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Silver-Catalyzed Radical Tandem Cyclization for the Synthesis of 3,4-Disubstituted Dihydroquinolin-2(1*H*)-ones

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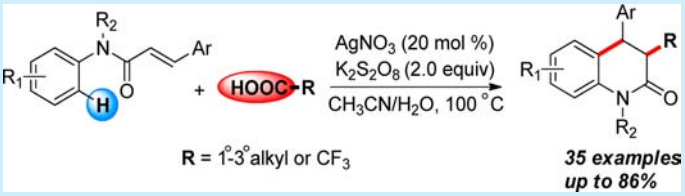
Supporting Information



ABSTRACT: A silver-catalyzed tandem decarboxylative radical addition/cyclization of *N*-arylcinnamamides with aliphatic carboxylic acids is reported. This method affords a novel and straightforward route to various 3,4-disubstituted dihydroquinolin-2(1*H*)-ones in aqueous solution.

Many substituted 3,4-dihydroquinolin-2(1*H*)-ones have attracted considerable attention in view of their cardiovascular, anti-inflammatory, and phosphodiesterase inhibitory activities.[1] Moreover, 3,4-dihydroquinolin-2(1*H*)-ones are a versatile structural unit for the preparation of other important pharmaceuticals and natural products such as 1,2,3,4-tetrahydroquinolines and quinolin-2(1*H*)-ones.[2] Thus, the development of a straightforward and highly efficient method for the construction of 3,4-dihydroquinolin-2(1*H*)-one is highly desirable. A general method for the preparation of a 3,4-dihydroquinolin-2(1*H*)-one system is the Friedel−Crafts cyclization requiring superacidity or stoichiometric amounts of metals.[3] Recently, several alternative methods such as Pd-catalyzed sequential Heck reduction−cyclization reactions, Pd-catalyzed cyclopropane ring expansions, Rh-mediated 1,4-additions of the boronic acid to enone, sequential Ugi/acrylanilide [6π]-photocyclizations, intermolecular tandem reactions, Mn-mediated intramolecular cyclizations, and Pd-catalyzed cyclocarbonylations reactions have been developed.[4] However, for 3,4-disubstituted dihydroquinolin-2(1*H*)-one, these processes still suffer from such drawbacks as the need for complicated starting materials[4g] or multistep synthesis.[4a,b,d,f] So far, radical reactions have widespread applications in organic synthesis, especially in cyclization reactions for the prepration of valuable heterocycles.[5] Recently, the synthesis of substituted oxindoles[6] and construction of multiple C−C/N bonds through radical cyclization to access 3,3-disubstituted oxindoles have attracted special attention.[7] These methods demonstrated that this kind of radical cyclization is a very powerful tool to construct oxindole's framework. Recent significant progress in radical cyclization inspired us to extend this highly efficient method to another prominent structural motif, 3,4-dihydroquinolin-2(1*H*)-one, because a general and tandem approach for the construction of its six-membered ring remains rare,[4f,g] in contrast to oxindole's synthesis. Herein we disclose the silver-catalyzed tandem decarboxylation and C−H functionalization in aqueous solution which provides a novel and simple protocol for valuable 3,4-disubstituted dihydroquinolin-2(1*H*)-ones (Scheme 1).

Scheme 1. Ring Closure for 3,4-Dihydroquinolin-2(1*H*)-one

We started our model reaction by investigating *N*-methyl-*N*-phenylcinnamamide **1a** and pivalic acid **2a** for the optimization of reaction conditions (Table 1). With 20 mol % $AgNO_3$ as the catalyst, the reaction of **1a** with pivalic acid (2.0 equiv) in aqueous solution (CH_3CN/H_2O) failed to provide the desired product at room temperature (Table 1, entry 1). To our delight, a 37% product yield was obtained when the temperature was increased to 70 °C (Table 1, entry 2). The expected product was obtained in 69% yield when the temperature was further improved to 100 °C with a 20% catalyst loading (Table 1, entry 4). The product yield decreased when the catalyst loading was reduced (Table 1, entries 5−7). However, no more conversion of **1a** to **3a** was observed with 30 mol % $AgNO_3$ as the catalyst at 110 °C (Table 1, entry 8). Other Ag(I) salts such as $AgBF_4$, Ag_2O, and Ag_2CO_3 showed similar catalytic activity under the same conditions (Table 1, entries 9−11). Investigation of other oxidants such as $(NH_4)_2S_2O_8$, TBHP, oxone, DTBP, and O_2 for this transformation showed that $K_2S_2O_8$ was the best choice (Table 1, entries 12−16). The transformation did not proceed in such aqueous solutions as DCE/H_2O, CH_2Cl_2/H_2O, EtOH/H_2O,

