Organic LETTERS

Letter

pubs.acs.org/OrgLett

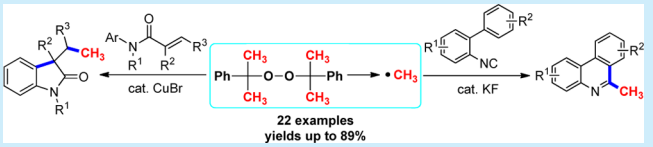
A Free-Radical Cascade Methylation/Cyclization of *N*-Arylacrylamides and Isocyanides with Dicumyl Peroxide

Zhengbao Xu, Chaoxian Yan, and Zhong-Quan Liu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, P. R. China

Supporting Information

ABSTRACT: A free-radical cascade methylation/cyclization of a wide range of *N*-arylacrylamides and isocyanides is demonstrated by using dicumyl peroxide as the methylating reagent, which provides a convenient and selective access to various methylated *N*-heterocycles such as oxindoles and phenanthridines.

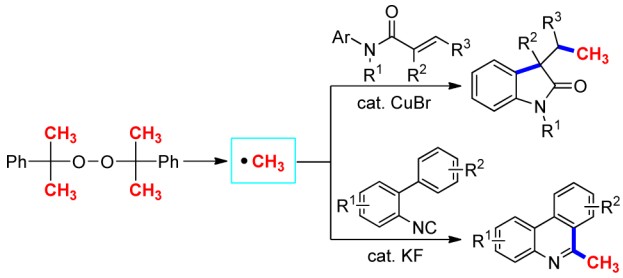


One of the most commonly occurring functional groups in bioactive compounds is the methyl group.[1] The so-called "magic methyl effect" makes it very popular in drug discovery, which also offers a continuing driving force for exploring new and more efficient strategies for incorporation of the methyl group into organic molecules.[2] Traditionally, direct C−H methylation has been achieved by using methyl metal reagents such as $SnMe_4$,[3] $MeB(OH)_2$,[4] $MeBF_3K$,[5] MeMgCl,[6] and Me_2CuLi as well as MeI,[7] DMSO,[8] and MeCOOH[9] with or without catalysis by a transition metal. Free-radical methylation by using acetic acid first developed by Minisci represents a very efficient and useful strategy.[10] Recently, Li and co-workers reported a Pd-catalyzed methylation of arene using dicumyl peroxide (DCP) as the effective methyl source.[11] Very recently, a Cu-catalyzed *N*-methylation of amides and *O*-methylation of carboxylic acids by using DCP was explored by Chen et al.[12] Although considerable advances have been made in the past decades, more efficient methylation strategies are highly desirable.

In our continuing studies on the C−C bond formation via free-radical cascade cyclization,[13] we began to envision that a series of methylated heterocycles could be synthesized by using this strategy. For example, addition of a methyl radical to *N*-arylmethacrylamides and biphenyl isocyanides followed by cyclization would lead to methylated oxindoles and phenanthridines, respectively. These *N*-heterocycles are valuable bioactive compounds and potential pharmaceutical candidates, and both *N*-arylmethacrylamides[14] and biphenyl isocyanides[15] have been proven to be excellent radical acceptors. Very recently, we have developed a series of free-radical-initiated addition/cyclization reactions of activated alkenes and isonitriles with simple alkanes and alcohols.[13] Herein we wish to report the first example of free radical cascade methylation of *N*-arylmethacrylamides and isonitriles by using DCP as the methyl radical source. This method allows convenient access to a variety of methylated *N*-heterocycles (Scheme 1).

Initially, to test our hypothesis for this novel free-radical methylation/cyclization cascade process, a series of peroxides that could be considered as potential methyl radical donors were screened (Table 1; also see the Supporting Information).

