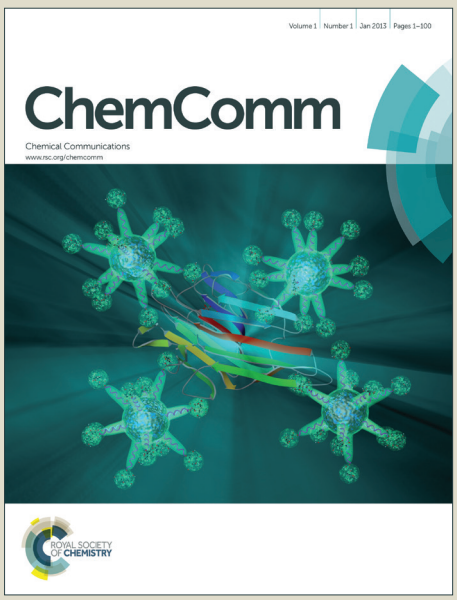
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

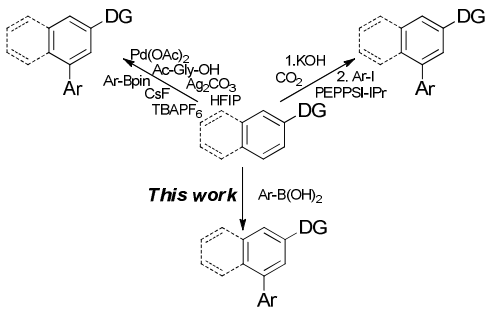
Palladium(II)-Catalyzed *meta*-Selective Direct Arylation of *O*-*β*-Naphthyl Carbamate

Jingchang Zhang,[a] Qingwen Liu,[a] Xufei Liu,[b] Suoqin Zhang,*[a] Pingping Jiang,[a] Yanxiang Wang,[a] Shengyuan Luo,[a] Yang Li[a] and Qifeng Wang*[a, b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Selective *meta*-arylation of *O*-*β*-naphthyl carbamate has been accomplished using $Pd(OAc)_2$ as catalyst precursor and $K_2S_2O_8$ with AgOAc as oxidants. A range of aryl boronic acids could be introduced in moderate to good yields. Mechanism investigation shows the carbamate substituent has unique effect and the reaction undergoes an *ortho*-carbometallation/*meta*-direct arylation process.

C-H bond direct functionalization represents one of the most efficient strategies for construction of complex molecules.[1] Currently one limitation of C-H bond direct functionalization is the control of regioselectivity when multiple C-H bonds exist in one molecule. Transition metal catalyzed *ortho* C-H bond direct arylation is a well-developed means which can selectively cleave *ortho* C-H bond with the aid of installed heteroatom-containing directing groups.[2] On the other hand, directing group mediated *meta*-selective C-H bond direct arylation is a great challenge in this field.[3] Very recently in Yu and co-workers' research, *meta*-selective direct arylation was accomplished by introducing an "end-on template" as the directing group. [3a,b] Larrosa and co-workers described direct *meta*-selective arylation of phenols using a traceless directing group relay strategy.[3c,d] Although great progress has been made, new strategies are still necessary to be encouraged for realizing *meta*-direct arylation of aromatics (Scheme 1).



Scheme 1. Pd-Catalyzed *meta*-Selective Direct Arylation in the Literature.

In our first step to this target, *β*-naphthol was selected as the substrate because not only its C-H bond is more active than its phenol cousin but also its functionality can be found in asymmetric catalysts or ligands, functional materials and biologically active substance[4] and therefore the method developed will be potentially practical. In the literature about direct arylation of phenol and its derivatives, [5] *ortho*-arylated products were mainly obtained by using arenes, aryl iodides or diaryliodonium salts as coupling partners. To the best of our knowledge, *meta*-direct arylation of *β*-naphthol derivatives has not been reported. In this paper, we report the first example of *meta*-selective direct arylation of *O*-*β*-naphthyl carbamate, using arylboronic acid as the coupling partner. Mechanism investigation shows the reaction follows an *ortho*-metallation/*meta*-direct arylation process, which is a new strategy for realizing the *meta*-direct arylation of arenes.

