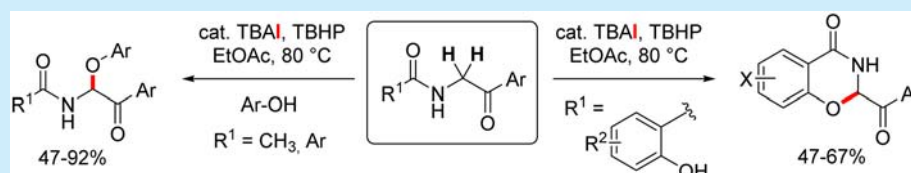


TBAI-Catalyzed Oxidative Cross-Coupling of Phenols and 2-Aminoacetophenones

Wei Xu and Boris J. Nachtsheim*

Institut für Organische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

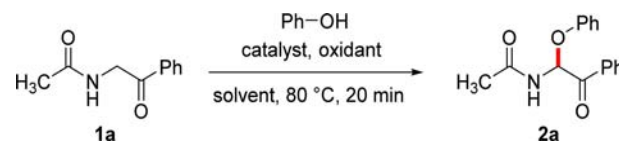
Supporting Information



ABSTRACT: An iodide-catalyzed oxidative cross-coupling between phenols and 2-aminoacetophenones has been developed. Using catalytic amounts of tetrabutylammoniumiodide (TBAI) as an iodine-containing catalyst and aqueous solutions of *tert*-butyl hydro-peroxide (TBHP) as the stoichiometric co-oxidant, a variety of α -phenoxyated 2-aminoacetophenones could be obtained in yields of up to 92% after remarkably short reaction times (20 min). This is a very rare example for an iodide-catalyzed intermolecular cross-coupling utilizing phenols. However, this efficient methodology could be further extended toward an intramolecular variant which gives direct access to a range of dihydro-4*H*-benzo[*e*][1,3]oxazin-4-ones.

The oxidative construction of C–O bonds from enolizable carbonyl compounds is a key transformation in organic synthesis.^{1,2} Besides organic peroxides and heavy metal salts, hypervalent iodine compounds have been widely utilized as effective mediators for these valuable transformations.^{3,4} It has recently been found that a simple catalytic system containing catalytic amounts of an iodide salt or molecular iodine, together with an external co-oxidant, can be very effective to perform such transformations.⁵ In a seminal work, Uyanik and Ishihara reported an oxidative cycloetherification of ketophenols mediated by in situ generated chiral quaternary ammonium hypiodites.^{6b} Very recently, the same group could apply this protocol toward an efficient enantioselective synthesis of α -tocopherols.^{6a} However, both protocols were restricted toward intramolecular oxidative C–O bond formations. Intermolecular oxygenations of sp^3 hybridized C–H bonds under similar conditions have been described, but so far all protocols are strictly limited to amines, carboxylic acids, or activated primary alcohols as oxygen-containing coupling partners.^{7–9} In this communication, we want to enhance the chemical space of (hypo)iodite-mediated cross-couplings by describing the first intermolecular oxidative C–O coupling using oxidatively labile phenols. As a model C-nucleophile we chose to use *N*-acyl 2-aminoacetophenone **1a**. By using molecular iodine as a catalyst and an aqueous TBHP solution as a co-oxidant we only detected traces of the desired product **2a** in the crude NMR (Table 1, entry 1). Changing the catalyst to potassium or sodium iodide resulted in the formation of **2a** in promising 52% and 48% yields, respectively (Table 1, entries 2 and 3). With copper(I) iodide no product formation was observed (Table 1, entry 4), while TBAI was the best iodine-containing catalyst yielding **2a** in 70% yield (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions for the Oxidative Coupling of *N*-Acyl α -Amino Acetophenone **1a and Phenol**



entry	catalyst	oxidant	solvent	yield (%) ^a
1	I ₂	aq TBHP	EtOAc	traces
2	KI	aq TBHP	EtOAc	52
3	NaI	aq TBHP	EtOAc	48
4	CuI	aq TBHP	EtOAc	0
5	TBAI	aq TBHP	EtOAc	70
6 ^b	TBAI	aq TBHP	EtOAc	52
7	TBAI	aq H ₂ O ₂	EtOAc	0
8	TBAI	oxone	EtOAc	0
9	TBAI	MeCO ₃ tBu	EtOAc	traces
10	TBAI	aq TBHP	DMSO	0
11	TBAI	aq TBHP	DMF	0
12	TBAI	aq TBHP	CH ₃ CN	traces
13	TBAI	aq TBHP	1,2-DCE	0

