAc (1 eq) in DCE (3 mL) at 100 °C for 12 h, as shown in Table 1. The structure of **3aa** was confirmed by its ^1H and ^{13}C NMR spectra, mass spectrometry data, and single-crystal X-ray diffraction analysis. Encouraged by this result, we further optimized the reaction condition by changing the solvent. H_2O was found to be superior, as the yield of **3aa** was increased to 75% (Table 1, entry 5). Since reactants **1a** and **2a** are soluble in water but the product **3aa** are insoluble and precipitates from water. Control experiments showed that acetate is indispensable and silver salt is not necessary in this reaction (Table 1, entries 5-7). Lower the loading of CsOAc to 0.25 equiv gave a comparable yield (Table 1, entry 8). To our delight, when 1 equiv of HOAc was added as additive, the yield of the desired product was improved to 80% yield. Very recently Glorius and coworkers have demonstrated that both of HCl and the cationic Rh(III) catalyst could promote the condensation.[16] So the role of HOAc additive may be also to promote the condensation. Changing the ratio of **1a** and **2a** from 1/1 to 1.2/1 further improved the yield, as we observed slightly decomposed of **1a** in water (Table 1, entry 10). When the loading of HOAc was decreased to 0.5 equiv, excellent yield was obtained (Table 1, entry 12). Surprisingly, no loss of the yield was observed when shortened the reaction time to 1 h (Table 1, entry 14). A slightly reduced yield was obtained when employed NaOAc as base (Table 1, entry 16). Control reactions revealed that the transformation does not occur in the absence of $[Cp^*RhCl_2]_2$ or using $[(p\text{-cymene})RuCl_2]_2$ as catalyst (Table 1, entries 17-18). The use of $[Cp^*Rh(OAc)_2]$ as catalyst afforded a similar yield to those obtained with $[Cp^*RhCl_2]_2$/CsOAc system, indicating that it might be the active catalyst (Table 1, entry 19). Based on the above results, we determined our best reaction condition as 2-acetyl-1-phenylhydrazines (**1a)** (0.6 mmol) and ethyl diazoacetoacetate (**2a**) (0.5 mmol) with $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOAc (0.25 eq), HOAc (0.5 eq), H_2O (3 mL) at 100°C, under Ar for 1 h.

With the optimized conditions in hand, various substituted 2-acetyl-1-arylhydrazines were tested. As summarized in Table 2, in general, the cyclization occurred very smoothly for 2-acetyl-1-arylhydrazines having substituents at para position. Substrates bearing an electron-donating group (e.g., Me, OMe, OCF_3) or a strong electron-withdrawing group (e.g., CF_3, CN, CO_2Me) at the aryl ring are tolerant in this transformation. It is noteworthy that the halo-substituted (e.g., F, Cl, Br) substrates performed well to afford the corresponding products in good yields. Surprisingly, when 2-naphthylacetohydrazine (**1l**) was used in the reaction, the 3-position C-H bond with less steric hinderance was selectively functionalized to afford the corresponding product (**3la**) in 78% yield, whereas the 1-naphthylacetohydrazine (**1k**) produced the **3ka** in only 11% yield. To our delight, this transformation showed excellent regioselectivities. The completely regioselective coupling occurred at the less hindered position for meta-substituted substrates (**3oa**, **3pa**, **3qa**). Gratifyingly, our method is not only suitable for diverse monosubstituted 2-acetyl-1-arylhydrazines, but also disubstituted derivatives (**3ra**, **3sa**, **3ta**, **3ua**). Unexpectedly, the C-H annulation reaction occurred at more hindered position for **3ua**, the strange effect is unknown at the moment. Unfortunately, as we observed, this reaction seems very sensitive to the steric hinderance of ortho position. **3na** was isolated in 83% yield, however, 2-methyl phenylacetohydrazine (**1m**) showed highly limited reactivity. In addition, our method can be conducted on a gram scale without a significant loss of yield (5 mmol scale, 1.16 g for **3aa**, 89% yield, see SI).