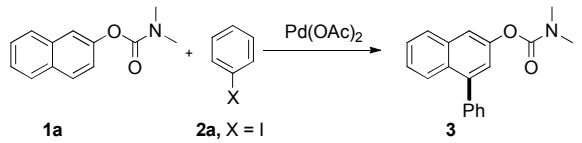
As confirmed in the literature, *ortho*-carbopalladation of phenol esters proceeds smoothly during the direct arylation in palladium chemistry [5e]. Although the interaction of this metallic intermediate with different coupling partners follows different pathway, reductive elimination step always gives *ortho*-arylated products. Thus, attempting to prevent or slow down this step will probably open the possibility for transformation in other pathways. Interestingly in the mechanisms of C-H bond direct arylation such as electrophilic aromatic substitution, S_E3, σ-bond metathesis or concerted metallation/deprotonation, C-H bond was always cleaved before reductive elimination. Thus, we think preserving this C-H bond may prevent or slow down reductive elimination step. Therefore, we preferred to perform the reaction under acidic conditions (Table 1).

Following the conditions in the literature firstly, we used phenyl iodide as the coupling partner, and the reaction was performed with 5 mol % $Pd(OAc)_2$ and 2 eq. AgOAc in TFA [5h]. The reaction could not proceed at 50°C (entry 1). However, a further increase of the temperature to 100°C led to a resulted mixture without main products (entry 2). Considering phenyl boronic acid was a good coupling partner but rarely used in direct arylation of phenol derivatives, we turn to use phenyl boronic acid as the coupling partner. Unfortunately, no product was formed in the presence of $Cu(OTf)_2/Ag_2O$ in toluene at 120°C (entry 3) [6a]. With $Cu(OAc)_2$ and O_2 (1 atm) as the oxidant, the coupling reaction cannot proceed in TFA at room temperature, either (entry 4)[6b].

It appeared that the *O*-*β*-naphthyl carbamate was not as active as it was expected. Thus, we turned to use $K_2S_2O_8$ as the terminal oxidant and we were delight to see the reaction generated mono-arylated product in 15% NMR yield together with other by-products in TFA at 70°C (Entry 5).[5f,7] As Liu and co-workers has

reported the *ortho* direct

Table 1. Optimization of the reaction conditions for *meta*-C-H bond direct arylation. [a]



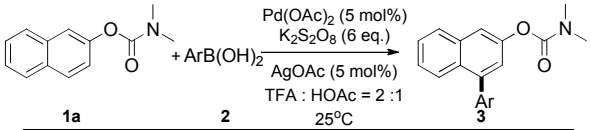
1a **2a,** X = I **2b,** X = $B(OH)_2$ **3**

Entry	Oxidant (eq.)	Solvent[b]	Additive (eq.)	T (^oC)	Yield (%)[c]
1	AgOAc (2.0)	TFA	--	50	--
2	AgOAc (2.0)	TFA	--	100	< 5
3	$Cu(OTf)_2$ (2.0)	Toluene	Ag_2O (0.5)	120	--
4	$Cu(OAc)_2$ (2.0)	TFA	O_2 (1atm)	25	--
5	$K_2S_2O_8$ (6.0)	TFA	--	70	15
6	$K_2S_2O_8$ (6.0)	TFA	--	50	42
7	$K_2S_2O_8$ (6.0)	TFA	--	25	45
8	$K_2S_2O_8$ (6.0)	TFA	--	100	< 5
9	$K_2S_2O_8$ (6.0)	TFA	AgOAc (5%)	25	56
10	$K_2S_2O_8$ (6.0)	TFA : HOAc = 1 : 1	AgOAc (5%)	25	72
11	$K_2S_2O_8$ (6.0)	TFA : HOAc = 2 : 1	AgOAc (5%)	25	84
12	$K_2S_2O_8$ (6.0)	TFA : HOAc = 3 : 1	AgOAc (5%)	25	70