^aGeneral reaction conditions: **1** (0.2 mmol), phenol (1.0 mmol), catalyst (0.04 mmol), oxidant (0.7 mmol), solvent (3 mL), 80 °C, 20 min. ^b0.4 mmol of K₂CO₃ was added.

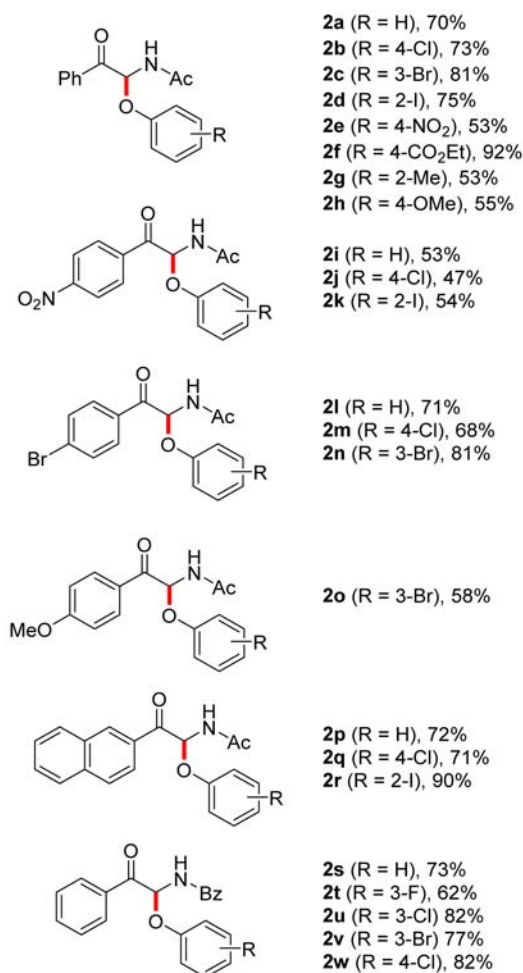
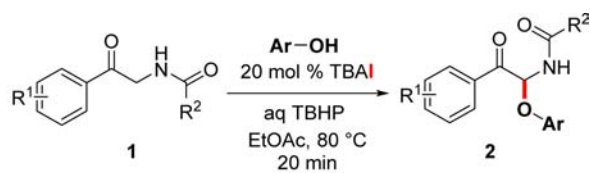
Addition of potassium carbonate as a base did not result in improved product yields (Table 1, entry 6). With other oxidants such as hydrogen peroxide, oxone (KHSO₅/KHSO₄/

Received: February 13, 2015

Published: March 12, 2015

K_2SO_4), or *tert*-butyl peracetate no product formation was observed (Table 1, entries 7–9). As solvent only ethyl acetate can be used in this transformation, whereas other polar aprotic solvents such as DMSO, DMF, MeCN, or 1,2-dichloroethane did not result in product formation (Table 1, entries 10–13). Therefore, we chose to take the optimal conditions as noted in Table 1 (entry 5) and investigated the substrate scope of this transformation (Scheme 1).