Scheme 1. Free Radical Methylation by Using Dicumyl Peroxide



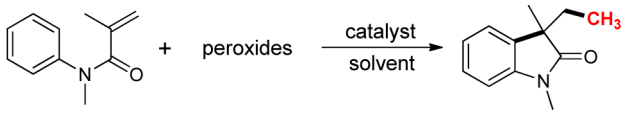
It was found that the dicumyl peroxide (DCP) was more efficient than *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide (DTBP) (Table 1, entries 1−3). The CuBr was found to be a more efficient catalyst than several others such as Cu powder, $FeCl_2$, Cu_2O, and CuI (Table 1, entries 3−7). The solvent was found to be a very important factor that critically affects the reaction efficiency. The *tert*-butanol was much better than others such as trifluoroethanol (TFE) and PhCl etc (Table 1, entries 7−11). The desired product 3-ethyl-1,3-dimethylindolin-2-one was isolated in a yield of 82% under the following conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), DCP (2 equiv, 0.4 mmol), CuBr (0.1 equiv, 0.02 mmol), *t*-BuOH (2.5 mL), 130 °C, 24 h, sealed tube. Other conditions led to lower yields of the product by varying the amount of the catalyst, radical initiator, and solvent (Table 1, entries 12−17).

To investigate the substrate scope of this strategy, a variety of *N*-methyl-*N*-arylmethacrylamides were prepared (Scheme 2). As a result, halogen atoms such as F, Cl, Br, and I as well as alkyl and methoxyl substituents on the *para*-position of the *N*-aryl moiety can be well-tolerated in this system (**1a**−**1h**). Gratifyingly, the hydroxyl group can also survive under the typical reaction conditions (**1i**). The *N*-methyl-*N*-(naphthalen-

Received: September 16, 2014
Published: October 15, 2014

dx.doi.org/10.1021/ol502738a | *Org. Lett.* 2014, 16, 5670−5673

Table 1. Modification of the Typical Reaction Conditions[a]



entry	catalyst (mol %)	radical initiator (equiv)	solvent (mL)	t (°C)[b]	yield (%)[c]
1	Cu (10)	TBHP (2)	TFE (2.5)	160	13
2	Cu (10)	DTBP (2)	TFE (2.5)	160	19
3	Cu (10)	DCP (2)	TFE (2.5)	160	35
4	$FeCl_2$ (10)	DCP (2)	TFE (2.5)	140	16
5	Cu_2O (10)	DCP (2)	TFE (2.5)	140	15
6	CuI (10)	DCP (2)	TFE (2.5)	140	35
7	CuBr (10)	DCP (2)	TFE (2.5)	140	39
8	CuBr (10)	DCP (2)	PhCl (2.5)	140	37
9	CuBr (10)	DCP (2)	*t*-BuOH (2.5)	110	61
10	CuBr (10)	DCP (2)	*t*-BuOH (2.5)	120	70
11	**CuBr (10)**	**DCP (2)**	***t*-BuOH (2.5)**	**130**	**82**
12	CuBr (5)	DCP (2)	*t*-BuOH (2.5)	130	73
13	CuBr (10)	DCP (3)	*t*-BuOH (2.5)	130	75
14	CuBr (10)	DCP (1)	*t*-BuOH (2.5)	130	54
15	CuBr (10)	DCP (2)	*t*-BuOH (1.5)	130	72
16	CuBr (10)	DCP (2)	*t*-BuOH (2.0)	130	76
17	–	DCP (2)	*t*-BuOH (2.5)	130	37

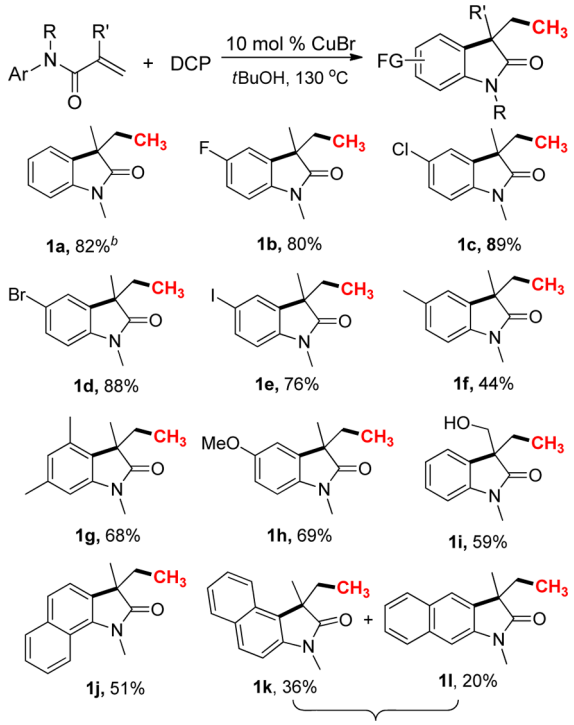
[a]Reaction conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), 24 h, sealed tube. [b]Measured temperature of the oil bath. [c]Isolated yields.

