Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Cai, Z. li and L. Jin, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB00022G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB00022G

Journal Name

COMMUNICATION

Nickel-Catalyzed Product-Controllable Amidation and Imidation of sp^3 C-H Bond in Substituted Toluenes with Sulfonamides

Ze-lin Li[a], Li-kun Jin[a],and Chun Cai*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

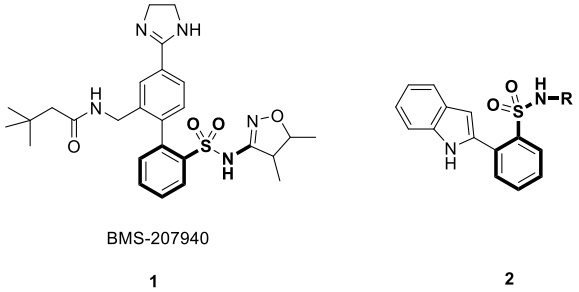
DOI: 10.1039/x0xx00000x

www.rsc.org/

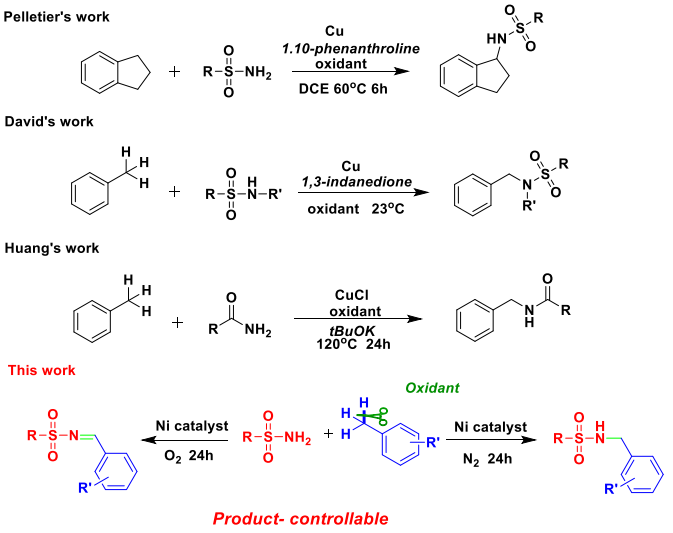
A nickel-catalyzed product-controllable imidation and amidation of sp^3 C-H bond in substituted toluenes with sulfonamides were developed. Based on the change of reaction time and atmosphere from N_2 to O_2, this reaction proceeded in high yields and excellent selectivity under different conditions. Mechanistic details were also described.

The effective method for the formation of C-N bonds in aryl imines and amines plays an important role in the organic synthetic chemistry because of the high prevalence of nitrogen-containing molecules in natural and pharmaceuticals[1]. Meanwhile, drugs containing the sulfonamide functional group[2] (Scheme 1, **1** and **2**) have long been identified as a potential ETA antagonists and showed good performance in the treatment of congestive heart failure.

In the past few years, direct transformation from C-H bonds to C-N bonds had attracted much attention and great progress[3-5] had been made. For example, ligand assisted copper-catalyzed amination of indane with benzenesulfonamide was reported in2006[6a], it provided a new route for the amidation of allylic and benzylic C−H bonds. Then, David and his co-workers reported a. ligand assisted amidation of primary benzylic C-H bonds by using toluene as the partner[6b]. Recently, a ligand-free copper-catalyzed amidation of benzylic hydrocarbons and inactive aliphatic alkanes with simple amides was developed by Huang's group[6c], this process was efficient in the formation of C−N bond and the scope was wide which tolerated a range of amides. However, the selectivity of amidation and imidation process has not been investigated. Previously, some metal catalysts such as ruthenium, palladium, and copper were used in the amidation of sp^3 C-H bond. Nickel is one of the most abundant, inexpensive, and environmentally friendly metals. To the best of our knowledge, no example concerning nickel-catalyzed selective amidation and imidaition of C-H bonds was reported. With respect to imidation, several catalytic systems have been reported[7]. However, the high cost of metal catalyst and poor selectivity inhibit its wide application in synthetic chemistry. In 2012[7d], a new method for oxidative imidation of toluene deriv-



Scheme 1. Drugs containing the sulfonamide functional group.

