# Gold Catalysis Coupled with Visible Light Stimulation: Syntheses of Functionalized Indoles

Shunyou Cai, Kai Yang, and David Zhigang Wang*

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen, China 518055

S *Supporting Information*

ABSTRACT: A judicious combination of Au-catalysis and synergistic visible-light stimulation formulates an exceptionally simple and mild reaction system capable of directly coupling anilines and alkynes to form multifunctionalized indoles.
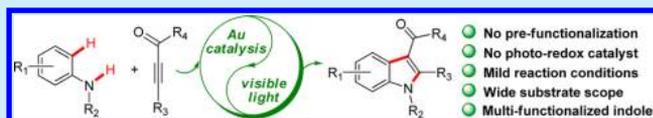
Indoles are highly versatile heterocyclic structural motifs present in many biologically meaningful natural products as well as pharmaceuticals and agrochemicals.[1] Their significant utilities thus have stimulated considerable synthetic efforts aimed at exploring efficient, mild, and direct methodologies toward their preparations, and such activities have been regularly updated and reviewed.[2] Although the classical Fischer indole synthesis[3] remains instrumental in constructing various indole skeletons, the method suffers from drawbacks such as harsh reaction conditions, moderate functional-group tolerance, and difficulty in hydrazine preparation. As a response to these challenges, a variety of milder approaches to indole syntheses involving strategic C−H functionalizations have been continuously documented in recent literature.[4]

In 1998, Larock and co-workers reported an inspirational indole synthesis via Pd-catalyzed annulation of internal alkynes with ortho-halogenated anilines (Scheme 1a).[4a] The work has subsequently stimulated several other studies aimed at directly utilizing substrates free of preactivations under transition-metal catalysis. For example, Jiao and co-workers developed a unique method for constructing indoles from readily available anilines and alkynes by C−H functionalizations.[4c] Other transition-

metal complexes, such as Rh[4f] and Ni[4g] catalysts, were demonstrated to be competent in similar contexts. Alternatively, intramolecular cyclizations of imines or enamines prepared by condensations of anilines and ketones were also explored in the presence of transition-metal catalysts or strong oxidants (Scheme 1b). Glorius and co-workers described a practical indole synthesis through Pd-catalyzed oxidative cyclizations of *N*-aryl enamines derived from anilines and β-dicarbonyl compounds.[4b] Within this scenario, similar successes were achieved by other research groups using various transition metals or oxidants. Despite these significant advances, there remains a strong need for discovering new and straightforward protocols that are capable of delivering indole motifs, ideally densely functionalized, with simpler substrate structures, minimal preactivations, less use of catalysts or oxidants, or milder reaction conditions.

We were intrigued by the possibility of merging potentially synergistic interactions of Au-catalysis[5] and visible-light-enabled photoredox catalysis[6−8] to explore a conceptually novel technology for indole synthesis. Such a design scenario, as summarized in Scheme 1c, leverages on cascade events of Au-catalyzed hydroamination and visible-light-enabled photoredox cross-dehydrogenative coupling that are capable of unifying readily available anilines and internal alkynes. We were delighted to disclose herein that, through careful optimizations of reaction conditions nurturing these strategic events, an unusually simple and versatile method was eventually established for rapidly accessing a variety of highly functionalized indoles at room temperature.

Initial reaction condition screenings quickly revealed that realization of the envisioned reactivity depends critically on the synergy of several factors, including the Au catalyst, additive, solvent, and Lewis acid. With *N*-methyl-4-nitroaniline **1a** and ethyl 3-phenylpropiolate **2a** as the model substrates, no desired product was detectable when the reaction was performed in 1,2-dichloroethane (DCE) at room temperature in the presence of a catalytic amount of catalyst PPh$_3$AuCl (5 mol %) under a

