Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Pd(II)-catalyzed C(sp^3)-H arylation of amino acid derivatives with click-triazoles as removable directing group

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

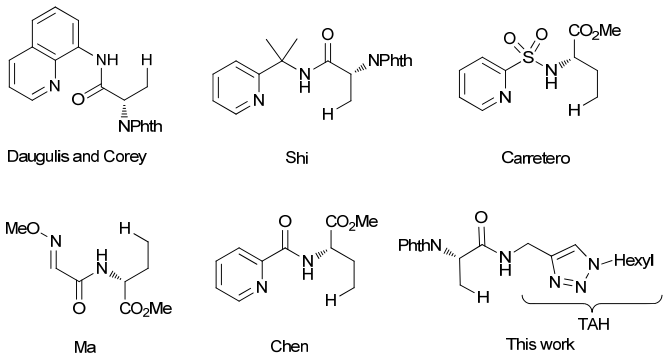
Guofu Zhang,[a] Xiaoqiang Xie,[a] Jianfei Zhu,[a] Shasha Li,[a] Chengrong Ding[a*] and Ping Ding [b]

By using click-triazoles as a conveniently approachable and removable directing group, the direct palladium-catalyzed C(sp^3)-H arylation of amino acid derivatives with various aryl iodides bearing different electronic properties has been achieved. Notably, the desired amino acid molecular can be obtained by the cleavage of the tethered click-triazoles after the catalytic reaction, which aims to provide a practical protocol for the accessibility of both nature and synthetic amino acids.

Introduction

Optically active unnatural amino acids are important structural motifs of pharmaceutical agents and biologically active compounds.[1] With the fast development of protein engineering and the discovery amino acid-based drugs, synthesis of high enantiopurity amino acids derivatives has attracted considerable attention over the past decades. Traditionally, unnatural amino acids can be obtained through enzymatic resolutions of the corresponding racemates or through asymmetric synthesis. While considering the extensive availability of natural amino acids, a new approach of transition-metal-catalyzed direct C-H functionlizations to access their unnatural counterparts is in rapid development.[2]

Transition-metal-catalyzed C-H functionalization represents one of the most powerful methods for the direct conversion of ubiquitous C-H bonds into diverse functional groups selectively in organic synthesis over the past decades.[3] Most efforts in this field have been focused on the activation of C(sp^2)-H bonds of (hetero)arenes for the formation of new C-X bonds (X = C, O, N, F, Cl, Br, I, Si, P, B et al.).[4] In comparison, the direct functionalization of unreactive C(sp^3)-H remains challenging, mainly due to the inertness of most C(sp^3)-H bonds and the related difficulties in regioselective functionalization.[5] To the best of our knowledge, the most common strategies for addressing the aforementioned problem involves the utilization of directing group that could coordinate to a metal center and thus deliver the catalyst to the desired C-H bond, which in general formed a thermodynamically stable five- or six-membered metallacyclic intermediate. Comparing with the monodentate directing group generally works on C(sp^2)-H activation, the bidentate directing groups have recently been demonstrated that they are able to promote metal-catalyzed C(sp^3)-H bond activation(Scheme 1). In 2005, Daugulis and coworkers first described the Pd-catalyzed β- arylation of carboxylic acid and the γ- arylation of amine derivatives by employing 8-aminoquinoline and picolinamide auxiliary as the directing groups.[6] This methodology has gradually been applied to the preparation of synthetic amino acids, which have broad applications in drug discovery and biotechnology. It's worth noting that Corey and coworkers demonstrated the pioneering examples of β- and γ- functionalization of N-phthaloyl-α-amino amides with the similar strategy.[7] An another elegant study reported by Chen and coworkers on the Pd-catalyzed picolinamide-directed C(sp^3)-H bond functionalization, in which some cases of γ-arylation of natural amino acids were described with moderate to excellent yields.[8] Other bidentate directing groups like N-(2-pyridyl)sulfamide, 2-methoxyiminoacetyl and 2-(pyridine-2- yl)propan-2-amine introduced by Carretero[9], Ma[10], and Shi[11] respectively have showed the great reactivity in the palladium-catalyzed arylation of amino acid derivatives.