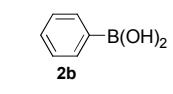
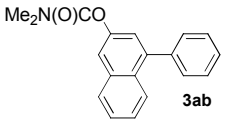
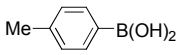
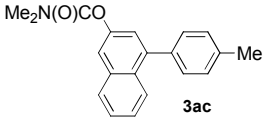
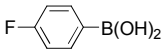
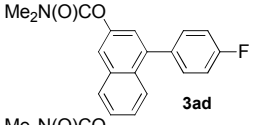
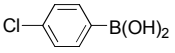
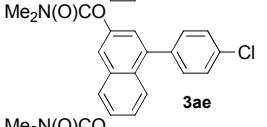
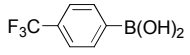
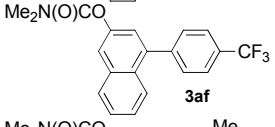
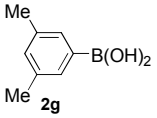
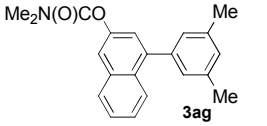
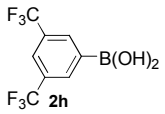
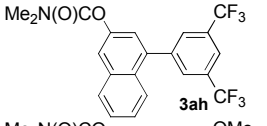
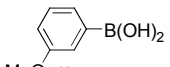
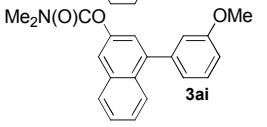
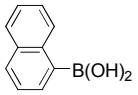
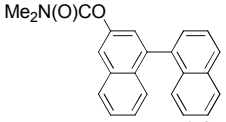
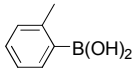
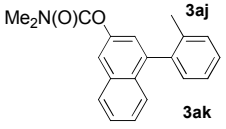
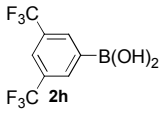
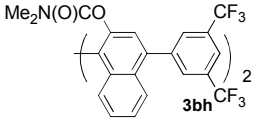
[a] All the reactions were performed using **1a** (1 mmol) with phenyl iodide or phenyl boronic acid (3 mmol) under N_2 atmosphere; [b] TFA = trifluoroacetic acid, HOAc = acetic acid. [c] Yields were calculated according to ^1H NMR using 1-(3-nitrophenyl) ethanone as internal standard.

arylation of *O*-*β*-naphthyl esters, we have to confirm the site selectivity. After a careful isolation of the mono-arylated product followed by removal of the ester group, the product was confirmed to be arylated at *meta*-position. Encouraged by this result, we continued to optimize the condition. The yields could be further improved to 42% and 45% at lower temperatures (entry 6 and 7). On the contrary, the reaction was hard to proceed at higher temperature, probably because the fast decomposition of $K_2S_2O_8$ could not recycle the Pd(0) to the active oxidation state (entry 8). To enhance the oxidizing ability of $K_2S_2O_8$, 5 mol% AgOAc was added to $K_2S_2O_8$ and the NMR yield was further modified to 56% (entry 9). During the condition optimizing process, we noticed the dimerization of *O*-*β*-naphthyl carbamate, which implied the C-H bond palladation occurred fast while transmetallation of aryl boronic acid was sluggish. To overcome this problem, we attempted to perform the reaction under less acidic conditions in order to facilitate the transmetallation step. Using the mixed solvents of trifluoroacetic acid (TFA) and acetic acid (HOAc) in ratio of 1 : 1, the NMR yield could be modified to 72% (Entry 10). In ratio of 2 : 1, the NMR yield could reach up to 84% (Entry 11). Continue to enhance the acidity led to a decrease of the yield (Entry 12). Therefore, TFA and HOAc in ratio of 1 : 1 was selected to be the best solvent.