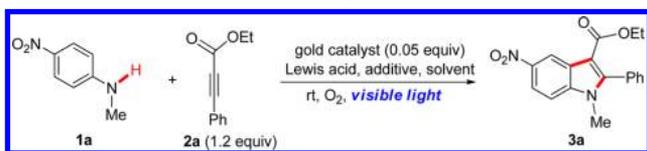**Scheme 1. Various Indole Syntheses Involving C−H Functionalizations**
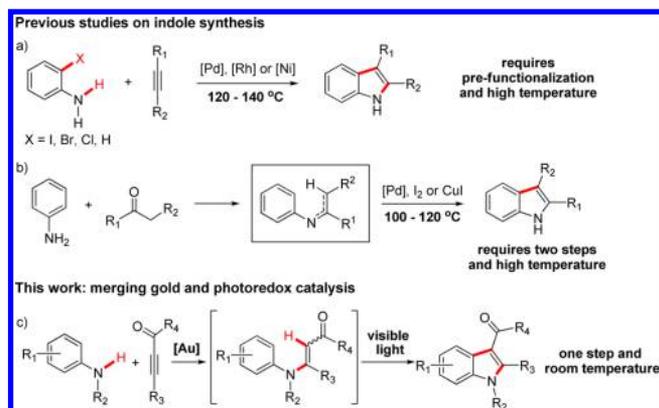
balloon-oxygen atmosphere and with visible-light irradiation from a 45 W household fluorescent compact bulb for 36 h at room temperature (entry 1, Table 1). Fortunately, a subsequent

Table 1. Identification of the Optimal Reaction Conditions

| entry	[Au] (0.05 equiv)	solvent	additive[d]	LA (equiv)	time (h)	yield (%)[e]
1	PPh₃AuCl	DCE	/	/	36	NR
2	PPh₃AuNTf₂	DCE	/	/	48	28
3	PPh₃AuNTf₂	DCE	MgSO₄	/	48	53
4	PPh₃AuNTf₂	DCE	4 Å MS	/	48	trace
5	PPh₃AuNTf₂	DCE	4 Å MS	LiClO₄ (1.0)	72	77
6	PPh₃AuNTf₂	DCE	4 Å MS	LiBF₄ (1.0)	72	76
7	PPh₃AuNTf₂	DCE	4 Å MS	TsOH·H₂O (1.0)	42	51
8	PPh₃AuNTf₂	DCE	4 Å MS	Mg(ClO₄)₂ (1.0)	50	79
9	**PPh₃AuNTf₂**	**DCE**	**4 Å MS**	**Mg(ClO₄)₂ (0.5)**	**52**	**83**
10	PPh₃AuNTf₂	DCE	4 Å MS	Sc(OTf)₃ (0.3)	50	61
11[a]	[Au]/AgOTf	DCE	4 Å MS	Mg(ClO₄)₂ (0.5)	40	53
12[b]	[Au]/AgOTf	DCE	4 Å MS	Mg(ClO₄)₂ (0.5)	40	58
13	AuCl₃	DCE	4 Å MS	Mg(ClO₄)₂ (0.5)	36	decomp
14	PPh₃AuNTf₂	MeOH	4 Å MS	Mg(ClO₄)₂ (0.5)	36	NR
15	PPh₃AuNTf₂	THF	4 Å MS	Mg(ClO₄)₂ (0.5)	36	trace
16	PPh₃AuNTf₂	ACN	4 Å MS	Mg(ClO₄)₂ (0.5)	36	NR
17	PPh₃AuNTf₂	DMF	4 Å MS	Mg(ClO₄)₂ (0.5)	36	NR
18	/	DCE	4 Å MS	Mg(ClO₄)₂ (0.5)	52	trace
19[c]	PPh₃AuNTf₂	DCE	4 Å MS	Mg(ClO₄)₂ (0.5)	52	trace

[a]IPrAuCl/AgOTf was used. [b](John-Phos)AuCl/AgOTf was used. [c]Reaction was performed in the absence of light. [d]100 wt % of additive was employed. [e]Yield of isolated product. IPr = 1,3-bis(2,6-diisopropyl-phenyl)imidazol-2-ylidene, John-Phos = (2-biphenyl)di-*tert*-butylphosphine.

