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A direct facile and effective synthesis of various 1,1-heterodiaryl alkenes through Pd catalyzed cross coupling reaction using *N*-tosylhydrazones via C–OH bond activation

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ABSTRACT

At this event for the first time, the direct arylation with the generation of a facile and effective process for the synthesis of alkenes has been established through in situ C–OH activation afterward Pd catalyzed C–C bond formation of heteroarenols with *N*-tosylhydrazones. The noticeable features of these reactions are (1) No stoichiometric organometallic reagents desired, (2) No necessity of halides or pseudohalides (3) Environmentally benign, low toxic, and step economical reaction, (4) Easy to handle, mild conditions required, and give moderate to excellent yield.

The heterodiaryl compounds are found in numerous naturally occurring compounds and major pharmacologically active substances exhibiting an extensive range of biological activity.[1,2] Moreover, they also possess numerous applications in materials sciences. They have directed extensive efforts devoted to a variation of synthetic methodologies and are studied widely over decades. In recent decades, α-substituted heterodiaryl olefins have also revealed numerous biological activities such as anti-tubulin[3] and cytotoxicity activity[4] and precursors of some important biologically active compounds.[5,6] Though, their various application in medicinal chemistry, very limited scopes are accessible for synthesis.[6–10] To enhance the scope of this class of derivatives; a novel, robust, effective, low toxic, inexpensive starting material, and environmentally companionable procedure is required.

Generally, traditional methods to prepare 1,1-diarylalkenes are typically synthesized by heck reaction,[11] Grignard reaction,[4] or by metal-catalyzed reactions using expensive, toxic, air/moisture sensitive organometallic reagents such as organotin,[10] organozinc,[8] organoboron,[7] oraganolithium, organomagnesium salts,[12] vinyl phosphates,[7] etc. Organometallic reagents are classically synthesized from heteroaryl halides using harsh reaction conditions such as halogen–lithium exchange reactions which necessitate low temperatures, inert atmosphere, and they are highly flammable.[2,13] It is a challenging reaction on industrial scale. Further, mostly all methods involve pre-activation of the both coupling partners which is inherently wasteful. Since, the insertion of the activating group (pseudo) of halides itself is not trivial, it often requires several steps and hazardous chemicals such as $POCl_3$, $SOCl_2$, PCl_5, PBr_3, $POBr_3$ etc. from various heteroarenols,[14,15] and therefore generates waste from reagents, solvents, and purifications. Hence, it is not a desirable approach.

For the advancement of feasible, environmentally compatible, and cheap chemical processes our attention has been moved to the novel type of coupling partners C–H activation[16–18] and C–OH activation.[19] The direct arylation of C–H bond activation is known to suffer from regioselective and over functionalization problems, while the direct arylation of heteroarenols C–OH bond activation is chemoselective, readily accessible, stable, low in toxicity and an inexpensive alternative of heteroaryl halides[14,20–23] (Fig. 1).

On the other hand, *N*-tosylhydrazones have emerged as a new type of versatile coupling partners because of their various valuable applications in synthesis.[24–30] They are swiftly synthesized from the corresponding ketones and can be used readily as precursors for the generation of the metal–carbene complex through the preparation of diazo compounds without employing any organometallic reagents. Further, to the best of our knowledge no single example of C–OH bond activation has hitherto been unreported with *N*-tosylhydrazones. In this context, inspired from