Table 2. Scope of Aryl Boronic Acids in *meta*-Direct Arylation of **1a.**[a]



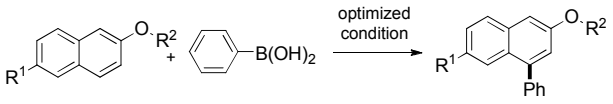
1a **2** **3**

Entry	2	3	Yield[%][b]
1	 **2b**	 **3ab**	74
2	 **2c**	 **3ac**	61
3	 **2d**	 **3ad**	69
4	 **2e**	 **3ae**	69
5	 **2f**	 **3af**	72
6[c]	 **2g**	 **3ag**	63
7	 **2h**	 **3ah**	71
8[c]	 **2i**	 **3ai**	63
9	 **2j**	 **3aj**	59
10	 **2k**	 **3ak**	66
11[c,d]	 **2h**	 **3bh**	40

[a] The reaction time depends on specific aryl boronic acid, please see SI. [b] Isolated yields. [c] TFA was used directly as the solvent. [d] *O,O'*-BINOL dicarbomate (**1b**) was tested and 10 mol% $Pd(OAc)_2$ was used.

With the optimized condition in hand, we tested the scope of aryl boronic acids. As shown in Table 2, under the optimized condition, using phenyl boronic acid as the coupling partner, the

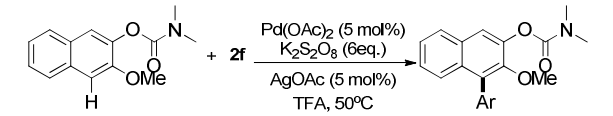
isolated yield of *meta*-arylated product **3ab** was 74 % (entry 1). More electron rich *p*-tolyl boronic acid could also supply the desired product **3ac** in 61 % yield (entry 2). Phenyl group bearing electron-withdrawing substituents such as *para*-F, -Cl and $-CF_3$ could generate the corresponding products **3ad, 3ae, 3af** in relatively higher yields (entry 3, 4, 5). *Meta*-substituted phenyl boronic acids were also effective for this reaction and 3,5-dimethyl, 3,5-di(trifluoromethyl) and 3-methoxyl phenyl boronic acids gave the *meta*-arylated products in 63%, 71% and 63% isolated yields, respectively (entry 6, 7, 8). Then we tested the steric bulkier aryl boronic acids and we found 1-naphthyl as well as *o*-tolyl substituents could be smoothly introduced in moderate to good yields (entry 9 and 10). We also tested the *meta*-arylation of *O, O*-BINOL dicarbamate and 3,5-di(trifluoromethyl)phenyl substituent could be introduced in a moderate yield (entry 11).



1c: R^1 = OMe, R^2 = $C(O)NMe_2$, **2b** **3cb**: 59%

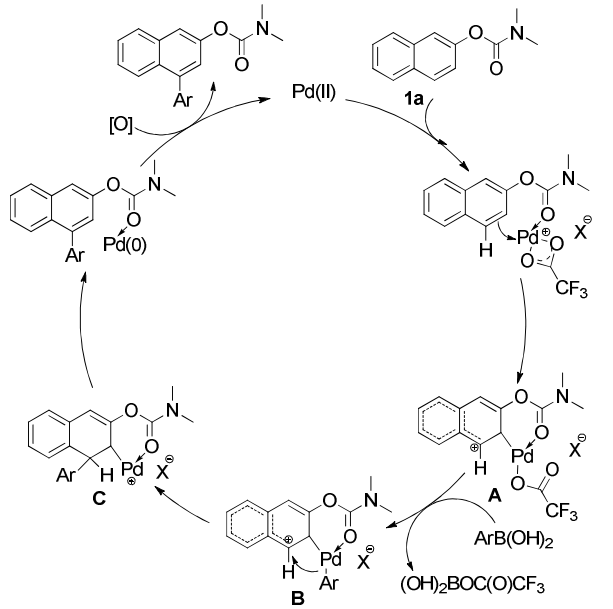
Scheme 2. Effects of carbamate Substituent versus methoxyl group in *meta*-Direct Arylation of 2-Naphthol Derivatives.