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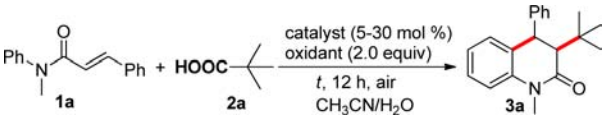
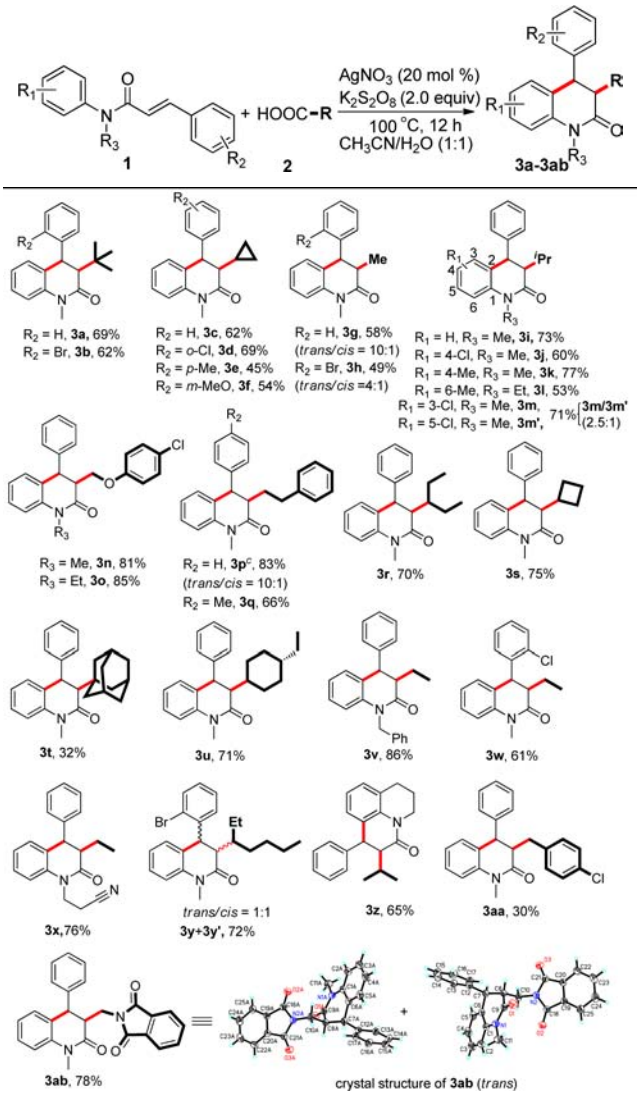
Table 1. Screening of Reaction Conditions[a]



entry	catalyst (mol %)	oxidant	t (°C)	yield[b]
1	$AgNO_3$ (20)	$K_2S_2O_8$	rt (18)	N.R.
2	$AgNO_3$ (20)	$K_2S_2O_8$	70	37
3	$AgNO_3$ (20)	$K_2S_2O_8$	90	65
4	$AgNO_3$ (20)	$K_2S_2O_8$	100	69 (35[c])
5	$AgNO_3$ (5)	$K_2S_2O_8$	100	22
6	$AgNO_3$ (10)	$K_2S_2O_8$	100	29
7	$AgNO_3$ (15)	$K_2S_2O_8$	100	47
8	$AgNO_3$ (30)	$K_2S_2O_8$	110	66
9	$AgBF_4$ (20)	$K_2S_2O_8$	100	57
10	Ag_2O (20)	$K_2S_2O_8$	100	48
11	Ag_2CO_3 (20)	$K_2S_2O_8$	100	60
12	$AgNO_3$ (20)	$(NH_4)_2S_2O_8$	100	55 (42[c])
13	$AgNO_3$ (20)	oxone	100	N.R.
14	$AgNO_3$ (20)	TBHP	100	N.R.
15	$AgNO_3$ (20)	DTBP	100	N.R.
16	$AgNO_3$ (20)	O_2	100	N.R.
17[d]	$AgNO_3$ (20)	–	100	N.R.
18[e]	–	$K_2S_2O_8$	100	N.R.
19[f]	$AgNO_3$ (20)	$K_2S_2O_8$	100	N.R. (N.R[h])
20[g]	$AgNO_3$ (20)	$K_2S_2O_8$	100	trace (N.R[i])
21[j]	$AgNO_3$ (20)	$K_2S_2O_8$	100	trace
22	Cu (20)	$K_2S_2O_8$	100	N.R.
23	CuCl (20)	$K_2S_2O_8$	100	N.R.
24	$Cu(OAc)_2$ (20)	$K_2S_2O_8$	100	N.R.
25	$FeSO_4$ (20)	$K_2S_2O_8$	100	N.R.
26	$FeCl_3$ (20)	$K_2S_2O_8$	100	N.R.

