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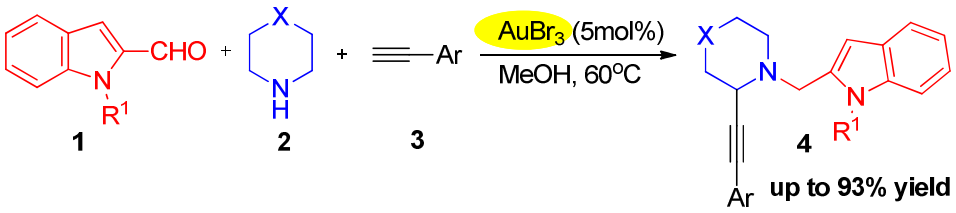

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Mild Gold-Catalyzed Three-Component Dehydrogenative Coupling of Terminal Alkynes to Amines and Indole-2-carboxaldehyde

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A mild gold-catalyzed three-component dehydrogenative coupling of terminal alkynes to amines and indole-2-carboxaldehyde has been developed, which provides a practical synthetic strategy for the synthesis of indole derivatives.

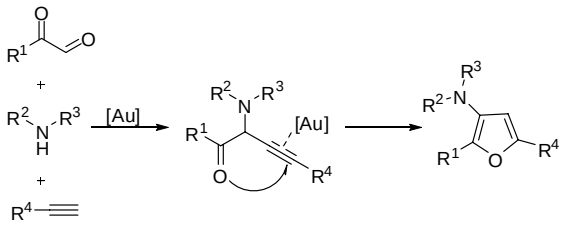
Introduction

Indole represents one important diverse family of pharmaceceuticals and biologically active natural compounds.[1] Not surprisingly, numerous studies and applications have been focus on the functionalization of indoles.[2] The efficiency of the synthesis can be increased significantly if the event of indole is coupled with the other two even more compounds in a cascade manner.[3] Such one-pot multicomponent coupling reactions have been developed as an attractive and powerful methodology for the formation of carbon-carbon and carbon-heteratom bond in a step- and atom-economical fashion.[4] Among these, a number of key building blocks synthesis using aldehydes, amines and alkynes as starting materials have been reported.[5] However, efficient synthesis with high chemo- and regioselectivity, which would enable access to complex indole derivatives via cascade manner, still remains challenging. We herein report a mild three-component cross-dehydrogenative coupling (CDC) of terminal alkynes to amines and indole-2-carboxaldehyde via a gold-catalyzed condensation/alkynylation cascade as a continuation of efforts in this area.

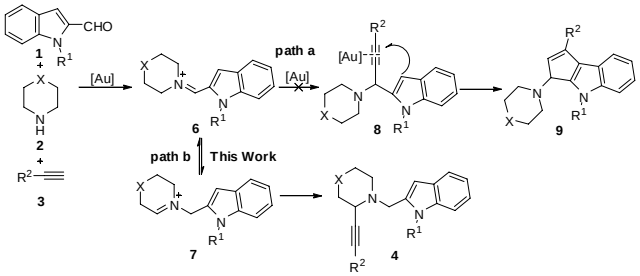
Gold, well known for their ability of promoting nucleophilic attack on acetylenes, has recently attracted interest from the synthetic chemistry community.[6] Gold catalysts have also been used in domino reaction.[7] We recently developed an efficient three-component coupling reaction of phenylglyoxal derivatives, secondary amines and terminal toward a variety of furan derivatives mediated by gold(III) (Scheme 1, a).[8] With this background in mind, we have been engaged in realized the abundance of indole derivatives via this one-pot multicomponent strategy. Then indole-2-carboxaldehyde was chosen as substrate coupling with secondary amines and terminal alkynes. We hypothesized that these three compounds would coupled together under the catalysis of gold catalyst to represent the required propargylamines intermediate **8**,[9] which, upon activation of the triple bond with gold, would undergo an intramolecular cyclization [10] into disubstituted cyclopenta indole **9**. However, when the reaction was conducted under the catalysis of gold, product **4** was found instead of indole **9** (Scheme 1, b**)**. We proposed that the *exo*-iminium ion **6** isomerized into *endo*-iminium ion **7**, the C(sp^3)-H bond of intermediate **7** at the C1 atom was directly activated and functionalized by terminal alkynes catalyzed by Au complexes. Such CDC style reaction has no limitations compared with the traditional CDC alkynylation reaction, which has to use N-aromatic or N-acyl substitutions and stoichiometric exogenous oxidants.[11] This strategy might be more potential in the synthesis of complex indoles as the substrates are simply and available. Recently, Seidel developed a Cu(II)-catalyzed alkynylation of pyrrolidines during a similar iminium isomerization process.[12a,b] And Nakamura reported a similar redox cross-dehydrogenative coupling of propargylic amines and terminal alkynes catalyzed by Zinc(II).[12c] Very recently, Yu reported the similar method to access C1-alkynylated tetrahydroisoquinoline (THIQ) products (*endo*-yne-THIQs) with CuI-mediated.[13a] But in their system some of products were mixed with *exo*- C1-alkynylated THIQ.