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0040-4039/

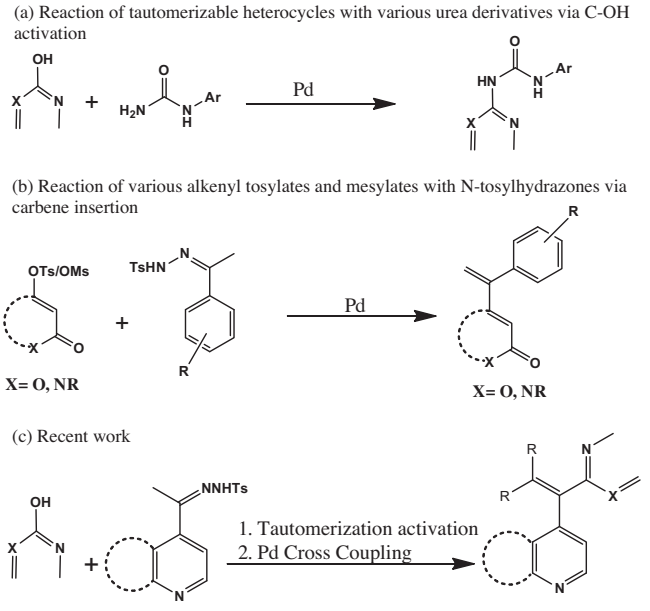


Figure 1. Recent and previous work of our group.

our previous work;[19,27] we have reported Pd catalyzed cross coupling of heteroarenols with *N*-tosylhydrazones (Fig. 1).

Herein, we represent a novel, effective, and alternate approach for the synthesis of 1,1-heterodiaryl alkenes by using Pd catalyzed cross coupling reaction of tautomerizable heterocycles with various *N*-tosylhydrazones via in situ C–OH activation.

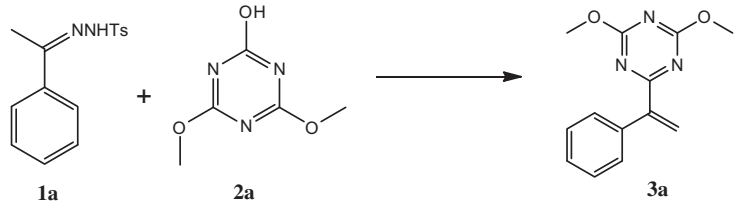
In our initial exploration to examine the optimum conditions for the direct synthesis of various 1,1-heterodiaryl alkene derivatives using mild reaction conditions, first 4,6-dimethoxy-1,3,5-triazin-2-ol (**1b**) was activated in situ with the phosphonium reagent, followed by C=C bond generation using acetophenone *N*-tosylhydrazones (**2a**) (Table 1, entry 1). These were the essential variety of C–OH bond activation by phosphonium coupling and subsequent Pd-catalyzed C=C coupling with *N*-tosylhydrazones in a one pot synthesis (Table 1).

To scrutinize the efficacy of the reaction firstly we activate 4,6-dimethoxy-1,3,5-triazin-2-ol (**1b**) using PyBroP. Kang et al. firstly proposed in situ generations of C–OH bond activation of a tautomerizable heterocycle, and demonstrated a wider range of functional group tolerance. For the most appropriate phosphonium coupling condition we get: PyBroP (1.2 equiv) and triethylamine (2 equiv) in 1,4-dioxane at rt for 2 h. However we have also summarized the results with the other phosphonium coupling reagents such as (BOP, PyBOP, BrOP, and PyAOP) but they were not found to be very productive. (Table 1).

After the activation of the C–OH bond, we inspected the numerous cross-coupling reaction conditions for C=C bond formation using *N*-tosylhydrazones as a coupling partner employing our previously optimized catalyst system: $Pd_2(dba)_3$ (1.5 mol %), *t*-BuBrettphos (3 mol %), in 1,4-dioxane at 90 °C for 1–2 h. To our delight, the desired coupling product was isolated in 87% yield (see Table 1) achieved the highest yield among all the other ligands. Form our observations we found that Xphos is also very good catalyst and gives better yield upto 83% and one can be used as an option of *t*-BuBrettphos at higher concentration. Inspired by preliminary results we continued to enhance the yield by screening the ligands, bases, and solvents for viability of the coupling tactics. The results of the reaction optimization are summarized in (Table 1, ESI).