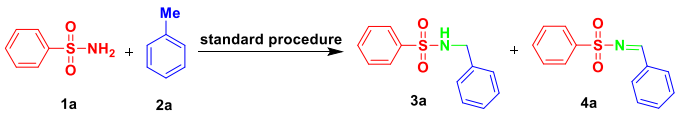


Scheme 2. Representative examples of amidation of sp^3 C-H bond in substituted toluenes.

[a]*Chemical Engineering College, Nanjing University of Science and Technology, 200 Xiao Ling Wei Street, Nanjing, Jiangsu, People's Republic of China*
** Corresponding Author E-mail: c.cai@ njust.edu.cn*

atives with sulfonamides was raised, but the catalyst consist of Pd-Au complexes was so expensive from the point of economy. Our group has developed a nickel-catalyzed regioselective cross-dehydrogenative coupling of inactive C(sp^3)–H bonds with indole derivatives to form C-C bonds[8]. So we next consider whether this system can be used in forming C-N bonds. Inspired by these, we herein demonstrated a new method for the selective amidation and imidation of sp^3 C-H bond in substituted toluenes with sulfonamides under solvent-free conditions.

Table 1. Optimization of the reaction conditions[a]



Entry	Cat.	Oxidant	Temp (°C)	Time (h)	Atm	3a(%)[b]	4a(%)[b]
1	$NiCl_2$	DTBP	120	24	Air	56	15
2	$NiCl_2$	DTBP	120	24	N_2	69	Trace
3	$NiBr_2$	DTBP	120	24	N_2	35	Trace
4	$NiCl_2(PPh_3)_2$	DTBP	120	24	N_2	20	0
5	$Ni(acac)_2$	DTBP	120	24	N_2	28	0
6	$Ni(OTf)_2$	DTBP	120	24	N_2	13	0
7	$Ni(OAc)_2$	DTBP	120	24	N_2	75	Trace
8	CuCl	DTBP	120	24	N_2	30	0
9	$Cu(OAc)_2$	DTBP	120	24	N_2	25	0
10	$FeCl_2$	DTBP	120	24	N_2	0	0
11	$CoCl_2$	DTBP	120	24	N_2	0	0
12	$Ni(OAc)_2$	TBHP[c]	120	24	N_2	15	0
13	$Ni(OAc)_2$	TBHP[d]	120	24	N_2	33	0
14	$Ni(OAc)_2$	TBPB	120	24	N_2	Trace	0
15	$Ni(OAc)_2$	DDQ	120	24	N_2	0	0
16	$Ni(OAc)_2$	$K_2S_2O_8$	120	24	N_2	Trace	0
17	$Ni(OAc)_2$	DTBP	100	24	N_2	24	0
18	$Ni(OAc)_2$	DTBP	140	24	N_2	50	0
19	$Ni(OAc)_2$	DTBP	120	24	Air	70	13
20	$Ni(OAc)_2$	DTBP	120	24	O_2	3	72
21	$Ni(OAc)_2$	DTBP	120	18	O_2	41	40
22	$Ni(OAc)_2$	DTBP	120	12	O_2	59	33
23	$Ni(OAc)_2$	DTBP	120	6	O_2	Trace	Trace

[a]Reaction condition: sulfonamide (0.5 mmol), cat.(10%mmol), toluene (1.5 mL), oxidant (2 equiv.). [b] Isolated yield. [c]70% aq. [d] 5N in decane.

Initially, benzenesulfonamide **1a** and toluene **2a** was chosen as model substrates to identify suitable reaction conditions (Table 1). To our delight, the yield was increased to 69% when we change atmosphere from air to N_2 (entry 2). Next, the choice of catalyst and oxidant were made, $Ni(OAc)_2$ (entries 3–11) and DTBP (entries 12–16) proved to be critical to the reaction efficiency. In addition, we explored the influence of reaction temperature on yield. Unfortunately, increasing the temperature and decreasing the temperature all decrease the yields (entries 17–18). After the optimization process of catalyst, oxidant, and reaction temperature, the following amidation was performed under our standard conditions: 10 mol% of $Ni(OAc)_2$ as the catalyst, 2 equiv. of DTBP as the oxidant. The reaction temperature was maintained at 120 °C under N_2. Furthermore, the condition of imidation was also investigated. The imidation product yield was improved under O_2 (entries 7, 19 and 20).The yields of imination product was improved with the increase of reaction time (entry 20-23).