Scheme 1. Substrate Scope for the Direct Phenoxylation of 2-Aminoacetophenones 1^a



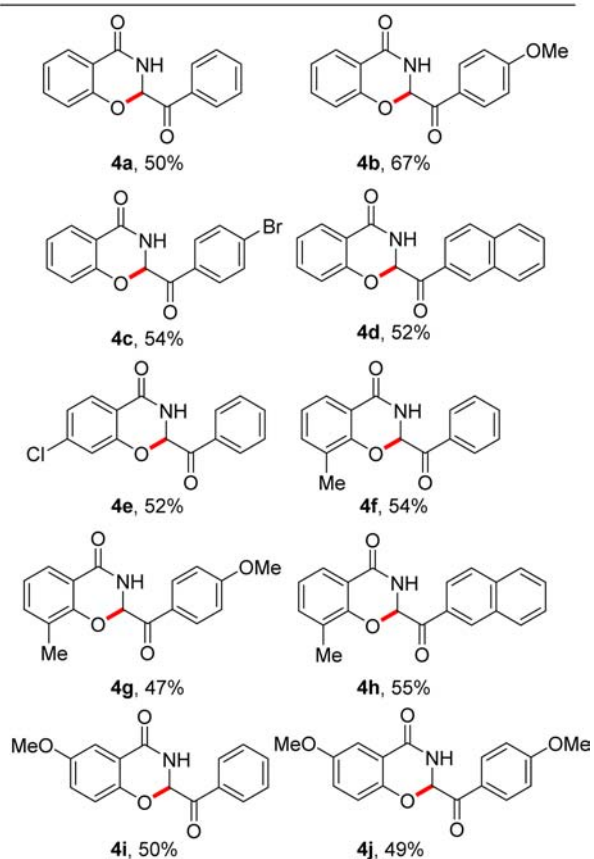
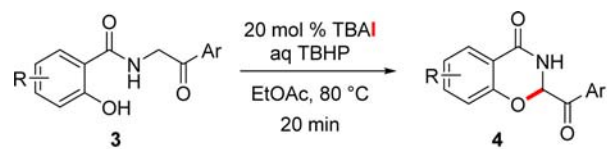
^aReaction conditions: **1** (0.2 mmol), Ar-OH (1.0 mmol), TBAI (0.04 mmol), aq TBHP (0.7 mmol), EtOAc, 80 °C.

First, a variety of differently substituted phenols were investigated. Halogenated phenol derivatives such as 4-chloro-, 3-bromo-, or 2-iodophenols can be applied giving the desired coupling products **2b–2d** in 73–81% yield. 4-Nitrophenol shows decreased reactivity; however, the desired product **2e** can be observed in 53% yield. 4-Carboxyethyl-substituted phenol reacted superior yielding **2f** (92%). Electron-rich phenols such as 2-methyl- and 4-methoxyphenol gave the

desired products **2g** and **2h** in 53% and 55% yield, respectively. Next, we introduced different substituents on the arene moiety of acetophenone. 4'-Nitro substitution resulted in decreased reactivity giving coupling products **2i–2k** in moderate yields (47–54%). The 4'-bromo substituted 2-aminoacetophenone derivative gave **2l–2n** in good yields between 68% and 81%. However, electron-rich 2-aminoacetophenones seem to be nonbeneficial for this transformation since its 4'-methoxy derivative gave **2o** in only 58% isolated yield. α -Amino-2-acetonaphthone gave a variety of cross-coupling products **2p–2r** in good to excellent yields (71–90%). Finally, we changed the nitrogen protecting group to *N*-benzoyl and observed a similar reactivity giving the desired products **2s–2w** in 62–82% yield. To further expand the substrate scope, we also investigated an intramolecular version of this reaction (Scheme 2).

For this purpose, we synthesized a variety of *N*-(2-hydroxybenzoyl)-protected α -aminoacetophenones **3** and reacted them under our optimized reaction conditions. To our delight, the desired dihydro-4*H*-benzo[*e*][1,3]oxazin-4-ones **4** can be formed directly in good yields (Scheme 2). Variation of the aryl substituent of the 2-aminoacetophenone with electron-

Scheme 2. Substrate Scope for the Direct Oxidative Synthesis of Dihydro-4*H*-benzo[*e*][1,3]oxazin-4-ones^a



^aReaction conditions: **3** (0.2 mmol), TBAI (0.04 mmol), aq TBHP (0.7 mmol), EtOAc, 80 °C.

donating and -withdrawing substituents gave products **4a–4d** in a close range of isolated yields between 50% and 67%. The *N*-(2-hydroxyaroyl) protecting group can be varied with halogen substituents, for example, to give **4e** in 52% yield. In addition, alkyl and alkoxy side chains are tolerated to yield products **4f–4j** in yields ranging from 49% to 55%.