1-yl)methacrylamide gave the corresponding product in 51% yield (**1j**). In the case of *N*-methyl-*N*-(naphthalen-2-yl)-methacrylamide, a regioselective isomer of the products were obtained (**1k**, 36%; **1l**, 20% yield).

Encouraged by the successful application of this strategy in preparing methylated oxindoles, we began to apply this method to other systems. Previous studies indicate that biaryl isocyanides were good free radical acceptors.[15] Hence, we proposed that a series of 6-methylated phenanthridines and its derivatives could be synthesized by using this free radical methylation/cyclization cascade protocol. DCP and 2-isocyano-5-methyl-1,1′-biphenyl were chosen as the model substrates to test the idea. A variety of catalysts were screened to optimize the typical reaction conditions (Table 2; see also the Supporting Information). It was found that various copper and iron salts such as CuBr, CuI, CuCl, Cu_2O, $FeCl_2$, etc. gave relatively low yields of the product (entries 1−5). Interestingly, several fluorides such as CsF and KF could efficiently promote this reaction (entries 6−11). However, only 42% of the desired product was isolated without any catalyst (entry 12).

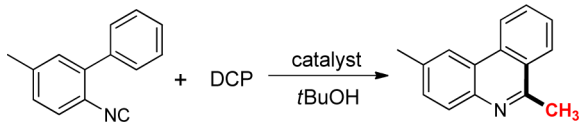
We next began to study the substrate scope of the free radical methylation of biphenyl isonitriles with DCP (Scheme 3). We found that a wide range of isocyanides containing bis-aromatic cores with both electron-donating and -withdrawing groups gave moderate to good yields of the desired products (**2a**−**2k**), which indicates that there was not obvious electronic effect on the substrate. Some hydrogenation phenanthridines **2′** were isolated as the major byproducts except for the desired

Scheme 2. CuBr-Catalyzed Methylation/Cyclization of *N*-arylmethacrylamides[a]



[a]Reaction conditions: *N*-methyl-*N*-arylmethacrylamide (1 equiv, 0.2 mmol), DCP (2 equiv, 0.4 mmol), CuBr (0.1 equiv, 0.02 mmol), *t*-BuOH (2.5 mL), 130 °C (measured temperature of the oil bath), 24 h, sealed tube. [b] Isolated yields.

Table 2. Modification of the Typical Reaction Conditions[a]



entry	catalyst (mol %)	t (°C)[b]	yield (%)[c]
1	CuBr (5)	130	46
2	CuI (5)	130	32
3	CuCl (5)	130	30
4	Cu_2O (5)	130	40
5	$FeCl_2$ (5)	130	38
6	CsF (50)	130	50
7	KF (50)	130	52
8	KF (100)	130	50
9[d]	**KF (50)**	**120**	**62**
10[d]	KF (30)	120	51
11[d]	KF (10)	120	45
12[d]	–	120	42