With a set of reaction conditions in hand, we then investigated the range of sulfonamide coupling partners that could be employed. Gratifyingly, this transformation showed excellent tolerance for sulfonamide derivatives and provided the corresponding amidation products in good to excellent yields. For example, benzenesulfonamides containing electron-donating groups (Me and OMe) could produce the desired products in 70% and 72% yields. Benzamides bearing electron-withdrawing groups, such as Cl and Br, proceeded the reaction in relatively lower yields (65% and 63%). Methanesulfonamide was also tolerated in the nickel-catalyzed amidation methodology. To our delight, xylenes and mesitylene coupled with benzamide well. Halogen-containing toluene was also tolerated and gave the N-alkylation products in good yields, however, the yields of ortho and meta substituted toluene was relatively lower than para substituted toluene because of steric effect.

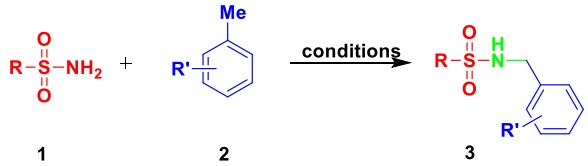
Furthermore, the imidation reaction of toluenes was investigated (Table 3). For the reaction of toluene with benzenesulfonamide, 72% isolated yield was obtained. Meanwhile, the reaction of toluenes and 4-methylbenzenesulfonamide proceeded well too.

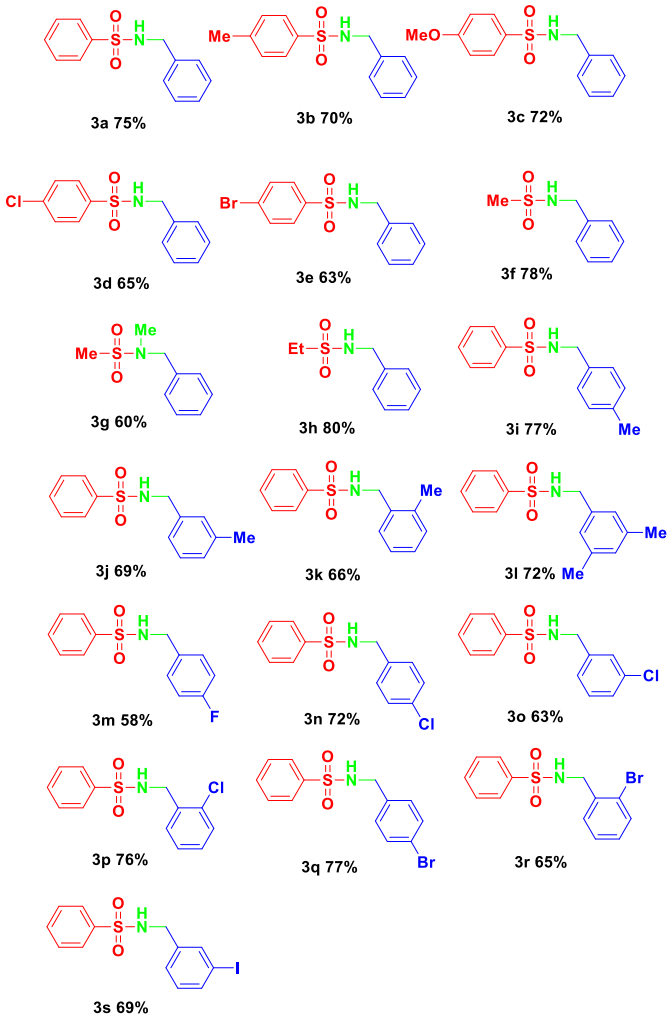
Some experiments were investigated to get insight into the reaction mechanism. Firstly, under standard conditions, 2.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) were added, no desired product was detected in the reaction mixture (determined by GC–MS; Scheme3, 1 and 2), which implied that the radical process proceeded in both amidation and imination. Subsequently, a series of reactions were conducted.

As shown in Scheme4, **(1)-(3)**, the results indicated that imidation progress is mainly consistent with the oxidative dehydrogenation pathway rather than aldehyde amine condensation. Therefore, a possible mechanism based on our experimental results and previous reports[9] for the amidation and imidation of benzylic sp^3 C-H bonds is proposed in Scheme 5. Our proposed mechanism begins with the decomposition of DTBP to produce a tert-butoxy radical and tert-butoxide anion assisted by $Ni(OAc)_2$. Then, the tert-butoxy radical abstract a hydrogen atom from toluene to form a benzyl radical. At the same time, sulfonamides react with the tert-butoxide anion and provides anion intermediate (C). Subsequently, the benzyl radical reacts. with intermediate (C) to provide radical anion (D). Next, (D) affording the amidation product (E) via SET process. Finally, (E) undergoes an oxidative dehydrogenation progress to produce the imidation product (F) assited by $Ni(OAc)_2$.