Scheme 1. Discovery of this Work and a Previous Report with a Similar Iminium Isomerization Process

a)Gold(III)-catalyzed three-component coupling reaction (TCC) selective towards furans



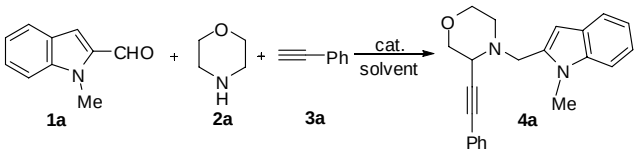
b) initial discovery of Three-Component dehydrogenative coupling



Results and Discussion

Initially, we began our exploration by using model substrate indole-2-carboxaldehyde **1a** (0.5 mmol), morpholine **2a** (0.75 mmol), and phenylacetylene **3a** (1 mmol) employing different catalysts. It was found that trace desired product **4a** was formed in the presence of copper salts such as CuI (Table 1, entry 1). A range of gold catalysts were subsequently evaluated, as summarized in Table 1. Ultimately, $AuBr_3$ was found to be the best catalyst for the reaction to afford the desired product **4a** in 62% yield. The other gold species gave lower efficiency (Table 1, entries 2-5). In an attempt to improve the yield of **4a** by surveying different solvents, various other solvents such as DCE, CH_3CN, DMF and toluene were tested in the reaction. They showed lower yields compared to MeOH (Table 1, entries 7-10). In addition, by lowering the temperature to 25 °C, the yield was decreased to 45%. The reaction was not improved by the presence of 10% mol or 20% mol of $AuBr_3$. Therefore, our optimization identified that treatment of indole **1a** with 5mol% of $AuBr_3$ as catalyst, 1.5 equiv. of **2a** and 2 equiv. of **3a** in MeOH at 60 °C afforded the **4a** in 62% isolated yield.

Table 1. Screening of reaction conditions for formation of **4a**[a]

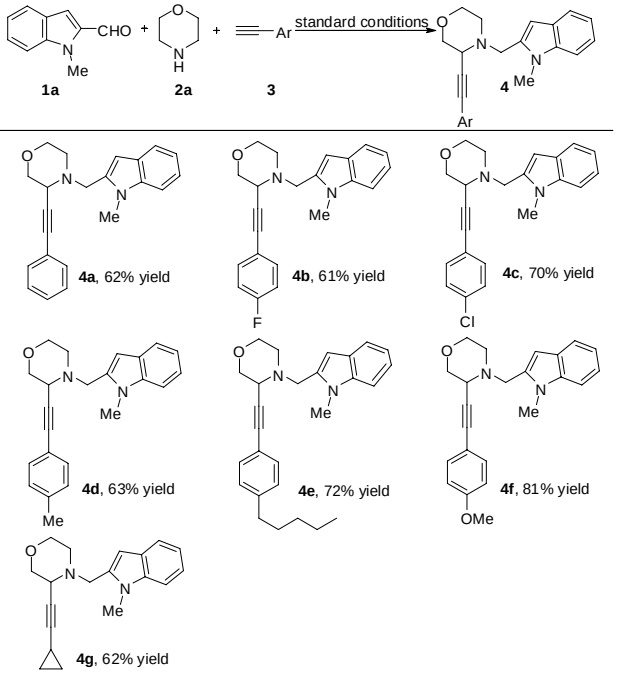


Entry	Catalyst	Solvent	Temp (°C)	Yield of **4a** (%) [b]
1	CuI	DCE	60	trace
2	Ph_3PAuCl	MeOH	60	11
3	AuCl	MeOH	60	7
4	$HAuCl_4$	MeOH	60	51
5	$NaAuCl_4$	MeOH	60	47
6	$AuBr_3$	MeOH	60	62
7	$AuBr_3$	Toluene	60	33
8	$AuBr_3$	CH_3CN	60	21
9	$AuBr_3$	DMF	60	0
10	$AuBr_3$	DCE	60	42
11	$AuBr_3$	MeOH	30	45
12	$AuBr_3$	MeOH	80	50
13[c]	$AuBr_3$	MeOH	60	65
14[d]	$AuBr_3$	MeOH	60	67