To prove the structure of our cyclized products, in particular to verify that no further oxidation to the corresponding fully unsaturated 4*H*-benzo[*e*][1,3]oxazin-4-one occurred, we performed single crystal X-ray analysis. Compound **4h** formed single crystals which could be analyzed by X-ray diffraction analysis (Figure 1). Here we were happy to find that the X-ray diffraction data undoubtedly indicated formation of the proposed dihydro derivative.

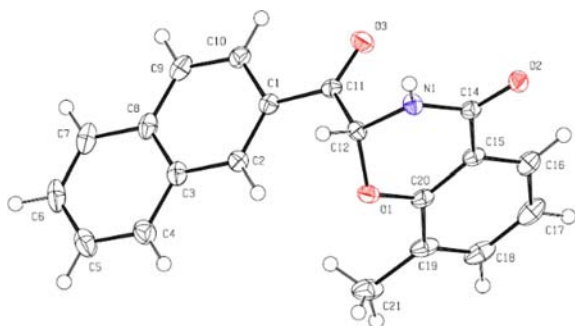
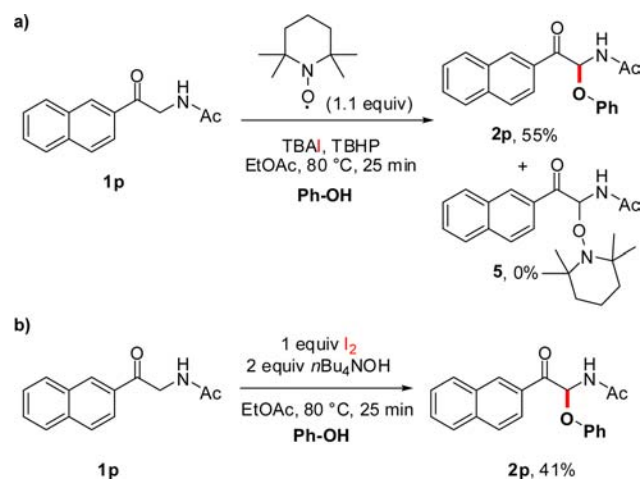


Figure 1. Plot of the X-ray crystallographic data of **4h**.

To elucidate the underlying reaction mechanism we performed two distinct control experiments. To exclude a radical-based mechanism we reacted *N*-acyl protected 2-amino-2-naphthophenone **1p** under our standard reaction protocol and additionally added TEMPO as a radical scavenger (Scheme 3a).

Scheme 3. Control Experiments

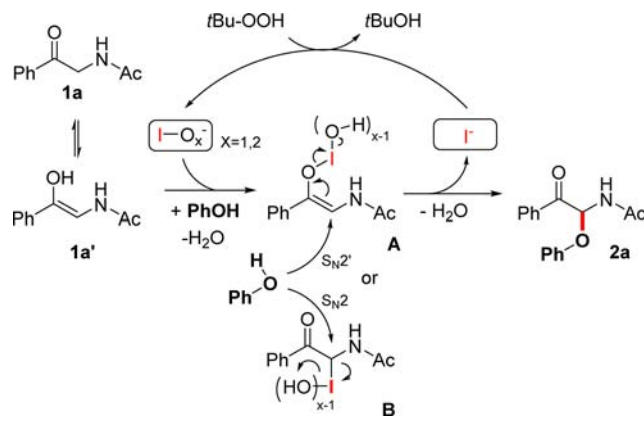


In this experiment, we observed the formation of **2p** in 55% yield and no TEMPO-bound intermediate such as **5** was detected. Therefore, we think that a radical-based reaction mechanism can be excluded. To prove the possible existence of hypoiodites (IO^-) as active species in this transformation, we reacted **1p** with stoichiometric amounts of molecular iodine and a 2-fold excess of $n\text{Bu}_4\text{NOH}$ without an additional co-oxidant (Scheme 3b). In this experiment the desired product **2p** could be obtained in an isolated yield of 41%, which is