Afterward, successful completion of the optimistic reaction outcomes, the substrate scope with respect to both coupling partners was discovered. First, we investigated a variety of

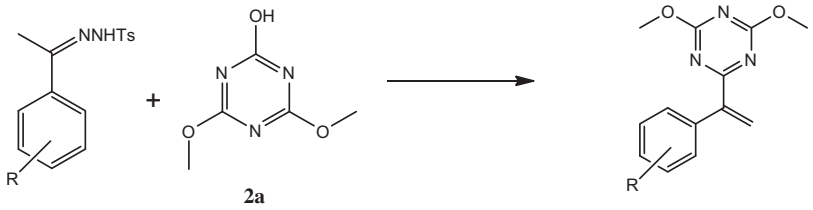
Table 1
Reaction optimization[a]

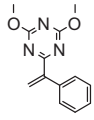
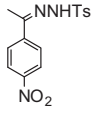
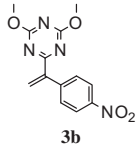
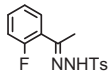
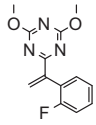
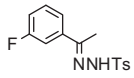
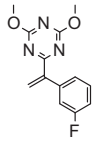
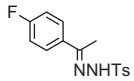
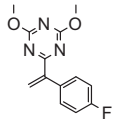
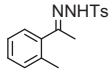
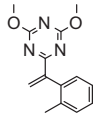
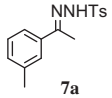
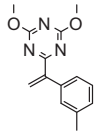
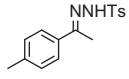
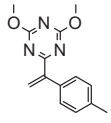
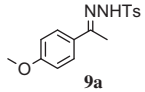
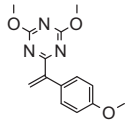


Phosphonium coupling			Pd catalyzed C=C coupling				
Entry	Phos-phonium salt	Solvent	Catalyst	Ligand	Base	Solvent	Yield[b] %
1	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	Xphos	Cs_2CO_3	1,4-Dioxane	83
2	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	1,4-Dioxane	37
3	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	Josiphos	Cs_2CO_3	1,4-Dioxane	49
4	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	1,4-Dioxane	67
5	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	1,4-Dioxane	53
6	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	Cs_2CO_3	1,4-Dioxane	87
7	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	LiOtBu	1,4-Dioxane	81
8	PyBroP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	KOtBu	1,4-Dioxane	63
9	BOP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	NaOtBu	1,4-Dioxane	61
10	BrOP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	Cs_2CO_3	THF	57
11	PyBOP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	Cs_2CO_3	Toluene	74
12	PyAOP	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	Cs_2CO_3	Acetonitrile	65
13	HATU	1,4-Dioxane	$Pd_2(dba)_3$	*t*-BuBrettphos	Cs_2CO_3	DMF	53
14	PyBroP	1,4-Dioxane	$Pd(OAC)_2$	*t*-BuBrettphos	Cs_2CO_3	1,4-Dioxane	59
15	PyBroP	1,4-Dioxane	$Pd(Ph_3P)2Cl_2$	*t*-BuBrettphos	Cs_2CO_3	1,4-Dioxane	43
16	PyBroP	1,4-Dioxane	$Pd(Ph_3P)_4$	*t*-BuBrettphos	Cs_2CO_3	1,4-Dioxane	48
17	PyBroP	1,4-Dioxane		*t*-BuBrettphos	Cs_2CO_3	1,4-Dioxane	0

[a] Phosphonium coupling: Ar-OH (1 mmol), Phosphonium salt (1.30 mmol), Et_3N (2.0 mmol), solvent (5.0 mL), rt, 2 h; Pd catalyzed C=C coupling: Catalyst: 5 mol %, Ligand: 3 mol %, *N*-tosylhydrazone 1.0 mmol, Base: 3.0 mmol, Solvent: 5 mL, at 100 °C for 2 h.
[b] Isolated yields.