Table 1 Optimization of reaction conditions[a]



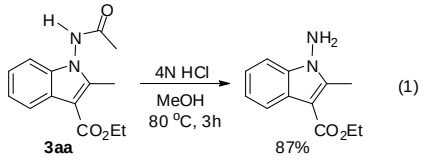
1a **2a** **3aa**

Entry	Ratio (**1a**/**2a**)	Base	Solvent	Additive	Time (h)	Yield[b]
1	1/1	CsOAc (1 eq)	DCE	$AgSbF_6$ (15%)	12	60%
2	1/1	CsOAc (1 eq)	MeOH	$AgSbF_6$ (15%)	12	61%
3	1/1	CsOAc (1 eq)	Toluene	$AgSbF_6$ (15%)	12	Trace
4	1/1	CsOAc (1 eq)	MeCN	$AgSbF_6$ (15%)	12	Trace
5	1/1	CsOAc (1 eq)	H_2O	$AgSbF_6$ (15%)	12	75%
6	1/1	/	H_2O	$AgSbF_6$ (15%)	12	Trace
7	1/1	CsOAc (1 eq)	H_2O	/	12	75%
8	1/1	CsOAc (25%)	H_2O	/	12	73%
9	1/1	CsOAc (25%)	H_2O	HOAc (1 eq)	12	80%
10	1.2/1	CsOAc (25%)	H_2O	HOAc (1 eq)	12	89%
11	1.2/1	CsOAc (25%)	H_2O	HOAc (1.2 eq)	12	88%
12	1.2/1	CsOAc (25%)	H_2O	HOAc (0.5 eq)	12	91%
13	1.2/1	CsOAc (25%)	H_2O	HOAc (0.25 eq)	12	81%
14	**1.2/1**	**CsOAc (25%)**	**H_2O**	**HOAc (0.5 eq)**	**1**	**91%**
15	1.2/1	CsOAc (25%)	H_2O	HOAc (0.5 eq)	0.5	75%
16	1.2/1	NaOAc (25%)	H_2O	HOAc (0.5 eq)	1	85%
17[c]	1.2/1	CsOAc (25%)	H_2O	HOAc (0.5 eq)	1	0
18[d]	1.2/1	CsOAc (25%)	H_2O	HOAc (0.5 eq)	1	0
19[e]	1.2/1	/	H_2O	HOAc (0.5 eq)	1	93%

[a] *Reaction conditions*: **1a** (0.5-0.6 mmol), **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), solvent (3 mL), 100 °C, under Ar. [b] Isolated yields based on **2a**. [c] Without $[Cp^*RhCl_2]_2$. [d] $[(Cymene)RuCl_2]_2$ was used as catalyst. [e] $[Cp^*Rh(OAc)_2]$ (5 mol %) was used as catalyst.

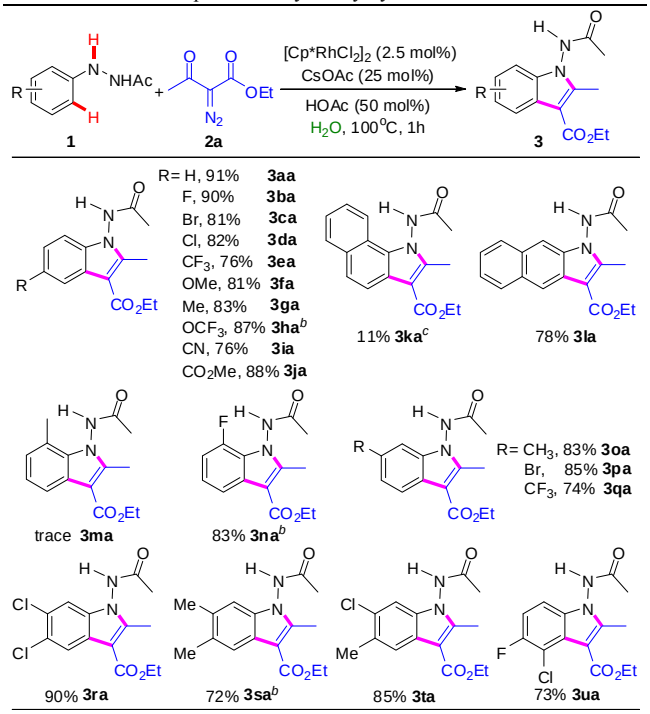
Subsequently, we investigated the scope of diazo compounds. Overall, we were pleased with the generality of this method. Diazo substrates bearing substituents such as phenyl, ketone, alkyl, and ether afforded the corresponding products in 48%-95% yield. Among them, unsymmetrical diketone (**2h**) underwent the desired reaction to give only one regioisomer of **3ah** in 48% yield. Interestingly, 2-diazo-5,5'-dimethylcyclohexane-1,3-dione (**2g**) also proceeded smoothly with **1a** to offer **3ag** in 73% yield (Table 3).