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (1 mmol), catalyst (5 mol %, 0.025 mmol), in solvent (2 mL) at 60 ºC overnight. [b]Isolated yields. [c]10mol% of catalyst was employed. [d] 20 mol% of catalyst was employed.

With the optimized reaction conditions in hand, the substrate scope of this $AuBr_3$-catalyzed cascade reaction was explored by using a wide range of different secondary amines **2** and alkynes **3** (Table 2 and Table 3). We were happy to find that aryl alkynes bearing electron-donating and electron-withdrawing substituents produced the desired products in good yields (**4a-4g**, Table 2). Various of different groups at the aromatic moiety of alkynes, such as halogen, methyl and methoxy, were well tolerated in these mild transformations. An aryl alkyne bearing long aliphatic chain such as 1-ethynyl-4pentylbenzen could be smoothly transformed into the desired product in 72% yield (**4e**, Table 2). Furthermore, aliphatic alkyne (**4g**, Table 2) was also applicable in the target reaction in 62% yield.

Table 2. Scope of Alkynes in the morphline C1-Alkynylation [a,b]



[a] **1** (0.5 mmol), **2a** (0.75 mmol), **3** (1 mmol), $AuBr_3$ (5 mol %, 0.025 mmol), in MeOH (2 mL) at 60 ºC overnight. [b] Isolated yields.

Next, the scope of indole aldehyde **1** and secondary amines **2** was then examined. Interestingly, replacing morpholine to tetrahydroisoquinolines, this transformation proceeded smoothly in excellent yields. As is shown in Table 3, various aryl alkynes **3** were found to be suitable reaction partners with 1-methyl-1H-indole-2-carbaldehyde and THIQ to provide the corresponding CDC products **5** (Table 3). Terminal alkynes **3** containing halo group (fluoro-), alkyl and methoxy, satisfactorily underwent reaction to afford the desired products in good yields (Table 3, **5a-5h**). *N*-Boc and *N*-Bn protected indoles were also tested. All of the reactions proceeded efficiently to afford the desired products in good yields (Table 3, **5f-5h**). Subsequently, the X-ray single crystal structure of **5b** was obtained, which further unambiguously confirmed the structures of these products (Fig 1).

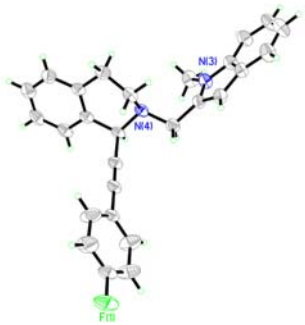
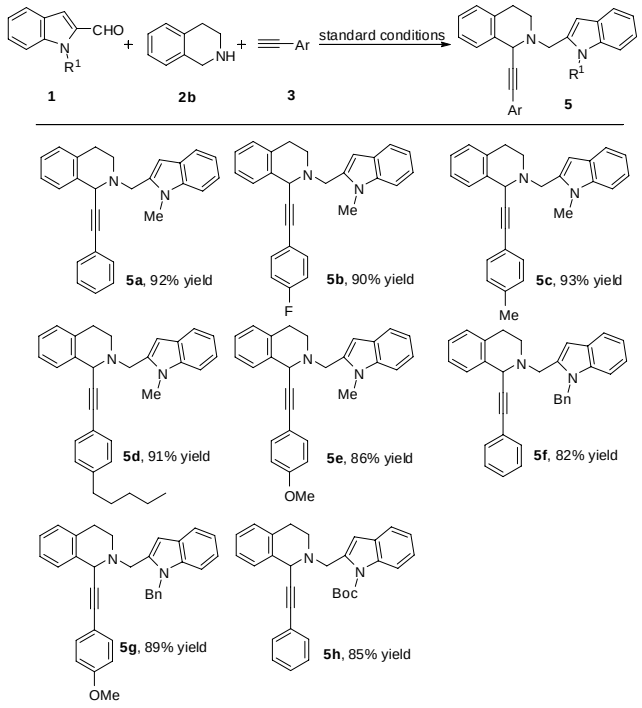