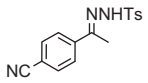
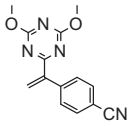
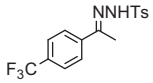
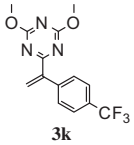
Table 2
Scope of the reaction of a variety of *N*-tosylhydrazones with tautomerizable heterocycles[a]



Entry	*N*-Tosylhydrazones	Product		Yield[b]
1	 **1a**	 **3a**	**3a**	87
2	 **2a**	 **3b**	**3b**	93
3	 **3a**	 **3c**	**3c**	86
4	 **4a**	 **3d**	**3d**	62
5	 **5a**	 **3e**	**3e**	74
6	 **6a**	 **3f**	**3f**	63
7	 **7a**	 **3g**	**3g**	46
8	 **8a**	 **3h**	**3h**	71
9	 **9a**	 **3i**	**3i**	80

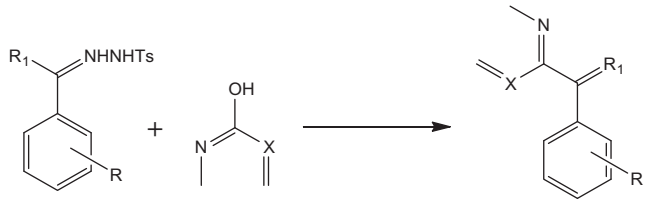
(*continued on next page*)

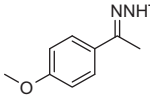
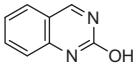
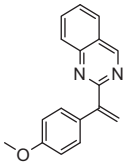
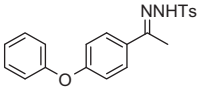
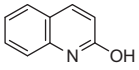
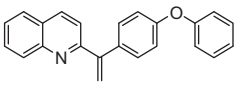
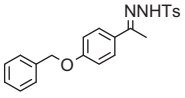
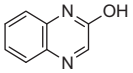
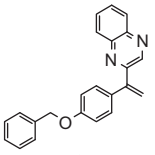
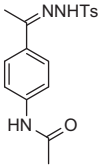
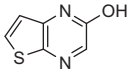
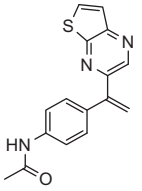
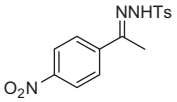
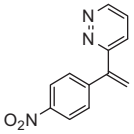
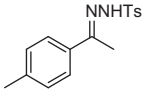
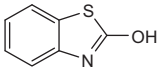
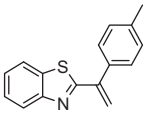
Table 2 (*continued*)

Entry	*N*-Tosylhydrazones	Product		Yield[b]
10		 **3k**	**3j**	87
11	 **11a**	 **3k**	**3k**	83

[a] Reaction condition: Ar-OH: 1.0 mmol, PyBroP: (1.3 mmol) and Et_3N: (2.0 mmol) in 1,4-dioxane: 5 mL at room temp for 2 h; then, $Pd_2(dba)_3$: 5.0 mol %, *t*-BuBrettphos: 3 mol %, *N*-tosylhydrazone: 1.0 mmol, CS_2CO_3: 3.0 mmol, and 1,4-dioxane: 5 mL, at 100 °C for 2 h.
[b] Isolated yields.

Table 3
Scope of the reaction of a variety of *N*-tosylhydrazones with various tautomerizable heterocycles[a]



Entry	*N*-Tosylhydrazones	Heteroarenols	Product		Yield[b]
1				**3l**	87
2				**3m**	73
3				**3n**	69
4				**3o**	77
5				**3p**	79
6				**3q**	80

[a] Reaction condition: Ar-OH: 1.0 mmol, PyBroP: (1.3 mmol) and Et_3N: (2.0 mmol) in 1,4-dioxane: 5 mL at room temp for 2 h; then, $Pd_2(dba)_3$: 5.0 mol %, *t*-BuBrettphos: 3 mol %, *N*-tosylhydrazone: 1.0 mmol, CS_2CO_3: 3.0 mmol, and 1,4-dioxane: 5 mL, at 100 °C for 2 h.
[b] Isolated yields.