View Article Online
DOI: 10.1039/C7OB00022G

Table 2. Nickel-catalyzed amidation of sp^3 C-H bond in substituted toluenes with sulfonamides

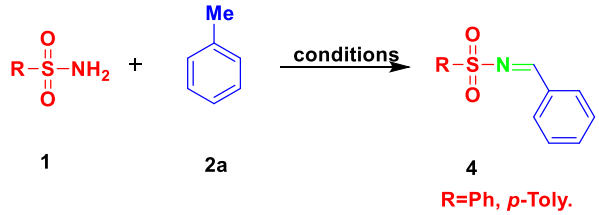




[a]Reaction condition: sulfonamide (0.5 mmol), cat. (10% mmol), toluene derivatives (1.5 mL), oxidant (2 equiv.), 24h under N_2

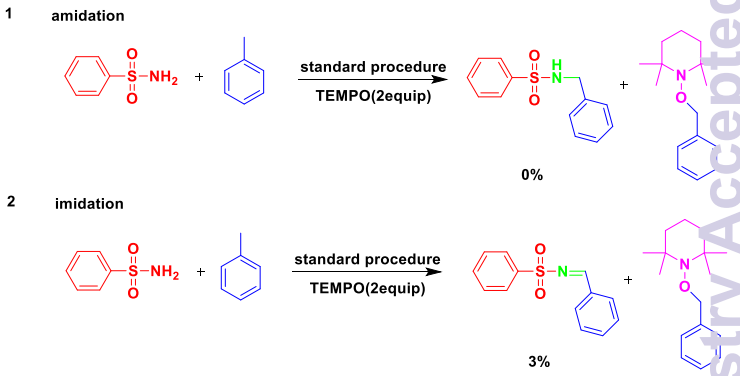
Nickel appears to play two roles in our system. First, nickel catalyzes the decomposition of DTBP to generate tert-butoxy radical and tert-butoxide anion, which are the species that cleave the C–H bond of the primary benzylic hydrocarbons and the N-H bond of sulfonamides. Second, nickel participates in the imidation after the amidation progress to form the imidation product.

Table 3. Two representative nickel-catalyzed imidation substrates were examined.



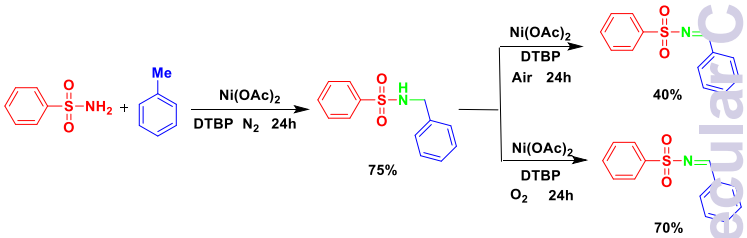
[a]Reaction condition: sulfonamide (0.5 mmol), cat. (10% mmol), toluene derivatives (1.5 mL), oxidant (2 equiv.), 24h under O_2.

Scheme 3. Control experiments.

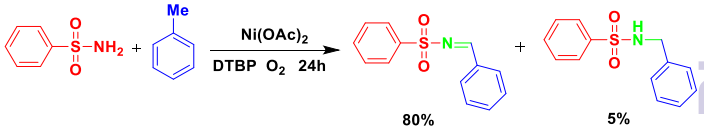


Scheme 4. Control experiments.