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), CH_3CN/H_2O (3/3 mL), under air atmosphere, 12 h, 100 °C. [b]Isolated yield. [c]DMF/H_2O as solvent. [d]Without catalyst. [e]Without oxidant. [f]CH_2Cl_2/H_2O as solvent. [h]DCE/H_2O as solvent. [g]Dioxane/H_2O as solvent. [i]EtOH/H_2O as solvent. [j]Acetone/H_2O as solvent. N.R. = No Reaction.

Table 2. Tandem Radical Addition/Cyclization of 1 and 2[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (2.0 mmol), CH_3CN/H_2O (3/3 mL), 100 °C, 12 h. [b]Isolated yield. [c]Crystal structure in Supporting Information.

dioxane/H_2O, and acetone/H_2O (Table 1, entries 19–21). We further explored other metals, such as copper powder, CuCl, $Cu(OAc)_2$, $FeSO_4$, and $FeCl_3$, as catalysts, but no reaction proceeded (Table 1, entries 22–26).

With the optimized conditions in hand, we then set out to explore the scope and limitations of the 6-*endo* radical cyclization, and the results are summarized in Table 2. In general, electron-donating or -withdrawing groups on aniline at the *ortho*, *meta*, and *para* positions did not affect the efficiency of the reaction, affording the desired products in moderate yields (Table 2, **3i–m**). Substituents such as Cl, Br, Me, and OMe at the *ortho*, *meta*, and *para* positions on the other aromatic ring of the substrate **1** were well tolerated in the process of ring closure under the optimal conditions and the corresponding products were obtained in moderate yields (Table 2, **3b–f**). The reaction still proceeded well when different *N*-protected groups (e.g., Me, Et, Bz, and CH_3CH_2CN) of substrate **1** were used (Table 2, **3m**, **3n–o**, **3v**, and **3x**). After investigating R_1, R_2, and R_3 of substrate **1**, aliphatic carboxylic acids were further tested under the optimal conditions. Various primary, secondary, and tertiary aliphatic carboxylic acids underwent efficient intermolecular ring closure to provide the expected products **3a–z** and **3aa–3ab** in moderate to good yields. With this method, methyl or ethyl could be introduced into the 3-position of 3,4-dihydroquinolin-2(1*H*)-one in one step only using cheap AcOH or propionic acid instead of MeLi or EtLi as substrates (Table 2, **3g–h** and **3v–x**).[8] Primary carboxylic acids containing aromatic ringlike 3-phenylpropanoic acid and 2-(4-chlorophenyl)-acetic acid showed different reactivity; products **3p** and **3aa** were obtained in 83% and 30% yields respectively. In addition, primary carboxylic acids containing heteroatoms (O, N) at adjacent positions of the carboxyl group also displayed high reactivity in this transformation (Table 2, **3n–o** and **3ab**). As for secondary alkyl acids, 4-ethylcyclohexanecarboxylic acid worked well in the same fashion and gave the corresponding product in 71% yield (Table 2, **3u**). Moreover, cyclopropanecarboxylic acid and cyclobutanecarboxylic acid were also successfully converted to the desired products without ring opening (Table 2, **3c–f** and **3s**). Interestingly, product **3y** was isolated in 72% yield as a 1:1 ratio of *cis*/*trans* isomers when 2-ethylhexanoic acid was explored as the substrate (Table 2, **3y** and **3y′**). However, in comparison with pivalic acid, 1-adamantanecarboxylic acid

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which is more congested gave a low yield under the same conditions (Table 2, **3t**).

The structure of product **3b** was clearly confirmed by single-crystal X-ray crystallographic analysis (Figure 1). Obviously, product **3b** is a *trans*-form which contains a six-membered ring.