Since we used *O*-*β*-naphthyl carbamate as the substrate to investigate the *meta*-direct arylation directly, we tried to find out the effect of the directing group. Under the optimized condition, 2-naphthol, *O*-*β*-naphthyl methyl ether and *O*-*β*-naphthyl acetate cannot be arylated. Using 6-methoxy-2-naphthyl carbamate **1c** as the substrate, mono-arylated product **3cb** was formed exclusively in 59 % isolated yield (Scheme 2).



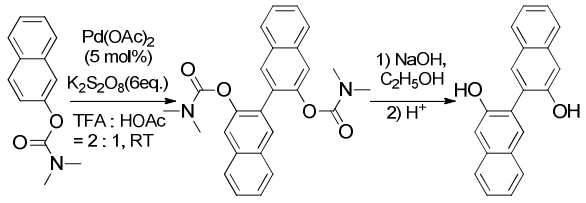
1d **3df**: 50%

Scheme 3. Direct Arylation of *ortho*-Site Occupied *O*-2-naphthyl Carbamate.



Scheme 4. Proposed Catalytic Cycle of *ortho*-metallation/*meta*-arylation of *O*-2-naphthyl carbamate.

Then we tested *meta*-selective direct arylation of 3-methoxyl substituted *O*-*β*-naphthyl carbamate **1d** to confirm whether the cleavage of *ortho*-C-H bond was necessary to accomplish the *meta*-direct arylation process (Scheme 3). The reaction could not proceed under the optimized condition, probably because of the steric effect of methoxyl group, which prevent the carbopalladation or aryl boronic acid transmetallation. Luckily, under stronger acidic condition and higher temperature, we found *para*-CF_3Ph-B(OH)$_2$ **2f** could be introduced successfully in a moderate yield. This result indicates that the *ortho* C-H bond cleavage is not involved in the *meta*-arylation process under acidic conditions.



1a 75% **4a** 88% **5a**

Scheme 5. Investigation of *ortho*-C-Pd bond formation by Dimerization of *O*-2-naphthyl Carbamate.

These two results prove that the carbamate group has unique effect for the *meta*-selective direct arylaton of **1a** and *ortho* C-H bond is preserved throughout the reaction. Since directed *ortho*-metallation (D*o*M) has been widely accepted as a law, we conclude that the mechanism involves a first *ortho*-carbometallation of **1a** to genetate cationic intermediate **A**. The cationic species is stabilized in a benzyl cation form and undergoes a sequent transmetallation to give intermediate **B**. Nucleophilic attack of aryl group to *meta*-carbon cation gives arylated intermediate **C**. **C** undergoes a *β*-hydrogen elimination or re-aromatization process to generate final product and reduced Pd(0). Pd(0) is oxidized to regenerate Pd(II) catalyst (Scheme 4)[8]. Thus, the reaction was performed in the absence of phenyl boronic acid to retard the transmetallation step (Scheme 5). Dimerized product was formed quickly in a high yield. After removal of ester group, the final product was characterized as [2,2'-binaphthalene]-3,3'-diol. This result indicates that carbopalladation occured at *ortho*-position. Probably after an oxidative coupling process, the dimer of *O*-*β*-naphthyl carbamate was generated. At this moment we think a Heck-type reaction mechanism cannot be completely ruled out.[3e] However, during the condition optimization, concerted C-C bond and C-Pd formation did not observed because arylated dimer had never been detected. Namely, if the reaction proceeded in Heck-type reaction pathway, the arylated intermediate will have C-Pd bond and undergo dimerization more or less. Thus, we favor the mechanism of *ortho*-metallation/*meta*-direct arylation.