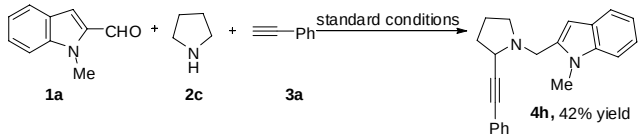
Figure 1. The X-ray diffraction of compound **5b.**

Table 3. Scope of Alkynes in the THIQ C1-Alkynylation [a,b]

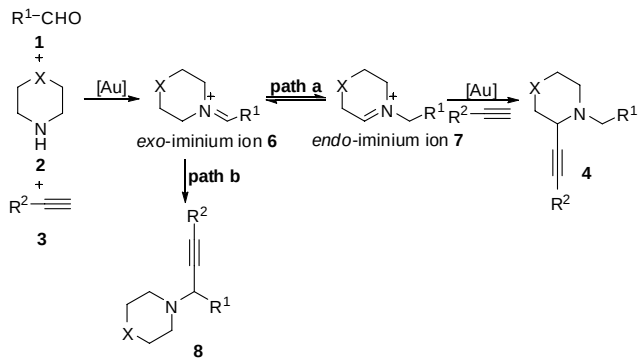


[a] **1a** (0.5 mmol), **2b** (0.75 mmol), **3a** (1 mmol), $AuBr_3$ (5 mol %, 0.025 mmol), in MeOH (2 mL) at 60 ºC overnight. [b] Isolated yields.

However, when pyrrolidine was chose as secondary amine, the reaction gave lower conversion and lower yield with 42% (Scheme 2). Other secondary amines as piperdine and acyclic amine were also tested, however, no desired products were found.



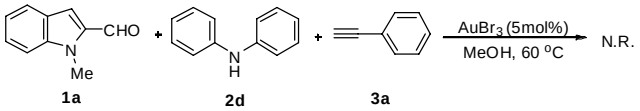
Scheme 2. Coupling of pyrrolidine to alkynes and indole-2-carboxaldehyde



Scheme 3. The proposed mechanism

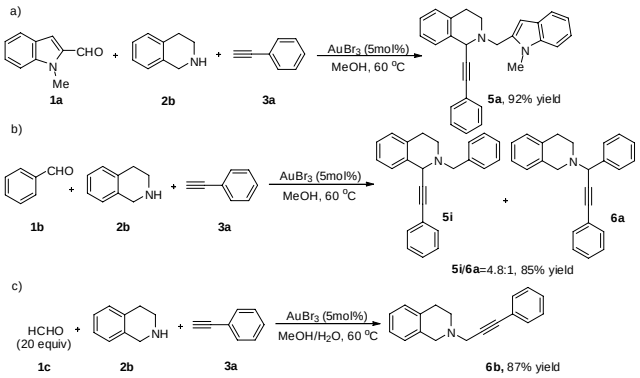
The reaction pathway was proposed as shown in Scheme 3 (path a). Initially, intermediate **6** is generated via the reaction of *N*-protected indole-2-carboxaldehyde **1** and secondary amines **2** promoted by Au-catalyst, which was further converted to *endo*-iminium ion **7**. The *endo*-iminium ion is more stable than the *exo*-iminium ion.[13] The terminal alkynes activated by gold [6] attacks C1 position of iminium ions **7** to afford the final *endo*- product **4**.

According to the proposed mechanism, secondary amines not bearing the α-H should not undergo this CDC process. With this idea in mind, diphenylamine was tested as secondary amine under standard conditions. The results confirmed our speculation and the reaction did not proceed at all (Scheme 4).



Scheme 4. Three-component coupling of diphenylamine to terminal alkynes and indole-2-carboxaldehyde

Control experiments were then performed to figure out whether the steric of aldehyde determined the *endo*/*exo* selectivity. First, we chose 1-methyl-1H-indole-2-carbaldehyde as the aldehyde source, which has greater steric hindrance beside aldehyde group, the reaction was complete in 8 hours to afford the *endo*- compound **5a** in 92% yield and no *exo*- isomer was observed. When benzaldehyde was employed in this reaction, a mixture of *endo*/*exo* **5i**/**6a** was obtained and the selectivity rate was 4.8/1 determined by NMR. Finally, the smallest aldehyde was selected, which could be converted to *exo*- product **6b** in 87% yield only (Scheme 5, path b). The above results clarified that the *endo*/*exo* selectivity was controlled by the steric of aldehyde.