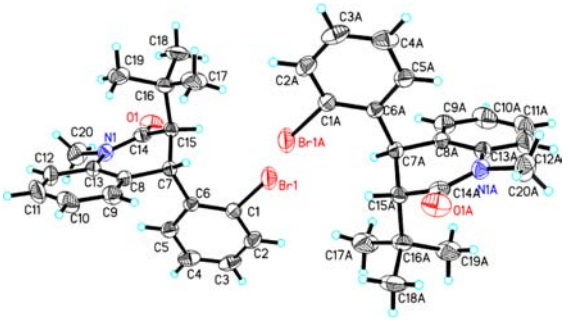
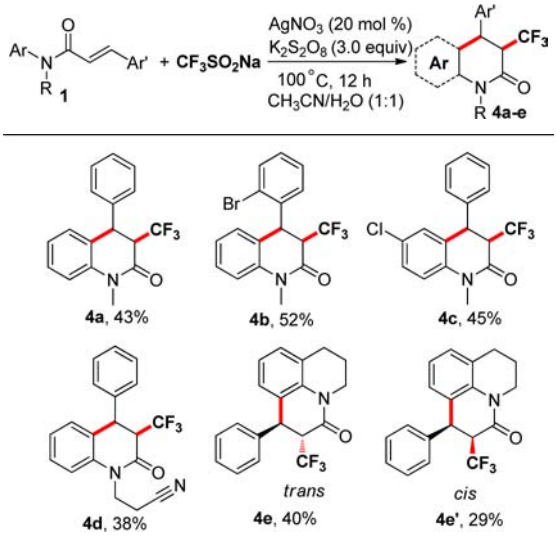


Figure 1. Molecular structure of **3b**.

Encouraged by this finding, we continued to explore the *trans*-selective 6-*endo* radical cyclization leading to 3,4-disubstituted dihydroquinolin-2(1*H*)-one derivatives. Trifluoromethylated heteroaryl compounds represent an important structural motif in pharmaceuticals and advanced organic materials.[9] Thus, two alkyl acids containing the CF_3 group were subjected to the reaction. Unfortunately, both TFA and 3,3,3-trifluoropropanoic acid failed to provide any of the desired products. The reason for this is still not clear at present. However to our delight, when CF_3SO_2Na (Langlois reagent) was employed as the source of the CF_3 radical,[10] the reaction took place under the slightly modified conditions, in which the CF_3 group was introduced into the 3-position of 3,4-dihydroquinolin-2(1*H*)-one successfully (Table 3). An investigation into different substituents (R_{1-3}) of substrate **1** showed that the transformation still proceeded well, affording the desired trifluoromethylated products **4a**–**4e** without much difference in yields. Products **4e** and **4e′** were isolated as two stereoisomers in a 4:3 ratio under the same reaction conditions.

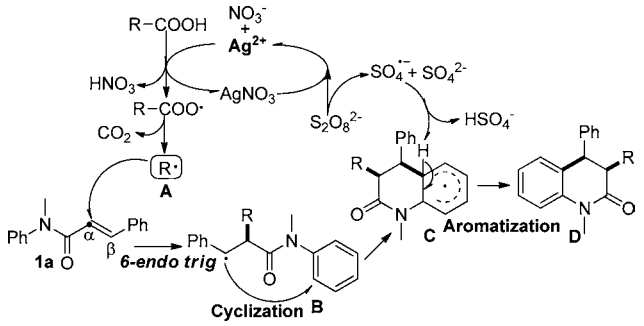
Table 3. Study of Trifluoromethylation in the Cyclization[a]



[a]Reaction conditions: **1** (1.0 mmol), CF_3SO_2Na (3.0 mmol), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3.0 mmol), CH_3CN/H_2O (3/3 mL), 100 °C, 12 h.

A postulated mechanism is described in Scheme 2. Initially, Ag^+ is oxidized by the persulfate anion ($S_2O_8^{2-}$) to generate the

Scheme 2. Postulated Mechanism for the Radical Tandem Cyclization



Ag^{2+} cation and sulfate radical anion. Then, the Ag^{2+} cation obtains a single electron from carboxylate to produce the carboxyl radical.[11] Quick decarboxylation of the carboxyl radical provides the corresponding alkyl radical **A**, followed by addition to the double bond of cinnamamide **1a**, thus leading to intermediate **B**. Intramolecular cyclization of **B** gives the intermediate **C**. Finally, intermediate **C** can be aromatized to the desired product **D** after hydrogen abstraction by the sulfate radical anion.

In summary, we have developed an unprecedented and highly efficient method for the preparation of biologically interesting 3,4-disubstituted dihydroquinolin-2(1*H*)-one derivatives by silver-catalyzed tandem decarboxylative radical addition/cyclization of *N*-arylcinnamamides with aliphatic carboxylic acids in aqueous solution. A significant feature of the novel protocol is the formation of a six-membered ring; meanwhile, it could be alkylated or trifluoromethylated. This approach represents one of the most straightforward routes to various functional 3,4-dihydroquinolin-2(1*H*)-one syntheses.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, and copies of ^1H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tominaga, M.; Tone, H.; Nakagawa, K.; Takada, K.; Hoshino, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1981**, *29*, 2166. (b) Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 798. (c) Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 1151. (d) Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu,

T.; Nakagawa, K. *Chem. Pharm. Bull.* **1985**, *33*, 1140. (e) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Morris, D. S.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1989**, *32*, 575.