Conclusions

A method for *meta*-selective direct arylation of *O*-*β*-naphthyl carbamate was developed using aryl boronic acid as the coupling partner. Carbamate group has unique effect in this process. According to the mechanism investigation, we found directed ortho-metallation occurred first, followed by meta-direct

arylation. *Ortho*-C-H bond was also confirmed to be remained during the reaction by using *O*-3-methoxy-2-naphthyl carbamate as the substrate. Therefore, the reaction proceeds via directed *ortho*-metallation/meta-arylation pathway. We expect this method is instructive for our continuous effort on meta-selective direct arylation of more stable arenes. Investigation of meta-selective direct aryaltion of arenes under more efficient catalytic system is in progress.

Acknowlegement

The work was supported by National Natural Sciences of Foundation of China (No. 21202060), Jilin University Start-up research Funding. Technology Foundation for Selected Oversea Chinese Scholar in Jilin Province and Creative Program in Jilin University (No. 336OEP01) are acknowledged together. X. Liu is grateful to Program KY-GS-13-01-02.

Notes and references

[a] *International Joint Research laboratory of Nono-Micro Architecture Chemistry (NMAC), Department of Organic Chemistry, College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, China. E-mail: wangqifeng@jlu.edu.cn, zhangsq@jlu.edu.cn*

[b] *State Grid Jilin Province Electric Power Research Institute, 4433 Renmin Street, Changchun 130021, China.*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 For selected reviews on C-H bond direct arylation, please see: a) L. H. Zhou, W. J. Lu, *Chem. Eur. J*., 2014, **20**, 634; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem*., 2012, **124,** 9092; *Angew. Chem. Int. Ed*., 2012, **51**, 8960; c) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res*., 2012, **45**, 936; d) J. F. Hartwig, *Acc. Chem. Res*., 2012, **45**, 864; e) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res*., 2012, **45**, 814; f) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res*., 2012, **45**, 788; g) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.,* 2012, **41**, 5588; h) C. Liu, H.Zhang, W. Shi, A.W. Lei, *Chem. Rev*., 2011, **111**, 1780; i) L. Ackermann, *Chem. Rev.,* 2011, **111**, 1315; j) C. S. Yeung, V. M. Dong, *Chem. Rev*., 2011, **111**, 1215; k) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev*., 2011, **40**, 5068; l) O. Baudoin, *Chem. Soc. Rev*., 2011, **40**, 4902; m) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev*., 2011, **40,** 4740; n) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev*., 2011, **40**, 1885; o) T. W. Lyons, M. S. Sanford, *Chem. Rev.,*2010, **110**,1147; p) P. Sehnal,; R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev*., 2010, **110**, 824; q) J.-Q. Yu, Z. Shi, *Top. Curr. Chem*., 2010, **292**, 1; r) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun*., 2010, **46**, 677. s) O. Daugulis, H.-Q. DO, D. Shabashov, *Acc. Chem. Res*., 2009, **42**, 1074; t) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.,* 2009, **38**, 2447; u) B.-J. Li, S.-D. Yang, Z.-J. Shi, Synlett., 2008, **2008**, 949. v) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev*., 2007, **36**, 1173; w) L.-C. Campeau, K. Fagnou, *Chem. Commun*., 2006, 1253.

2 a) D. A. Colby , R. G. Bergman, J. A. Ellman, *Chem. Rev.,* 2010, **110**, 624; b) S. D. Sarkar, W. P. Liu,S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.,* 2014, **356**, 1461.

3 a) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature*., 2012, **486**, 518; b) L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 18056; c) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc*., 2014, **136**, 4109; d) P. MacLellan, *Nat. Chem*., 2014, **6**, 375. e) Y. Izawa, C. W. Zheng, S. S. Stahl, *Angew. Chem.,* 2013, **125**, 3760; *Angew. Chem. Int. Ed.,* 2013, **52**, 3672; In Gaunt and coworker's research, *meta*-direct arylation was accomplished successfully, probably in a Friedel-Craft reaction mechanism. Please see: f) R. J. Phipps, M. J. Gaunt, *Science*., 2009, **323**, 1593; g) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem*., 2011**, 123**, 483; *Angew. Chem. Int. Ed.,* 2011, **50**, 463.