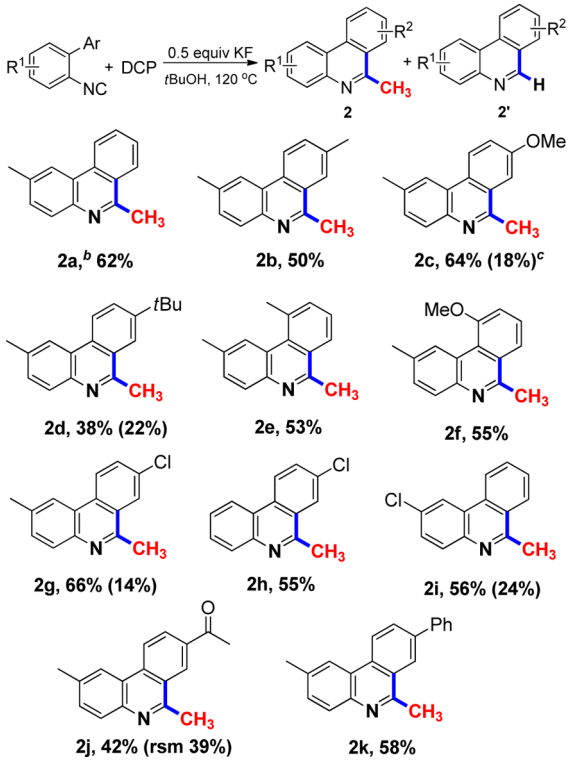
[a]Reaction conditions: 2-isocyano-5-methyl-1,1′-biphenyl (1 equiv, 0.2 mmol), DCP (2 equiv, 0.4 mmol), *t*-BuOH (2.5 mL), 24 h, sealed tube, unless otherwise noted. [b]Measured temperature of the oil bath. [c]Isolated yields. [d]18 h.

methylated phenanthridines (**2c**, **2d**, **2g**, and **2i**). It suggests that H atom transfer would be involved in this reaction.[13]

No desired product was observed by the addition of TEMPO into the system, which indicates that a free radical process would be involved. Based on the experimental data and precedent literatures, a plausible mechanism for this reaction

dx.doi.org/10.1021/ol502738a | *Org. Lett.* 2014, 16, 5670−5673

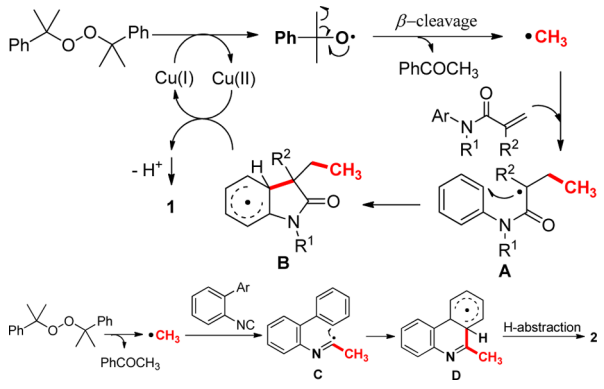
Scheme 3. Free-Radical Methylation/Cyclization of Biaryl Isocyanides[a]



[a]Reaction conditions: isocyanide (1 equiv, 0.2 mmol), DCP (2 equiv, 0.4 mmol), KF (0.5 equiv, 0.1 mmol), *t*-BuOH (2.5 mL), 120 °C (measured temperature of the oil bath), 18 h, sealed tube. [b] Isolated yields. [c] The isolated yield of **2′** in the parentheses.

has been proposed in Scheme 4. Homolysis of DCP with the assistance of Cu(I) followed by *β*-cleavage of the cumyloxyl

Scheme 4. Proposed Mechanism



radical would form the methyl radical and acetophenone which has been obtained as a byproduct. Two steps of radical addition would successively produce intermediates **A** and **B**. Single-electron oxidation by Cu(II) followed by deprotonation of the corresponding carbocation would give the product and regenerate the Cu(I). In the case of biphenyl isocyanide, addition of the methyl radical to the isonitrile would give a radical intermediate **C**, which then adds to the aromatic ring resulting in an aromatic radical **D**. Direct hydrogen abstraction by the cumyloxyl or methyl radical would produce the final product.

In conclusion, a free-radical methylation/cyclization cascade reaction of various *N*-arylmethacrylamides and biphenyl isonitriles by using dicumyl peroxide as the methylating reagent has been achieved. This strategy allows convenient and selective access to a wide range of methylated *N*-heterocycles such as oxindoles and phenanthridines. Further studies on the development of novel free radical methylation reactions are ongoing in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuzhq@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is supported by the National Science Foundation of China (Nos. 21272096, 21472080) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-58).