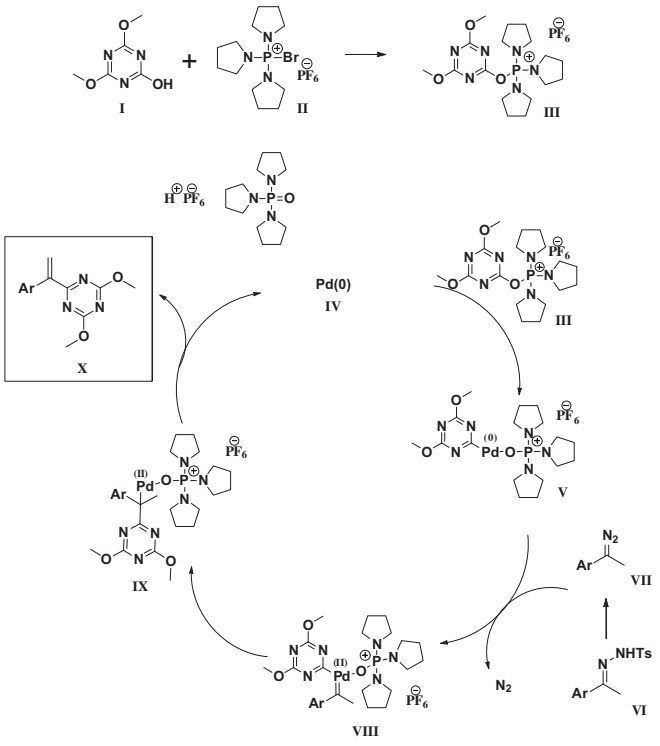


Figure 2. Proposed reaction mechanism.

N-tosylhydrazones with 4,6-dimethoxy-1,3,5-triazin-2-ol through Pd catalyzed direct arylation via C–OH bond activation (Table 2) for the generation of various 1,1-heterodiaryl olefin derivatives. The acquired results summarized in Table 2 explain that the enhanced conditions evidenced are to be simplified for the coupling of *N*-tosylhydrazones with 4,6-dimethoxy-1,3,5-triazin-2-ol.

The tosylhydrazones bearing electron donating groups were efficaciously engaged and afforded good yields at their C2, C3 and C4 positions (entries 6–9, Table 2), formed their analogous adducts in good to excellent yields. The reaction was also well-organized with *N*-tosylhydrazones containing electron-withdrawing groups, producing excellent yields of the corresponding coupling products (entries 2–5, 10–11; Table 2). In general, diverse *N*-tosylhydrazones were found to couple smoothly with tautomerizable heterocycles to give the corresponding adducts in decent yields.

Next, the prospect of variation in tautomerizable heteroarenols involving quinazoline, quinoline, quinoxaline, thieno pyrazine, pyridazine was also explored (Table 3). The list of the compounds summarized in Table 3, suggest that the Pd catalyzed PyBroP enabled phosphonium coupling condition was very useful for the direct arylation of various tautomerizable heteroarenols with *N*-tosylhydrazones. Both electron-releasing and electron-withdrawing groups, including methoxy, alkyl, benzyl, nitro, fluoro, cyano, $-CF_3$, etc. groups are well-suited with the reaction, giving the analogous in moderate to high yields. Further, in most cases, the reaction advanced effortlessly and the anticipated products were formed in satisfactory yields (Table 3).