Scheme 1. Different bidentate directing groups for the arylation of amino acid derivatives

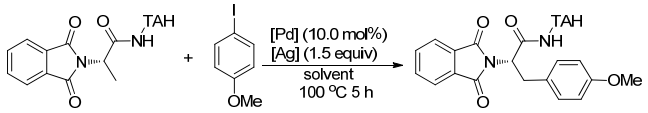
In spite of these achievements in the functionalization of natural amino acids, there is still much more room for further improvements regarding catalytic efficiency of the process, the scope of the amino acids, as well as designing easy accessible yet novel directing groups.[12] Recently, the'click-1,2,3-triazole' unit has emerged as a chelator showing great potential for metal

coordination, and many metal ions like Cu, Ru, Pd, etc. have been successfully explored. Our group also designed some solid catalysts based on the utilization of the versatile click-triazole, which not only works as a stable linker to graft catalysts onto the supports but also as a good chelator to participate in the catalytic reactions.[13] Inspired by these attractive finding, we wish to report a palladium-catalyzed C(sp3)-H arylation of amino acid derivatives by employing click-1,2,3-triazoles as the removable directing group, which are easily accessible through copper(I)-catalyzed 1,3-dipolar Huisgen cycloaddition between substituted alkynes and azides.

Results and discussion

At the outset, a representative set of novel amino acids benzamides **1a** containing 1,2,3-triazoles through [3+2] Huisgen cycloaddition under mild conditions was prepared(For details, please see ESI)[11]. With **1a** as the model substrate, the condition optimization for Pd(II)-catalyzed C(sp^3) -H arylation was carried out, and results were summarized in Table 1. Gratifyingly, the combination of **1a** with 10 mol% $Pd(OAc)_2$, AgOAc (1.5 equiv.) and 1-iodo-4-methoxybenzene (**2a**, 1.5 equiv.) at 100 ℃ in 1,2-dichloroethane (DCE) can afford the desired product **3aa** in 39% yield (entry 1). With the initial result, we then testified the solvent effect in this transformation. For those solvents such as *o*-xylene, toluene, DMF, DMSO, *t*-BuOH, *t*-Amyl-OH, there is no apparent improvement in terms of reaction yield (entries 2-6). Yet, when 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was employed as the solvent, the desired product could be achieved in 93% yield (entry 7). In addition, other palladium catalysts and oxidant were also screened, which were unable to yield the desired product with competitive yield (entries 8-10). Generally $Pd(TFA)_2$ shows higher catalytic activity than $Pd(OAc)_2$ in the C-H bond activation reaction, but in this catalytic system the ligand exchange step may to reduce its catalytic activity. By switching from AgOAc to other silver salts like Ag_2CO_3, $AgNO_3$ or $AgSbF_6$, decreased yields were observed (entries 11-14, For details, please see ESI). This result is in agreement with findings by Ma and coworkers.[10]

Table 1 Optimization of reaction conditions[a]



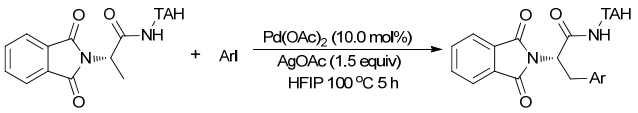
1a 2a 3aa

Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	AgOAc	DCE	39
2	$Pd(OAc)_2$	AgOAc	DMF	trace
3	$Pd(OAc)_2$	AgOAc	*o*-xylene	ND[c]
4	$Pd(OAc)_2$	AgOAc	toluene	ND
5	$Pd(OAc)_2$	AgOAc	*t*-BuOH	24
6	$Pd(OAc)_2$	AgOAc	*t*-AmylOH	31
7	**$Pd(OAc)_2$**	**AgOAc**	**HFIP**	**93**
8	$Pd(TFA)_2$	AgOAc	HFIP	50
9	$PdCl_2$	AgOAc	HFIP	57
10	$Pd(PPh_3)_4$	AgOAc	HFIP	trace
11	$Pd(OAc)_2$	Ag_2CO_3	HFIP	27
12	$Pd(OAc)_2$	$AgNO_3$	HFIP	15
13	$Pd(OAc)_2$	$AgSbF_6$	HFIP	ND
14	$Pd(OAc)_2$	Ag_2O	HFIP	ND

[a] The reactions were conducted as follows unless otherwise noted: **1a** (0.20 mmol), $Pd(OAc)_2$ (10.0 mol%), **2a** (0.30 mmol), additive (0.30 mmol), solvent (1 mL), 5 h. [b] Determined by **^{1}H NMR** spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Not detected.