Scheme 5. Control experiments.

Conclusions

In summary, a mild gold-catalyzed three-component dehydrogenative coupling of terminal alkynes to amines and indole-2-carboxaldehyde has been developed. Only *endo*-products were obtained in good to excellent yields under standard conditions. This method provides an avenue for the easy assembly of complex indole derivatives efficiently. Further studies on the scope and synthetic applications of this transformation are ongoing.

Experimental section

General Experimental Methods.

All experiments were conducted under air atmosphere. Flasks were flame dried and cooled under nitrogen before use. All solvents were dried appropriately. For column chromatography,

200-300 mesh silica gel was employed. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz, 400MHz or 500 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). For HRMS measurements, the mass analyzer is GC-TOFMS. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All the indole-2-carboxaldehyde was prepared according to the reference.[14]

General Procedure for Three-component Dehydrogenative Coupling. To a solution of 1 (0.5 mmol), 2 (0.75 mmol), 3 (1 mmol) in MeOH (2 mL) in a 10 mL Schlenk tube, $AuBr_3$ (5 mol %, 0.025 mmol) was added in one portion. The resulting solution was stirred at 60 ºC overnight. After cooling to room temperature, the resulting mixture was filtered through a pad of celite. The volatile compounds were removed in vacuo and the residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate =10:1- 4:1) to give target compound.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, all of the spectra data of the compounds. See DOI: 10.1039/b000000x/

1 (a) W. J. Houlihan, Ed. *The chemistry of heterocyclic compounds*, Vol. 25; Wiley: New York, 1972. (b) R. J. Sundberg, *The Chemistry of Indoles*; Academic Press: London, 1996. (c) K. C. Nicolaou, and S. A. Snyder, *Classics in Total Synthesis II, 1st ed.;* Wiley-VCH: Weinheim, 2003. (d) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.* 2010, **110,** 4489. (e) Z. Zuo, W. Xie and D. Ma, *J. Am. Chem. Soc.,* 2010, **132,** 13226.

2 (a) L. S. Hegedus, *Angew. Chem.* 1988, **100,** 1147. (b) M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *Synlett* 2005, **8,** 1199. (c) S. Cacchi and G. Fabrizi, *Chem. Rev*. 2005, **105,** 2873. (d) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.* 2009, **48,** 9608. (e) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.* 2010, 39, 4449. (f) S. Patil, and R. Patil, *Current Organic Synthesis* 2007, 4, 201.

3 M. Shiri, *Chem. Rev.* 2012, **112,** 3508.

4 (a) J. Zhu, H. Bienaymé, Eds.; Wiley-VCH: Weinheim, 2005. (b) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.* 1996, **29,** 123. (c) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem.-Eur. J.* 2000, **6,** 3321. (d) G. Balme, *Angew. Chem., Int. Ed.* 2004, **43,** 6238. (e) L. El Kaim and L. Grimaud, *Tetrahedron* 2009, **65,** 2153. (f) A. Jacobi von Wangelin, H. Neumann, D. Goerdes, S. Klaus, D. Struebing, M. Beller, *Chem. – Eur. J.* 2003, **9,** 4286.

5 (a) B. Yan, Y. Liu, *Org. Lett.* 2007, **9,** 4323. (b) N. Chernyak, V. Gevorgyan, *Angew. Chem., Int. Ed.* 2010, **49,** 2743. (c) D. Chernyak, N. Chernyak and V. Gevorgyana, *Adv. Synth. Catal.* 2010, **352**, 961. (d) Q. Zhang, M. Cheng, X. Hu, B.-G. Li and J.-X. Ji, *J. Am. Chem. Soc.* 2010, **132,** 7256.