(2) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031 and references therein. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (c) Park, K. K.; Jung, J. Y. *Heterocycles* **2005**, *65*, 2095.

(3) (a) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881. (b) Cherest, M.; Lusinchi, X. *Tetrahedron Lett.* **1989**, *30*, 715.

(4) (a) François, X. F.; Jérôme, C.; Cécile, Z.; Eric, F. *Chem.—Eur. J.* **2009**, *15*, 7238. (b) Tsuritani, T.; Yamamoto, Y.; Kawasaki, M.; Mase, T. *Org. Lett.* **2009**, *11*, 1043. (c) Joachim, H.; Ho, Y. L.; Stephen, P. M.; Adam, N.; Rachel, J. S.; Amanda, J. C.; David, H.; Gordon, G. W. *Tetrahedron* **2009**, *65*, 9002. (d) Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785. (e) Irini, A. Z.; Alan, W.; Jan, E. W.; Rodger, F. H.; Stevan, W. D. *Tetrahedron Lett.* **2007**, *48*, 3549. (f) Zhou, W.; Zhang, L. R.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982. (g) Tsubusaki, T.; Nishino, H. *Tetrahedron* **2009**, *65*, 9448. (h) Çağatay, D.; Metin, B. *Turk. J. Chem.* **2013**, *37*, 220. (i) Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264.

(5) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, U.K., 1986. (b) Curran, D. P. In *Comprehensive Organicl Synthesis*; Pergamon: Oxford, U.K., 1991; Vol. *4*, pp 715−831. (c) Perchyonok, T. *Radical Reactions in Aqueous Media*; Pergamon: RSC, U.K., 2009. (d) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (e) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.

(6) (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (b) Mu, X.; Wu, T.; Wang, H. Y.; Guo, Y. L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (c) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (d) Tsukano, C.; Okuno, M.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 2763. (e) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (f) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (g) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274. (h) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. *J. Org. Chem.* **1998**, *63*, 6546. (i) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (j) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961. (k) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (l) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (m) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, *6*, 934. (n) Dey, C.; Kündig, E. P. *Chem. Commun.* **2012**, *48*, 3064. (o) Beyer, A.; Buendia, J.; Bolm, C. *Org. Lett.* **2012**, *14*, 3948. (p) Wei, H. L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. P. *Org. Lett.* **2011**, *13*, 2244. (q) Fabry, D. C.; Stodulski, M.; Hoerner, S.; Gulder, T. *Chem.—Eur. J.* **2012**, *18*, 10834.

(7) (a) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (b) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (c) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690. (d) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (e) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540. (f) Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672. (g) Wang, H.; Guo, L.-N.; Duan, X.-H. *Adv. Synth. Catal.* **2013**, *355*, 2222. (h) Zhou, S.-L.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.—Eur. J.* **2013**, *19*, 12970. (i) Wei, X.-H.; Li, Y.-M.; Zhou, A.-X.; Yang, T.-T.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 4158. (j) Xu, P.; Xie, J.; Cai, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem.—Eur. J.* **2013**, *19*, 14039. (k) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 10370. (l) Zhou, M.-B.; Wang, C.-Y.; Song, R.-J.; Liu, Y.; Wei, W.-T.; Li, J.-H. *Chem. Commun.* **2013**, *49*, 10817. (m) Yuan, Y.; Shen, T.; Wang, K.; Jiao, N. *Chem.—Asian J.* **2013**, *8*, 2932.

(8) (a) Park, Y. S.; Yum, E. K.; Basu, A.; Beak, P. *Org. Lett.* **2006**, *8*, 2667. (b) Kim, Y.; Shin, E.; Beak, P.; Park, Y. S. *Synlett* **2006**, *22*, 3805.

(9) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (b) Müller, K.; Faeh, C.; Diederich, F. *Science.* **2007**, *317*, 1881.

(10) (a) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmon, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (b) Ye, Y.; Künzi, S. A.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4979. (c) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406. (d) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. (e) Yang, Y. D.; Iwamoto, K.; Tokunaga, E.; Shibata, N. *Chem. Commun.* **2013**, *49*, 5510.

(11) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651. (b) Anderson, J. M.; Kochi, J. K. *J. Org. Chem.* **1970**, *35*, 986. (c) Minisci, F.; Vismara, E.; Morini, G.; Fontana, F.; Levi, S.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1986**, *51*, 476. (d) Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron.* **1990**, *46*, 2525. (e) Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 14330. (f) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401.