significantly lower than the yield observed with the original protocol (72%). However, as already stated by Uyanik and Ishihara in their hypoiodite-mediated transformations,⁶ formation of **2p** under these conditions can be seen as a strong indicator that hypoiodite species are involved in the catalytic cycle.

Therefore, we propose a reaction mechanism as shown in Scheme 4. The enolized form of the starting material **1a'**

Scheme 4. Proposed Reaction Mechanism



condensates with an in situ generated (hypo)iodite species to generate oxygen- or carbon-iodinated species **A** or **B**. Depending on the nature of this intermediate a subsequent $\text{S}_{\text{N}}2'$ or $\text{S}_{\text{N}}2$ reaction occurs at the α -carbon to generate the desired product **2a**.

In summary we have described a convenient method for the direct oxidative coupling between phenols and α -aminoacetophenones. This reaction is a very rare example for a metal-free oxidative coupling between an oxidatively labile phenol and an α -enolic carbon atom. The unique substrate scope, the use of simple tetraalkylammonium iodides as oxidation catalysts, and the fact that easy to handle aqueous oxidants (TBHP) can be used render this novel transformation a convenient alternative to existing hypervalent iodine mediated α -oxygenations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data as well as ^1H and ^{13}C NMR spectra of compounds **2a–2w** and **4a–4g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: boris.nachtsheim@uni-tuebingen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding by the DFG (NA 955/1-1) and the Fonds der Chemischen Industrie (Sachkostenzuschuss) is gratefully acknowledged.

■ REFERENCES

(1) For reviews about the oxidative construction of C–O bonds, see: (a) Krylov, I. B.; Vil', V. A.; Terent'ev, A. O. *Beilstein J. Org. Chem.* **2015**, *11*, 92. (b) Mehta, V. P.; Punji, B. *RSC Adv.* **2013**, *3*, 11957. (c) Song, G. Y.; Wang, F.; Li, X. W. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Turner, N. J. *Chem. Rev.* **2011**, *111*, 4073. (e) Yoo, W. J.; Li, C. J. *Top. Curr. Chem.* **2010**, *292*, 281.

(2) For reviews about oxygenation of α -carbonyl bonds, see: (a) Streuff, J. *Synlett* **2013**, *24*, 276. (b) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (c) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143. (d) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

(3) *Hypervalent Iodine Chemistry: Topics in Current Chemistry*, Vol. 224; Wirth, T., Ed.; Springer: Berlin, 2003.

(4) For reviews, see: (a) Singh, F. V.; Wirth, T. *Chem.—Asian J.* **2014**, *9*, 950. (b) Dong, D. Q.; Hao, S. H.; Wang, Z. L.; Chen, C. *Org. Biomol. Chem.* **2014**, *12*, 4278. (c) Brown, M.; Farid, U.; Wirth, T. *Synlett* **2013**, *24*, 424. (d) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517. (e) Quideau, S.; Wirth, T. *Tetrahedron* **2010**, *66*, 5737. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (g) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (h) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893.

(5) For reviews, see: (a) Wu, X. F.; Gong, J. L.; Qi, X. X. *Org. Biomol. Chem.* **2014**, *12*, 5807. (b) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, *45*, 979. (c) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177.

(6) (a) Uyanik, M.; Hayashi, H.; Ishihara, K. *Science* **2014**, *345*, 291. (b) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.