Compound **3aa** was further deprotected under acid condition to provide the corresponding product in 87% yield (eq 1).[17]



3aa 87% (1)

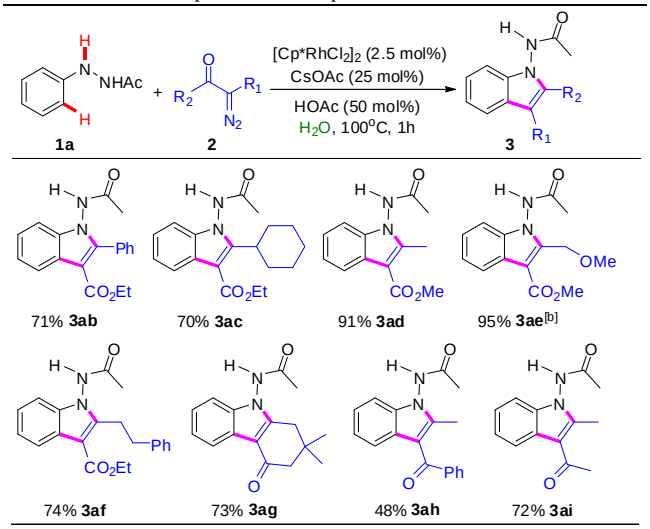
Table 2 Substrate scope of 2-acetyl-1-arylhydrazines[a]



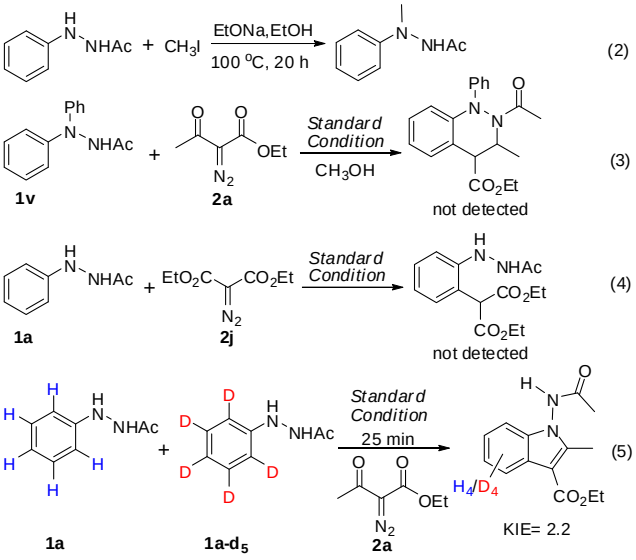
[a] *Reaction conditions*: **1** (0.6 mmol), **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (25 mol%), HOAc (50 mol%), H_2O (3 mL), 100 °C, 1 h, under Ar, isolated yields based on **2a** are shown. [b] Reaction time: 2 h. [c] Reaction time : 12 h.

To gain more insight into the mechanism, control experiments were conducted. Firstly, we tested which N-H bond is more acidic, it showed that the N-H at 1-position is more acidic (Scheme 1, eq 2),[18] which may react preferentially in condensation step. Besides, the formation of indole cycle can obtain aromaticity, which makes it more stable. Both reasons above may explain why this transformation selectively formed the five-member ring. We then used **1v** as substrate to react with **2a** under a slightly modified condition (considering **1v** has low solubility in water). Unexpectedly, no reaction was detected (Scheme 1, eq 3). Replace **2a** with **2j** to react under standard condition, no reaction was detected either (Scheme 1, eq 4). These results revealed that the six member ring is not favored even when the N-H at 1-position is blocked and the condensation step may play a vital role in this reaction. Finally, the kinetic isotope effect experiment was carried out. It gave a K_H/K_D ratio of 2.2 (Scheme 1, eq 5), thus indicating that the C-H bond cleavage may be involved in the rate determining step.[19]