Based on the literature survey,[23,26,28] the proposed plausible mechanism for the generation of 1,1-heterodiarylalkenes is outlined in Figure 2. It most likely proceeds through the following steps: (1) Tautomerization and activation in the presence of Et_3N and PyBroP (**II**) to form the heterocycle–phosphonium intermediate (**III**); (2) Oxidative addition of Pd^0 (**IV**) catalyst to the heterocycle–phosphonium intermediate to generate heteroaryl-Pd^{II}-phosphonium species (**V**) via C–OH bond activation; (3) in situ generation of diazo compounds (**VII**) from *N*-tosylhydrazones (**VI**) in the presence of base; (4) it inserts into heteroaryl-Pd^{II}-phosphonium complex (**VIII**) to give a palladium–carbene species; (5) obtaining of unstable Pd carbene complex that undergoes migratory insertion of the heteroaryl group to synthesize the alkyl palladium complex (**IX**); (6) in the end, β-hydrogen elimination would provide the 1,1-heterodiaryl alkenes (**X**) and regenerate Pd^0 complex.

In summary, we have demonstrated a viable, economical, very effectual method for the synthesis of Pd catalyzed C–C coupling of a wide-ranging heteroarenols with various substituted *N*-tosylhydrazones, via in situ C–OH bond activation using phosphonium coupling reagent under mild and effective reaction conditions to synthesize various 1,1-heterodiaryl alkenes in moderate to excellent yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.022.

References and notes

1. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
2. Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058.
3. Tréguier, B.; Lawson, M.; Bernadat, G.; Bignon, J.; Dubois, J.; Brion, J.-D.; Alami, M.; Hamze, A. *ACS Comb. Sci.* **2014**, *16*, 702.
4. Froimowitz, M.; Gu, Y.; Dakin, L. A.; Nagafuji, P. M.; Kelley, C. J.; Parrish, D.; Deschamps, J. R.; Janowsky, A. *J. Med. Chem.* **2007**, *50*, 219.
5. Rennison, D.; Bova, S.; Cavalli, M.; Ricchelli, F.; Zulian, A.; Hopkins, B.; Brimble, M. A. *Bioorg. Med. Chem.* **2007**, *15*, 2963.
6. Liu, J.; Yi, H.; Zhang, X.; Liu, C.; Liu, R.; Zhang, G.; Lei, A. *Chem. Commun.* **2014**, 7636.
7. Hansen, A. L.; Ebran, J.-P.; Gogsig, T. M.; Skrydstrup, T. *Chem. Commun.* **2006**, 4137.
8. Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464.
9. Ojha, D. P.; Prabhu, K. R. *J. Org. Chem.* **2012**, *77*, 11027.
10. Chen, S.-H. *Tetrahedron Lett.* **1997**, *38*, 4741.
11. Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.
12. Gauthier, D.; Beckendorf, S.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536.
13. Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
14. Kumar, Y. S.; Dasaradhan, C.; Prabakaran, K.; Nawaz Khan, F.-R.; Jeong, E. D.; Chung, E. H.; Hyun Gyu, K. *RSC Adv.* **2014**, *4*, 40259.
15. Peng, Y.; Huang, P.; Wang, Y.; Zhou, Y.; Yuan, J.; Yang, Q.; Jiang, X.; Deng, Z.; Xu, J. *Org. Biomol. Chem.* **2014**, *12*, 5922.
16. Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
17. McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.
18. Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.
19. Dalvadi, J. P.; Patel, P. K.; Chikhalia, K. H. *Tetrahedron* **2014**, *70*, 9394.
20. Kang, F.-A.; Lanter, J. C.; Cai, C.; Sui, Z.; Murray, W. V. *Chem. Commun.* **2010**, 1347.
21. Li, S.-M.; Huang, J.; Chen, G.-J.; Han, F.-S. *Chem. Commun.* **2011**, 12840.
22. Sharma, A.; Vachhani, D.; Van der Eycken, E. *Org. Lett.* **2012**, *14*, 1854.
23. Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300.
24. Barroso, R.; Valencia, R. A.; Cabal, M.-P.; Valdés, C. *Org. Lett.* **2014**, *16*, 2264.
25. Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486.
26. Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560.
27. Patel, P. K.; Dalvadi, J. P.; Chikhalia, K. H. *RSC Adv.* **2014**, *4*, 55354.
28. Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587.
29. Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.
30. Ye, F.; Wang, C.; Ma, X.; Hossain, M. L.; Xia, Y.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 647.