4 a) M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J*., 2010, **16**, 13116; b) K. Tsubaki, M. Miura, H. Morikawa, H. Tanaka, T. Kawabata, T. Furuta, K. Tanaka, K. Fuji, *J. Am. Chem. Soc.,* 2003, **125**, 16200; c) T. Hashimoto, Y. Tanaka, K. Maruoka*, Tetrahedron: Asymmetry,* 2003*,* **14***,* 1599; d) H. Maeda, Y. Bando, K. Shimomura, I. Yamada, M. Naito, K. Nobusawa, H. Tsumatori, T. Kawai, *J. Am. Chem. Soc.,* 2011, **133**, 9266; e) L. Q. Ma, D. J. Mihalcik, W. B. Lin, *J. Am. Chem. Soc.,* 2009, **131**, 4610; f) F. Pertusati, K. Hinsinger, Á. S. Flynn, N. Powell, A. Tristram, J. Balzarini, C. McGuigan*, Eur. J. Med. Chem.,* 2014*,* **78***,* 259; g) A. M. Petros, S. L. Swann, D. Y. Song, K. Swinger, C. Park, H. C. Zhang, M. D. Wendt, A. R. Kunzer, A. J. Souers, C. H. Sun, *Bioorg. Med. Chem. Lett*., 2014, **24**, 1484.

5 a) D.-G. Yu, F. D. Azambuja, F. Glorius, *Angew. Chem*., 2014, **126**. 7842; *Angew. Chem. Int. Ed.,* 2014, **53**, 7710; b) T. Truong, O. Daugulis, *Chem. Sci*., 2013, **4**, 531; c) T. Dohi, T. Kamitanaka, S. Watanabe, Y. J. Hu, N. Washimi, Y. Kita, *Chem. Eur. J.,* 2012, **18**, 13614; d) K. Beydoun, H. Doucet, *Catal. Sci. Technol*., 2011, **1**, 1243; e) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu**,** *J. Am. Chem. Soc.,* 2010, **132**, 468; f) X. D.Zhao , C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.,* 2010, **132**, 5837; g) X. W.Guo, W. J. Li, Z. P. Li, *Eur. J. Org. Chem*., 2010, **30**, 5787; h) R. B. Bedford, R. L. Webster, C. J. Mitchell, *Org. Biomol. Chem.,* 2009, **7**, 4853; i) R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. Lewis-Alleyne, P. D. Long, D. Polo-Cerón, S. Prashar, *Chem. Commun.,* 2008, **8**, 990; j) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem.,* 2003, **115**, 116; *Angew. Chem. Int. Ed.,* 2003, **42**, 112; k) T. Satoh, J. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.,* 1998, **71**, 2239; l) D. D. Hennings, S. Iwasa, V. H. Rawal, *J. Org. Chem*., 1997, **62**, 2.

6 a) Z. J. Shi, B. J. Li, X. B. Wan, J. Cheng, Z. Fang, B. Cao, C. M. Qin, Y. Wang, *Angew. Chem*., 2007, **119**, 5650; *Angew. Chem. Int. Ed*., 2007, **46**, 5554; b) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem*., 2008, **120**, 1495; *Angew. Chem. Int. Ed*., 2008, **47**, 1473.

7 W. Lu, Y. Yamaoka, Y. Taniguchi, T. Kitamura, K. Takaki, Y. Fujiwara, *J. Organomet. Chem.,*1999, **580**, 290.

8 K. Ueda, S. Yanagisawa, J. Yamaguchi and K. Itami, *Angew. Chem.*, 2010, **122**, 9130; *Angew. Chem. Int. Ed.,* 2010, **49**, 8946.