6 (a) J. Wilkens, A. Kuehling and Blechert, S., *Tetrahedron* 1987, **43,** 3237. (b) J. A. Marshall and E. D. Robinson, *J. Org. Chem.* 1990, **55,** 3450. (c) J. A. Marshall and X. Wang, *J. Org. Chem.* 1991, **56,** 960. (d) J. A. Marshall and G. S. Bartley, *J. Org. Chem.* 1994, ***59,*** 7169. (e) S. Ma and L. Li, *Org. Lett.*, 2000, **2**, 941. (f) S. Ma and J. Zhang, *Chem. Commun.*, 2000, 117. (g) Y. Xia, A. S. Dudnik, V. Gevorgyan and Y. Li, *J. Am. Chem. Soc.*, 2008, **130**, 6940. (h) X. Fan, Y. He, L. Cui, X. Zhang and J. Wang, *Green Chem.*, 2011, **13**, 3218. (i) N. T. Patil, *Current Science* 2013, 104, 1671. (j) D.-H. Zhang, X.-Y. Tang and M. Shi, *Acc. Chem. Res.*, in press, DOI: 10.1021/ar400159r

7 (a) S. F. Kirsch, J. T. Binder, C. Liébert and H. Menz, *Angew. Chem., Int. Ed.* 2006, **45,** 5878. (b) A. S. K. Hashmi and L. Grundl, *Tetrahedron* 2005, 61, 6231. (c) J. Li, Y. Liu, C. J. Li, H. Jie and X. S. Jia, *Advanced Synthesis & Catalysis,* 2009, **351,** 129. (d) H. A. Wegner, S. Ahles, M. Neuburger, *Chem – Eur. J.* 2008, **14,** 11310. (e) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, *Org. Lett.* 2010, **12,** 2594. (f) G. Zhou, F. Liu and J. Zhang, *Chem. – Eur. J.* 2011, **17,** 3101.

8 J. Li, L. Liu, D. Ding, J. Sun, Y. Ji, and J. Dong, *Org. Lett.*, 2013, **15,** 2884.

9 For selected examples of syntheses of propargylamines via TCC, see: (a) C.-J. Li, C. M. Wei, *Chem. Commun,* 2002, 268. (b) C. M. Wei, Z. Li and C.-J. Li, *Org. Lett.* 2003, **5,** 4473. (c) V. K.-Y. Lo, K. K.-Y. Kung, M.-K. Wong and C.-M. Che, *J. Organomet. Chem.* 2009, **694,** 583. (d) X. Zhang and A. Corma, *Angew. Chem.* 2008, **120,** 4430; *Angew. Chem. Int. Ed.* 2008, **47,** 4358. (e) M. Kidwai, V. Bansal, A. Kumarb and S. Mozumdar, *Green Chem.* 2007, **9,** 742. (f) B. Huang, X. Yao and C.-J. Li, *Adv. Synth. Catal.* 2006, **348,** 1528. (g) V. K.-Y. Lo, Y. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.* 2006, **8,** 1529. (h) B. T. Elie, C. Levine, I. Ubarretxena-Belandia, A. Varela-Ramírez, R. J. Aguilera, R. Ovalle and M. Contel, *Eur. J. Inorg. Chem.* 2009, 3421.

10 (a) A. S. K. Hashmi, L. Schwarz, Choi, J.-H.; Frost, T. M. *Angew. Chem*., *Int. Ed.* 2000, **39,** 2285. (b) T. Yao, X. Zhang and R. C. Larock, *J. Org. Chem*. 2005, **70,** 7679. (c) T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc*. 2004, **126,** 11164.

11 (a) Z. Li and C.-J. Li, *J. Am. Chem. Soc.* 2004, **126,** 11810. (b) Z. Li and C.-J. Li, *Org. Lett.* 2004, **6,** 4997. (c) R. Hudson, S. Ishikawa, C.-J. Li and A. Moores, *Synlett* 2013, **24,** 1637.

12 (a) D. Das, A. X. Sun and D. Seidel, *Angew. Chem., Int. Ed.* 2013, **52,** 3765. (b) C. Zhang, D. Das and D. Seidel, *Chem. Sci.,* 2011, **2,** 233. (c) T. Sugiishi and H. Nakamura, *J. Am. Chem. Soc.* 2012, **134,** 2504.

13 (a)Q.-H. Zheng, W. Meng, G.-J. Jiang and Z.-X. Yu, *Org. Lett,* 2013, **15**, 5928. (b) L. Ma, W. Chen and D. Seidel, *J. Am. Chem. Soc.* 2012, **134,** 15305. (c) C. Zhang, C. Kanta De, R. Mal and D. Seidel, *J. Am. Chem. Soc.* 2008, **130,** 416.

14 C. Zheng, Y. Lu, J. Zhang, X. Chen, Z. Chai, W. Ma and G. Zhao, *Chem – Eur. J.* 2010, **16,** 5853.