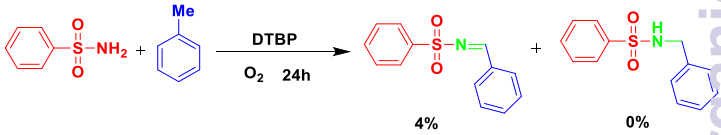
(1)



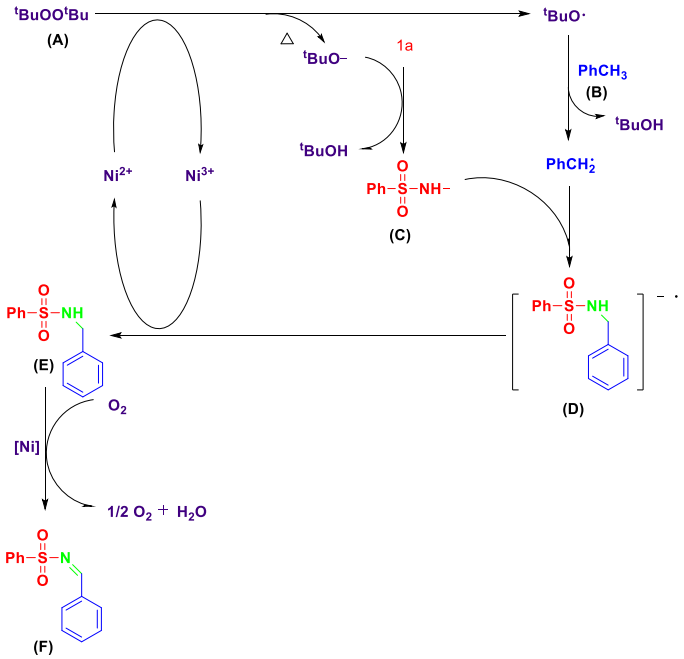
(2)



(3)



Scheme 5. Possible mechanism.



Conclusions

In summary, we described an efficient and excellent chemo-selective nickel-catalyzed amidation and imination of primary benzylic hydrocarbons and sulfonamides. The protocol uses cheap $Ni(OAc)_2$ as the catalyst, DTBP as the oxidant under ligand-free and solvent-free conditions. Worth noting is that the reactions are influenced by oxygen and reaction time. Besides, benzenesulfonamide, methanesulfonamide and a variety of toluene derivatives were all tolerated well in this procedure. Further studies along mechanistic details and more mild reaction conditions are under investigation.

Notes and references

(1) (a) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem., Int. Ed*. 2011, **50**, 1380–1383. (b) X.-X. Zhang, W.-T. Teo, P. W. H. J. Chan, *Organomet. Chem*. 2011, **696**, 331–337. (c) J. M. Chong and T.-R. Wu, *J. Am. Chem. Soc.*, 2006, **128**, 9646. (d) T. Mita, J.-Y. Chen, M. Sugawara and Y. Sato, *Angew. Chem., Int. Ed*., 2011, **50**, 1393. (e) S. E. Denmark and T. W. Wilson, *Nat. Chem*., 2010, **2**, 937.

(2) (a) N. Murugesan, Z. Gu, P. D. Stein, S. Bisaha, S. Spergel, R. Girotra, V. G. Lee, J. Lloyd, R. N. Misra, J. Schmidt, *J. Med. Chem.* 1998, **41**, 5198–5218. (b) N. Murugesan, Z. Gu, S. Spergel, M. Young, P. Chen, A. Mathur, L. Leith, M. Hermsmeier, E. C.-K. Liu, R. Zhang, *J. Med. Chem.* 2003, **46**, 125–137.

(3) Representative intramolecular metal-nitrene based amidations: (a) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem., Int. Ed.* 2002, **41**, 3465–3468. (b) J.-L. Liang, S.-X. Yuan, J.-S. Huang, C.-M. Che, *J. Org. Chem.* 2004, **69**, 3610–3619. (c) M. Kim, J. V. Mulcahy, C. G. Espino, Du Bois, *J. Org. Lett.* 2006, **8**, 1073–1076. (d) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem., Int. Ed.* 2008, **47**, 6825–6828. (e) K. W. Fiori, C. G. Espino, B. H. Brodsky, J. DuBois, *Tetrahedron* 2009, **65**, 3042–3051. (f) M. Yang, X. Jiang, Z.-J. Shi, *Org. Chem. Front.* 2015, **2**, 51–54. (g) Q. Qin, S. Yu, *Org. Lett.* 2015, **17**, 1894–1897. (h) A. Verma, S. Patel, Meenakshi, A. Kumar, A. Yadav, S. Kumar, S. Jana, S. Sharma, C. D. Prasad and S. Kumar, *Chem. Commun.*, 2015, **51**, 1371--1374