With the optimal reaction conditions in hand, we next examined the substrate scope of different aryl iodides and the results were summarized in Table 2. In general, the demonstrated transformation was found to be compatible with a variety of aryl iodides bearing either electron-withdrawing or electron-donating groups, providing the corresponding arylated products with 68-90% isolated yields. For example, fluoro (entry **3ae**), chloro (entry **3af**), bromo (entry **3ag**), nitro (entries **3ai - 3ak**), and ester (entry **3an**) groups are excellent tolerated, which are convenient handles for further functionality. The electronic property of the aryl iodides has an effect on its reactivity toward arylation. Generally, electron-deficient aryl iodides (entries **3ae-3an**) provided better yields than electronic-rich aryl iodides (entries **3aa-3ac**), probably due to electron-deficient aryl iodides are favorable to the reductive elimination step. While steric factors may not play an important role in the reaction reactivity (entries **3ai - 3ak**). For reactions using less effective arylating reagents, more catalysts (entry **3ap**) and prolonged reaction time (entries **3ac, 3ap**) were required. However, heteroaryl iodides like 2-iodothiophene and 2-iodopyridine can't transform smoothly for heteroatoms in heterocycles coordinate strongly to Pd(II) catalysts and result in catalyst poisoning.

Table 2 Pd(II)-catalyzed arylation of **1a** with aryl iodides[a]



1a 2 3

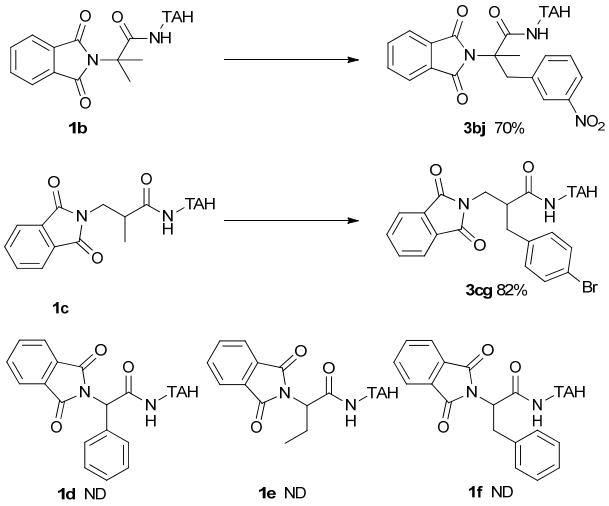
Entry	Ar	Product	Yield[b](%)
1	4-$MeOC_6H_4$	**3aa**	80
2	2-$MeOC_6H_4$	**3ab**	76
3	4-$EtOC_6H_4$	**3ac**	75[c]
4	C_6H_5	**3ad**	83
5	4-FC_6H_4	**3ae**	84
6	4-ClC_6H_4	**3af**	83
7	4-BrC_6H_4	**3ag**	86
8	2-F-4-BrC_6H_3	**3ah**	87
9	4-$NO_2C_6H_4$	**3ai**	90
10	3-$NO_2C_6H_4$	**3aj**	86
11	2-$NO_2C_6H_4$	**3ak**	88
12	4-$CH_3COC_6H_4$	**3al**	82
13	4-$CF_3C_6H_4$	**3am**	80
14	4-$MeO_2CC_6H_4$	**3an**	76
15	4-PhenylC_6H_4	**3ao**	82
16	1-naphthyl	**3ap**	68[cd]

[a]The reactions were conducted with 0.40 mmol of **1a**, $Pd(OAc)_2$ (10.0 mol%), **2** (0.60 mmol), AgOAc(0.60 mmol), HFIP(2 mL) and stirred at 100 ℃ for 5h unless other noted. [b]Isolated yield. [c]12 h. [d] $Pd(OAc)_2$ (20.0 mol%) was used.

The present reaction was next applied to other substituted N-phthaloylalanine triazolylmethylhexyl(TAH) amide derivatives (Table 3). When **1b** was used as the substrate under the optimal

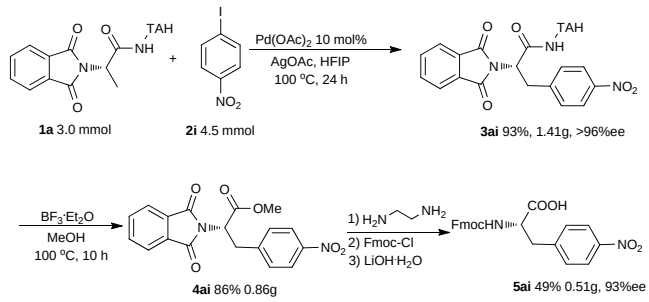
conditions, though there are two methyl groups that are able to undergo arylation, the monoarylated product **3bj** was isolated in 70% yield. To our delight, the arylation of β- amino acid 3-aminoisobutyric acid derivative **1c** was also accessible, thus yielding the formation of **3cg** in 82% yield. The cheeringly result indicated that this method can also be applied to the arylation of β- amino acid derivatives, which are key structural motifs of peptides and pharmaceutically important compounds. However, other amino acid derivatives like 2-amino-2-phenylacetic acid(**1d**), 2-aminobutanoic acid(**1e**) or phenylalanine(**1f**) couldn't be arylated in this reaction. It may formed a five-membered cyclopalladated intermediate Pd(II) in the reaction, not the six-membered or seven membered ring cyclopalladated intermediate.