Table 3 Substrate scope of diazo compounds [a]



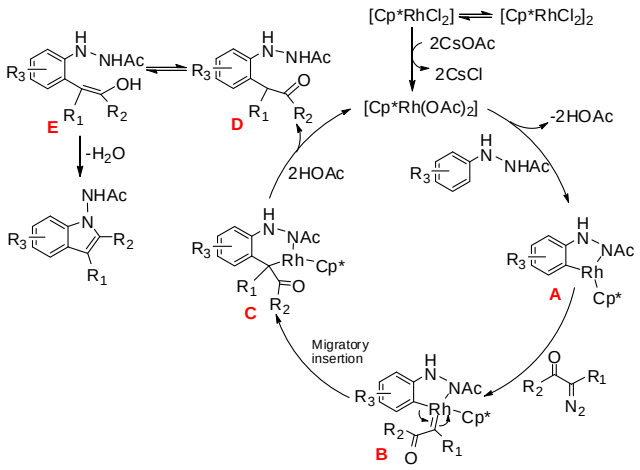
[a] *Reaction conditions*: **1a** (0.6 mmol), **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOAc (25 mol%), HOAc (50 mol%), H_2O (3 mL), 100 °C, 1 h, under Ar, isolated yields based on **2** are shown. [b] Reaction time: 0.5 h.



Scheme 1 mechanistic studies.

On the basis of mechanistic studies and literature reports,[4,10] a plausible mechanism was proposed (Scheme 2). First, an active catalyst $[Cp^*Rh(OAc)_2]$ is generated through anion exchange, then undergoes directed C-H cleavage to form intermediate **A**, which is followed by generation of Rh(III)-carbene **B**. Subsequently, migratory insertion of the carbene into the Rh-C bond affords rhodacyclic intermediate **C**. Upon protonation by acetic acid, intermediate **D** is formed along with the regeneration of Rh(III) catalyst. In the catalytic cycle, the Rh(III) catalyst is redox-neutral. Then tautomerization of intermediate **D** delivers enol intermediate **E** in suit. After eliminating water through intramolecular condensation, the final product is formed.

In summary, we have developed the first example of a Rh(III)-catalyzed synthesis of 1-aminoindole derivatives in which aryl C-H activation serves as the initiating step. This cyclization reaction displays excellent regioselectivity and functional groups compatibility, and can be performed on a gram-scale without suffering from notable loss of yield. Water is not only an environmental benign reaction medium, but also the most efficient solvent in this reaction, it significantly simplifies the separating process. In most cases the final products separate out as precipitate directly from water and afford enough pure samples after simple filtration and drying. Further purification is just needed to pass through a short silica pad. We believe this protocol is superior to those utilizing HOSA or other synthetic NH_2^+ transfer reagents, offering a faster and more convenient access to 1-aminoindole derivatives. Further application of this kind of reaction and the detailed mechanistic investigation are in progress.



Scheme 2 Proposed mechanism.

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Notes and references

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1 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (*b*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278; (*c*) S. B. Herzon and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 5342; (*d*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73; (*e*) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**,761.
2 (*a*) R. A. Le and C. Harpey, FR2911143, 2008; (*b*) F. P. Huger, C. P. Smith, S. Kongsamut and L. Tang, US5776955, 1998; (*c*) R. C. Effland, J. T. Klein, L. Davis and G. E. Olson, EP0402752, 1990; (*d*) T. Itoh, M. Miyazaki, H. Maeta, Y. Matsuya, K. Nagata and A. Ohsawa, *Bioorg. Med. Chem.*, 2000, **8**, 1983; (*e*) J. T. Klein, L. Davis, G. E. Olsen, G. S. Wong, F. P. Huger, C. P. Smith, W. W. Petko, M. Cornfeldt, J. C. Wilker, R. D. Blitzer, E. Landau, V. Harautunian, L. L. Martin and R. C. Effland, *J. Med. Chem.*, 1996, **39**, 570.
3 (*a*) R. Raap, *Can. J. Chem.*, 1969, **47**, 3677; (*b*) J. Hynes Jr., W. W. Doubleday, A. J. Dyckman, J. D. Godfrey Jr., J. A. Crosso, S. Kiau and K. Leftheris, *J. Org. Chem.*, 2004, **69**, 1368; (*c*) B. A. Frontana-Uribe, C. Moinet and L. Toupet, *Eur. J. Org. Chem.*, 1999, 419; (*d*) M. Watanabe, T. Yamamoto and M. Nishiyama, *Angew. Chem., Int. Ed.*,