key observation was made that the desired indole **3a** was produced in 28% isolated yield by using the Gagosz catalyst PPh₃AuNTf₂ in place of PPh₃AuCl (entry 2). In this case, accompanying **3a** was the formation of ethyl 3-oxo-3-phenyl-propanoate as the major byproduct (43% isolated yield), arising apparently from direct hydration of **2a** or a putative enamine intermediate. Remarkably, the yield of **3a** was improved to 53% when a moisture scavenger MgSO₄ was added into the reaction (entry 3). By contrast, when powdered 4 Å molecular sieves were employed as the moisture scavenger, the reaction was virtually completely inhibited (entry 4). These results collectively implied that MgSO₄ might have additionally functioned as a Lewis acidic activator. Indeed, when the Lewis acid LiClO₄ was used in conjunction with 4 Å molecular sieves, a respectable 77% yield of **3a** was recorded, albeit with a longer reaction time (72 h, entry 5). Thus, a range of acids, such as LiBF₄, TsOH·H₂O, Sc(OTf)₃, and Mg(ClO₄)₂, were subsequently screened at various loadings and reaction times (entries 5–10), from which the utilization of a substoichiometric amount of Mg(ClO₄)₂ (0.50 equiv) clearly stood out to be optimal (83%, entry 9). It merits a note that other attempts by employing other Au-catalysts, such as IPrAuCl/AgOTf, (John-Phos)AuCl/AgOTf, and AuCl₃, led to either a lower product yield or decomposition (entries 11–13). Furthermore, the solvent effect was found to be very significant in this transformation. When the solvent was MeOH, THF, ACN, or DMF, the reactivity was almost completely inhibited under otherwise identical reaction conditions (entries 14–17). Finally, control experiments conducted in the absence of either the PPh₃AuNTf₂ catalyst or visible-light exposure resulted in no

formation of the indole **3a** at all, thereby confirming both of them to be essential factors for reproducible production of **3a** (entries 18–19). It is interesting to note here that, somewhat contrary to the original design hypothesis, the uncovered reactivity requires the participation of visible light but without any photocatalyst. Collectively, these screening results established the optimal reagent system to be the following: 5 mol % of Gagosz catalyst PPh₃AuNTf₂, 100 wt % of activated powdered 4 Å molecular sieves, and 0.50 equiv of Mg(ClO₄)₂ in DCE under a balloon oxygen atmosphere at room temperature.

With the optimized reaction conditions identified, a range of anilines having various electron-withdrawing substituents were next attempted to couple with ethyl 3-phenylpropiolate **2a**, and the results are compiled in Scheme 2. In most cases, the