■ REFERENCES

(1) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215.
(2) Schönherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256.
(3) Chen, X.; Li, J.; Hao, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.
(4) (a) Giri, R.; Maugel, N.; Li, J.; Wang, D.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Romero-Revilla, J. A.; Garcia-Rubia, A.; Arrayas, R. G.; Fernandez-Ibanez, M. A.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 9525. (c) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
(5) Neufeldt, S. R.; Seigerman, C. K.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 2302.
(6) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232.
(7) (a) Barsky, L.; Gschwend, H. W.; McKenna, J.; Rodriguez, H. R. *J. Org. Chem.* **1976**, *41*, 3651. (b) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (c) Zhao, Z.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.
(8) Yao, B.; Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H.; Wang, M.-K.; Tang, R.-Y.; Zhang, X.-G.; Deng, C.-L. *Adv. Synth. Catal.* **2012**, *354*, 1890.
(9) Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2063.
(10) (a) Minisci, F. *Tetrahedron* **1971**, *27*, 3575. (b) Ahn, S. K.; Choi, N. S.; Jeong, B. S.; Kim, K. K.; Journ, D. J.; Kim, J. K.; Lee, S. J.; Kim, J. W.; Hong, C. I.; Jew, S.-S. *J. Heterocycl. Chem.* **2000**, *37*, 1141.
(11) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900.
(12) Xia, Q.; Liu, X.; Zhang, Y.; Chen, C.; Chen, W. *Org. Lett.* **2013**, *15*, 3326.
(13) (a) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382. (b) Li, Z.; Fan, F.; Yang, J.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 3396. (c) Zhang, L.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 3688.
(14) For selected reviews on oxindoles, see: (a) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. For selected recent examples of the synthesis of

dx.doi.org/10.1021/ol502738a | *Org. Lett.* 2014, 16, 5670−5673

oxindoles, see: (d) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (e) Wu, T.; Mu, X.; Liu, G.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (f) 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. (g) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (h) 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. (i) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (j) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (k) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540. (l) Wei, X.; Li, Y.; Zhou, A.; Yang, T.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 4158.

(15) For selected reviews on phenanthridines, see: (a) Theobald, R. S.; Schofield, K. *Chem. Rev.* **1950**, *46*, 170. (b) Simeon, S.; Rios, J. L.; Villar, A. *Pharmazie* **1989**, *44*, 593. (c) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. (d) Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, *62*, 864. For selected recent examples of preparation of phenanthridine and its derivatives, see: (e) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363. (f) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289. (g) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (h) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (i) Leifert, D.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2013**, *15*, 6286. (j) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846. (k) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 5520. (l) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (m) Gu, L.; Jin, C.; Liu, J.; Ding, H.; Fan, B. *Chem. Commun.* **2014**, *50*, 4643. (n) Zhu, T.-H.; Wang, S.-Y.; Tao, Y.-Q.; Wei, T.-Q.; Ji, S.-J. *Org. Lett.* **2014**, *16*, 1260. (o) Wang, L.; Sha, W.; Dai, Q.; Feng, X.; Wu, W.; Peng, H.; Chen, B.; Cheng, J. *Org. Lett.* **2014**, *16*, 2088. (p) Cao, J.-J.; Zhu, T.-H.; Wang, S.-Y.; Gu, Z.-Y.; Wang, X.; Ji, S.-J. *Chem. Commun.* **2014**, *50*, 6439. (q) Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z.-W.; Zhou, L. *Green Chem.* **2014**, *16*, 2418. (r) Liu, J.; Fan, C.; Yin, H.; Qin, C.; Zhang, G.; Zhang, X.; Yi, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 2145. (s) Xia, Z.; Huang, J.; He, Y.; Zhao, J.; Lei, J.; Zhu, Q. *Org. Lett.* **2014**, *16*, 2546.