(4) Representative intermolecular metal-nitrene based amidations: (a) S.-M. Au, J.-S. Huang, C.-M. Che, W.-Y. Yu, *J. Org. Chem*. 2000, **65**, 7858. (b) Y. Cui, C. He, *J. Am. Chem. Soc.* 2003, **125**, 16202. (c) C. Liang, F. Robert-Peillard, C. Fruit, P. M€uller, R. H. Dodd, P. Dauban, *Angew. Chem., Int. Ed.* 2006, **45**, 4641–4644. (d) Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* 2007, **9**, 3813. (e) X. Liu, Y. Zhang, L. Wang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* 2008, **73**, 6207. (f) H. Lu, V. Subbarayan, J. Tao, X.- P. Zhang, *Organometallics* 2010, **29**, 389–393. (g) D. Ramesh, U. Ramulu, K. Mukkanti, Y. Venkateswarlu, *Tetrahedron Lett.* 2012, **53,** 2904–2908. (h) F. Teng, S. Sun, Y. Jiang, J.-T. Yu, J. Cheng, *Chem. Commun.* 2015, **51**, 5902–5905.

(5) For recent reviews: (a) H. M. L. Davies, M. S. Long, *Angew. Chem., Int. Ed.* 2005, **44,** 3518. (b) H. M. L. Davies, *Angew. Chem., Int. Ed.* 2006, **45**, 6422. (c) H. M. L. Davies, J. R. Manning, *Nature* 2008, **451**, 417–424. (d) C.-M. Che, V. K.-Y. Lo, C.-Y. Zhou, J.-S. Huang, *Chem. Soc. Rev.* 2011, **40**, 1950–1975.

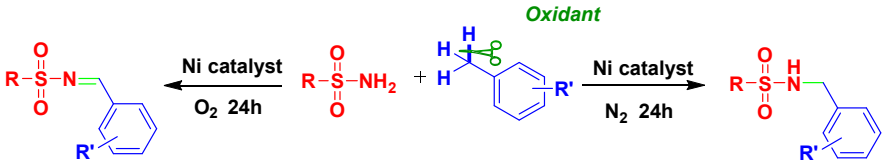
(6) (a) G. Pelletier, D. A. Powell, *Org. Lett.* 2006, **8**, 6031-6034. (b) D. A. Powell, H. Fan, *J. Org. Chem.* 2010, **75**, 2726-2729. (c) H.-T. Zeng, J. Huang, *Org. Lett.* 2015, **17**, 4276-4279.

(7) (a) B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem., Int. Ed.* 2010, **49**, 1468–1471. (b) X.-J. Cui, Y. Zhang, F. Shi, Y. Q. Deng, *Chem. Eur. J.* 2011, **17**, 1021 – 1028. (c) C.-Z. Liu, S.-H. Liao, Q. Li, S.-l. Feng, Q. Sun, X.-C. Yu, Q. Xu, *J. Org. Chem.* 2011, **76**, 5759-5773. (d) X.-J. Cui, F. Shi, Y.-Q. Deng, *Chem. Commun.* 2012, **48**, 7586–7588. (e) R, Cano, D.- J, Ramon, M. Yus, *J. Org. Chem.* 2011, **76**, 5547-5557.

(8) Li.-K. Jin, L. Wan, J. Feng, C. Cai, *Org. Lett.* 2015, **17**, 4276-4279.

(9) (a) K. Yamaguchi, N. Mizuno, *Angew. Chem., Int. Ed.* 2003, **42**, 1480–1483. (b) J.-R. Wang, Y. Fu, B.-B. Zhang, X. Cui, L. Liu, Q.-X. Guo *Tetrahedron Lett.* 2006, **47**, 8293–8297. (c) Y.-M. Zhang, H. Fu, Y.-Y. Jiang, Y.-F. Zhao, *Org. Lett.* 2007, **9**, 3813-3816. (d) R.-H. Fan, W.-X. Li, D.-M. Pu, L. Zhang, *Org. Lett.* 2009, **11**, 1425-1428. (e) S. Guin, S. K. Rout, A. Banerjee, S. Nandi, B. K. Patel, *Org. Lett.* 2012, **20**, 5294-5297. (f) S. Lei, Y.-Y. Mai, C.-J. Yan, J.-W. Mao, H. Cao, *Org. Lett.* 2016, **18**, 3282-3285. (g) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* 2013, **135**, 5308–5311.

View Article Online
DOI: 10.1039/C7OB00022G



Graphical abstract