**Scheme 2. Reactivity Screenings on Substituted Aniline Substrates 1**
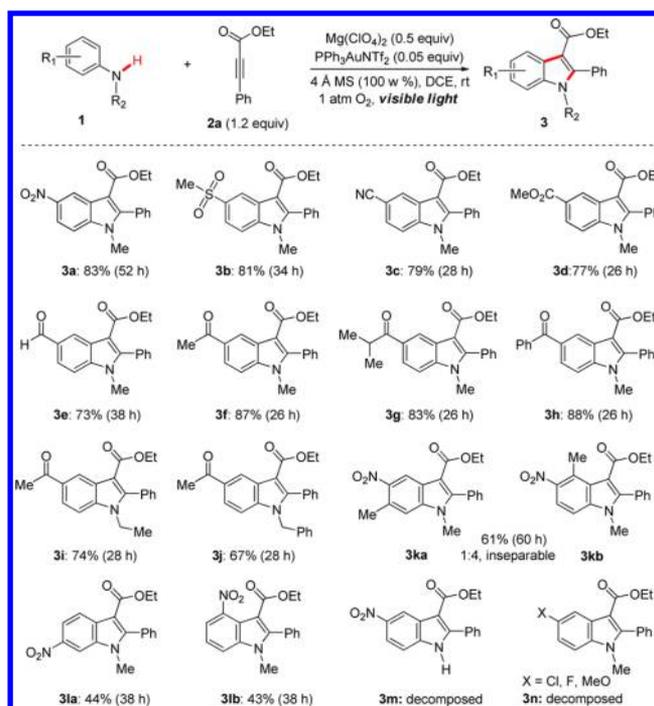
reactions proceeded smoothly to afford the corresponding indole product **3** in various isolated yields (61–88%). Some of the widely encountered election-withdrawing groups, such as the nitro (**3a**), sulfonyl (**3b**), carbonyl (**3d-3h**), and cyano (**3c**) group, were shown to be well accommodated in the reactions in terms of product yield (73–88%). A closer inspection revealed that the most strongly electron-withdrawing nitro group in **3a** appeared to have retarded the reaction to some extent, as a significantly longer reaction time (52 h) was required to achieve a comparable yield (83%), hinting at the possibility that the increased difficulty of electron abstraction from the corresponding nitrogen lone pair might have negatively influenced the photoredox process. The reactions were also successful with ethyl- or benzyl-substituted anilines (i.e., R₂ = Et, Bn), and the indoles **3i** and **3j** were thus uneventfully produced in 74% and 67% yields, respectively. Notably, reaction decomposition was observed with the free aniline (i.e., R² = H in **3m**). When an unsymmetrically substituted aniline **3k** was used, the reaction led to two inseparable regioisomers in a 1:4 ratio and 61% yield

over 60 h. Similarly, *meta*-substituted aniline **1l** was found to afford two separable regioisomers in a 1:1 ratio and 87% yield within 38 h. Furthermore, it merits attention that the electronic characteristics of the aniline aromatic ring substituents (R_1) had evidently a rather sensitive influence on the reaction, where complicated mixtures resulted with substrates bearing R_1 that is electron-releasing in nature (R_1 = Cl, F, or MeO in **3n**).

To further examine the substrate scope of the methodology, direct condensations of several diversely substituted alkynes **2** and the commercial available methyl 4-(methylamino)benzoate **1d** were next investigated. As summarized in Scheme 3, the

Scheme 3. Reactivity Screenings on Alkyne Substrates 2
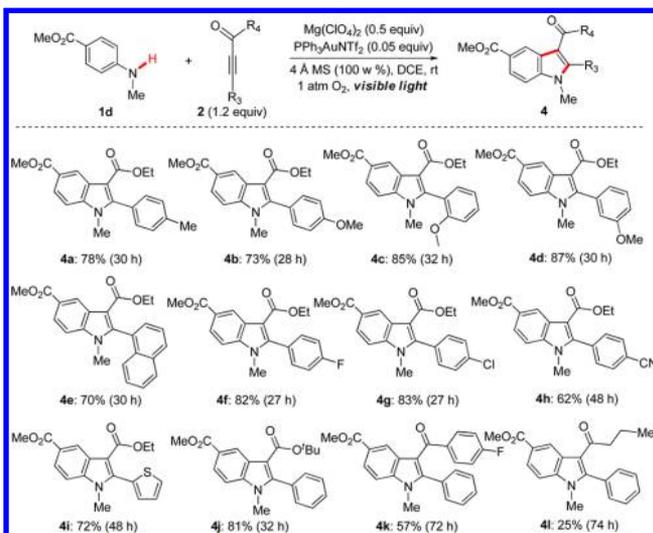
corresponding indoles **4a**−**4l** were generally delivered in moderate-to-good isolated yields (up to 87%). These results demonstrated that both of the aryl ring sizes (**4a** and **4e**) and the electron-withdrawing as well as -donating nature of the substituents on the R_3 (**4b**−**4h**) on the alkynes **2** seemed to have posed little influence on the reactivities. Moreover, the substrate carrying a heterocyclic group (**2i**) or a sterically bulkier ester (**2j**) was comparably efficient in both instances (72% of **4i** and 81% of **4j**, respectively). Notable reactivity decreases were reorded in the cases of **4k** and **4l** when ketones were employed as the substrates, and the formations of **4k**−**4l** required more reaction time for completion (57% of **4k** after 72 h and 25% of **4l** after 74 h, respectively).