2000, **39**, 2501; (*e*) F. Melkonyan, A. Topolyan, M. Yurovskaya and A. Karchava, *Eur. J. Org. Chem.*, 2008, 5952; (*f*) N. Halland, M. Nazaré, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, **47**, 1042; (*g*) E. Brachet, S. Messaoudi, J.-F. Peyrat, J.-D. Brion and M. Alami, *Adv. Synth. Catal.*, 2012, **354**, 2829.

4 For reviews, see: (*a*) T. Satoh and M. Miura, *Chem. Eur. J.*, 2010, **16**, 11212; (*b*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*c*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (*e*) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichim. Acta*, 2012, **45**, 31; (*d*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651.

5 For selected examples: (*a*) N. Umeda, H. Tsurugi, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2008, **47**, 4019; (*b*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474; (*c*) N. Guimond and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 12050; (*d*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (*e*) S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585; (*f*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565; (*g*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; (*h*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (*i*) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3948; (*j*) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318; (*k*) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 9372; (*l*) M. V. Pham, B. Ye and N. Cramer, *Angew. Chem., Int. Ed.*, 2012, **51**, 10610; (*m*) W. Zhen, F. Wang, M. Zhao, Z. Du and X. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 11819; (*n*) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 12343; (*o*) D. Wang, F. Wang, G. Song and X. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 12348; (*p*) R. Zeng, C. Fu and S. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9597; (*q*) X. Tan, B. Liu, X. Li, B. Li, S. Xu and B. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 16163; (*r*) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 19592; (*s*) T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500; (*t*) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2013, **52**, 629; (*u*) Z. Shi, C. Grohmann and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5393; (*v*) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033; (*w*) J. M. Neely and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 66; (*x*) G. Zhang, L. Yang, Y. Wang, Y. Xie and H. Huang, *J. Am. Chem. Soc.*, 2013, **135**, 8850; (*y*) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang and M. M. Bio, *J. Am. Chem. Soc.*, 2013, **135**, 14492; (*z*) B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 16625.

6 D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013. **52**, 12426.

7 H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417.

8 Z. Liu and J. Wang, *J. Org. Chem.*, 2013, **78**, 10024.

9 (*a*) X. Zhao, G. Wu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 3296; (*b*) T. Yao, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 775.

10 W.-W. Chan, S.-F. Lo, Z. Zhou and W.-Y. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 13565.

11 T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364.

12 Z. Shi, D. C. Koester, M. Boultadakis-Arapinis and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 12204.

13 X. Yu, S. Yu, J. Xiao, B. Wan and X. Li, *J. Org. Chem.*, 2013, **78**, 5444.

14 S. Cui, Y. Zhang, D. Wang and Q. Wu, *Chem. Sci.*, 2013, **4**, 3912.

15 F. Hu, Y. Xia, F. Ye. Z. Liu, C. Ma, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1364.

16 D.-G. Yu, F. de Azambuja and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 2754.

17 V. M. Lyubchanskaya, S. A. Savina, L. M. Alekseeva, A. S. Shashkov, V. V. Chernyshev and V. G. Granik, *Russ. Chem. Bull.*, 2004, **53**, 2834.

18 F. Zhan and G. Liang. *Angew. Chem., Int. Ed.*, 2013, **52**, 1266.

19 (*a*) W. D. Jones, *Acc. Chem. Res.*, 2003, **36**, 140; (*b*) E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.