(7) Recent examples for C–O bond forming reactions with iodine-containing catalysts, see: (a) Majji, G.; Guin, S.; Rout, S. K.; Behera, A.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 12193. (b) Boominathan, S. S. K.; Hu, W.-P.; Senadi, G. C.; Vandavasi, J. K.; Wang, J.-J. *Chem. Commun.* **2014**, *50*, 6726. (c) Yu, H.; Huang, W. H.; Zhang, F. L. *Eur. J. Org. Chem.* **2014**, *2014*, 3156. (d) Yu, H.; Shen, J. *Org. Lett.* **2014**, *16*, 3204. (e) Yu, H.; Zhang, F. L.; Huang, W. H. *Synlett* **2014**, *25*, 843. (f) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092. (g) Majji, G.; Guin, S.; Gogoi, A.; Rout, S. K.; Patel, B. K. *Chem. Commun.* **2013**, *49*, 3031. (h) Zhang, S.; Guo, L. N.; Wang, H.; Duan, X. H. *Org. Biomol. Chem.* **2013**, *11*, 4308. (i) Yoshimura, A.; Zhu, C. J.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Maskaev, A. V.; Zhdankin, V. V. *Chem. Commun.* **2013**, *49*, 4800. (j) Feng, J.; Liang, S.; Chen, S. Y.; Zhang, J.; Fu, S. S.; Yu, X. Q. *Adv. Synth. Catal.* **2012**, *354*, 1287. (k) Li, X. Q.; Zhou, C.; Xu, X. S. *ARKIVOC* **2012**, 150. (l) Liu, X.; Cheng, R.; Zhao, F. F.; Zhang-Negrerie, D.; Du, Y. F.; Zhao, K. *Org. Lett.* **2012**, *14*, 5480. (m) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331.

(8) Recent examples for (hypo)iodite-mediated oxidative aminations: (a) Chen, J.; Yan, W.-Q.; Lam, C. M.; Zeng, C.-C.; Hu, L.-M.; Little, R. D. *Org. Lett.* **2015**, *17*, 986. (b) Zhang, J.; Shao, Y.; Wang, Y.; Li, H.; Xu, D.; Wan, X. *Org. Biomol. Chem.* **2015**, DOI: 10.1039/C5OB00109A. (c) Sharif, M.; Gong, J.-L.; Langer, P.; Beller, M.; Wu, X.-F. *Chem. Commun.* **2014**, *50*, 4747. (d) Yuan, Y.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. *Org. Lett.* **2014**, *16*, 5410. (e) Sharif, M.; Chen, J.; Langer, P.; Beller, M.; Wu, X.-F. *Org. Biomol. Chem.* **2014**, *12*, 6359. (f) Wang, L.; Zhu, K.; Chen, Q.; He, M. *J. Org. Chem.* **2014**, *79*, 11780. (g) Li, D.; Yang, T.; Su, H.; Yu, W. *Adv. Synth. Catal.* **2014**, *356*, 3148. (h) Sun, K.; Wang, X.; Li, G.; Zhu, Z.; Jiang, Y.; Xiao, B. *Chem. Commun.* **2014**, *50*, 12880.

(9) Recent examples for (hypo)iodite catalysis in the synthesis of heterocycles: (a) Li, X.; Fang, M.; Hu, P.; Hong, G.; Tang, Y.; Xu, X. *Adv. Synth. Catal.* **2014**, *356*, 2103. (b) Naresh, G.; Kant, R.; Narender, T. J. *Org. Chem.* **2014**, *79*, 3821. (c) Huang, H.-M.; Li, Y.-J.; Ye, Q.; Yu, W.-B.; Han, L.; Jia, J.-H.; Gao, J.-R. *J. Org. Chem.* **2014**, *79*, 1084. (d) Gogoi, A.; Modi, A.; Guin, S.; Rout, S. K.; Das, D.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 10445. (e) Zhao, D.; Wang, T.; Shen, Q.; Li, J.-X. *Chem. Commun.* **2014**, *50*, 4302. (f) Naresh, G.; Narender, T. *RSC Adv.* **2014**, *4*, 11862.