Structurally densely functionalized indoles prepared by this new protocol are amendable for further synthetic editing. Disclosed in Scheme 4 are two illustrative examples. The nitro group in **3a** could be readily reduced to amine in 90% yield by

Scheme 4. Illustrative Synthetic Transformations
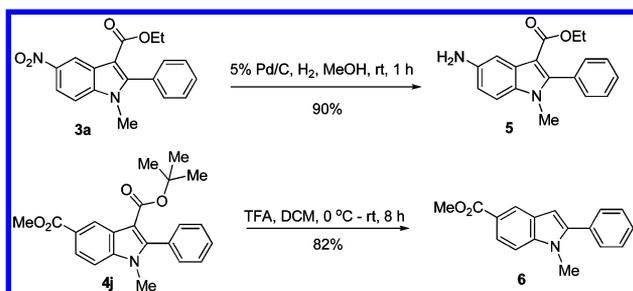
the action of Pd/C-mediated hydrogenation, and the ester functionality in **4j** was efficiently removed through acid-promoted decarboxylation.[9] These new indole derivatives could serve as important intermediates for pharmaceutical as well as natural products syntheses.

The insignificance of a photocatalyst in such observed reactivity is intriguing and merits further investigations. Some control experiments were therefore subsequently performed to shed light on the reaction pathways (Scheme 5). The direct

Scheme 5. Control Experiments on Reaction Parameters
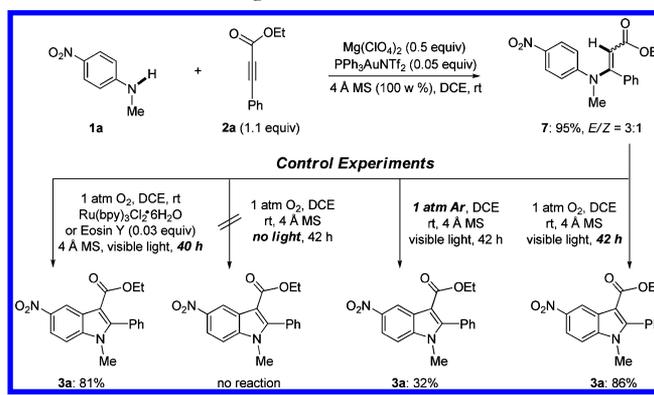
coupling of two representative substrates **1a** and **2a** in the presence of Mg(ClO$_4$)$_2$, PPh$_3$AuNTf$_2$, and 4 Å molecular sieves yielded initially enamine **7** as a 3:1 mixture of *E/Z* isomers in 95% yield within 12 h, which, in conjunction with an earlier finding (entry 18 in Table 1), points to the operation of a Au-catalyzed hydroamination event. When **7** was exposed to visible-light stimulation under a ballooned O$_2$ atmosphere and in the presence of a photosensitizer,[10] Ru(bpy)$_3$Cl$_2$ or Eosin Y, indole **3a** was furnished in 81% yield over 40 h. Performing the reaction in the absence of O$_2$ or visible light led to either a dramatic reduction in the yield of **3a** (32%) or complete reactivity inhibition, suggesting that their participations are essential for reproducible operation of the reactivity. In marked contrast, the yield of **3a** was not at all compromised (86%) when the said photosensitizer was removed from the reaction.

A plausible mechanistic rationale enabled by these observations is briefly depicted in Scheme 6. Dual Au/Mg Lewis acidic activations on **2** would trigger hydroamination addition[11] of **1** to give an enamine species **7**, whose highly polarizable electron densities distributed along the extended conjugative system would undergo photoexcitation (intermedi-

Scheme 6. A Plausible Mechanistic Proposal
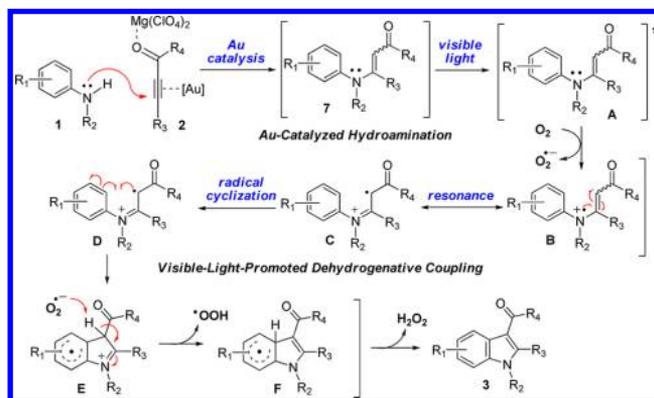
ate **A**) under visible-light stimulation and subsequent electron transfer with molecular oxygen,[12] thereby leading to the formation of radical cation species **B/C**. Radical cyclization[13] would then take place in the shown deprotonation—aromatization sequence of **D**–**E**–**F** to yield the final indole product **3** with the elimination of hydrogen peroxide, thus concluding a formal visible-light-mediated dehydrogenative coupling cascade.

In summary, motivated by the initial design concept of exploring possibly synergistic Au-catalysis as well as visible-light photoredox catalysis, we have described herein some unusually simple and mild reactivities allowing for direct preparations of a diverse range of indole substances bearing multiple useful functionalities. This new protocol accommodates various anilines and alkyne substrates and mechanistically operates through a fascinating cascade of Au-catalyzed hydroamination, visible-light-promoted electron transfer, and dehydrogenative coupling. The reactivity, not requiring the assistance of any photosensitizer, adds further to its practicality. Given the widely appreciated significance of indole-type substances in pharmaceutical and chemical contexts, it is well anticipated these discoveries would find applications and stimulate further studies in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dzw@pkusz.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) M. Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (c) Krüger née Alex, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (d) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29 and references cited therein.

(2) For recent reviews on indole synthesis, see: (a) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 215. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.

(4) (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (c) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (d) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (e) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (f) Huestis, M. P.; Chan, L. N.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*,

1338. (g) Song, W.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638. (h) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.

(5) For recent reviews on Au catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Corma, A.; Leyva-Perez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (d) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (e) Liu, L.-P.; Hammond, G. B. *Chem. Soc. Rev.* **2012**, *41*, 3129.

(6) For selected reviews on photoredox catalysis, see: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (c) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(7) Our previous studies on transition-metal catalysis and photoredox catalysis, see: (a) Cai, S. Y.; Liu, Z.; Zhang, W. B.; Zhao, X. Y.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 11133. (b) Wang, L.; Cai, S. Y.; Xing, X. Y.; Gao, Y.; Wang, T.; Wang, D. Z. *Org. Lett.* **2013**, *15*, 2362. (c) Cai, S. Y.; Zhao, X. Y.; Wang, X. B.; Liu, Q. S.; Li, Z. G.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050. (d) Cai, S. Y.; Zhang, S. L.; Zhao, Y. H.; Wang, D. Z. *Org. Lett.* **2013**, *15*, 2660.

(8) (a) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (b) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (c) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (d) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505.

(9) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298.

(10) (a) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (b) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (c) Zhu, S.-Q.; Das, A.; Bui, L.; Zhou, H.-J.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823. (d) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (e) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.

(11) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

(12) Maity, S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 9562.

(13) He, Z.; Liu, W.; Li, Z. *Chem.—Asian J.* **2011**, *6*, 1340.