Table 3. Pd(II)-catalyzed arylation of substituded N-phthaloylalanine-TAH amide derivatives[a]



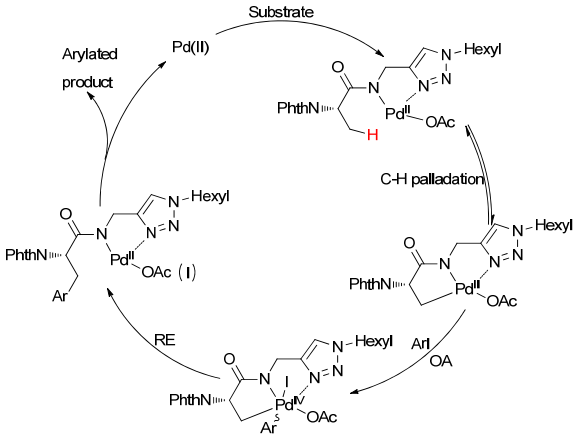
[a]The reactions were conducted with 0.40 mmol of **1**, $Pd(OAc)_2$ (10.0 mol%), **2**(0.60 mmol), AgOAc(0.60 mmol), HFIP(2 mL) and stirred at 100 ℃ for 5h. ND = Not Detected.

To highlight the synthetic utility of this process in non-natural amino acid synthesis, we then explored the gram-scale synthesis of **4ai** by using this protocol and removed the TAH directing group under mild conditions.[6d] As shown in Scheme 2: we were pleased to find that although the Pd-catalyzed arylation reactions were generally run on a 0.40 mmol scale, a 3.0 mmol scale reaction provided **3ai** with high yield(93%, 1.41g) and excellent enantiopurity(>96% ee). Then the TAH directing group could be removed in high yield with N-phthaloylphenylalanine methyl ester **4ai** being obtained in 86%(0.86g) isolated yield and 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-nitrophenyl)propanoic acid **5ai** can be obtained in 49%(0.51g) with simple treatment thus demonstrating the synthetically useful of the protocol.



Scheme 2. Removal of the TAH group

On the basis of the above observations and other literatures[8], we proposed a plausible mechanism for the palladium-catalyzed C(sp^3)-H arylation of amino acid derivatives(Scheme 3). Similar to previously reported Pd-catalyzed N,N-bidentated-directed C−H functionalization systems, the TAH-directed arylation reaction likely proceeds through a $Pd^{II/IV}$ catalytic cycle involving C−H palladation, oxidative addition(OA), and reductive elimination (RE). First, coordination of Pd(II) with the N,N-bidentate directing group triggered the methyl C-H palladation and formed a cyclopalladation intermediate Pd(II), then the five-membered cyclopalladated intermediate Pd(II) was oxidized to a high-valent Pd intermediate Pd(IV), which undergone ligand exchange progress. Subsequently, the arylated product was formed by following reductive elimination and released Pd(II) catalyst, thus completing the whole catalytic redox cycle.



Scheme 3. Plausible reaction mechanism

Conclusions

In summary, an effective Pd(II)-catalyzed C(sp^3)-H arylation of amino acid derivatives using removable 1,2,3-triazoles as removable directing group was developed. The demonstrated protocol could be applied to synthesis some unnatural amino acids in moderate to high yield and has shown high level compatibility with a variety of functional groups. Further researches to extend the applications of click-triazoles directing group in the C-H activation filed are currently underway.

Experimental

The amino acid derivatives were synthesized according to the procedure reported in the literature.[2,12]

General procedure for Pd(II)-catalyzed C(sp^3)-H arylation of amino acid derivatives.

$Pd(OAc)_2$ (9.0mg, 0.04 mmol, 10 mol%), AgOAc (99.6mg, 0.60 mmol, 150 mol%) , 1-iodo-4-methoxybenzene (140.4mg, 0.60 mmol, 150 mol%), amino acid derivative **1a** (153.3 mg, 0.4 mmol, 100 mol%), HFIP(2 mL) were introduced into a 15 mL seal tube equipped with a magnetic stirrer in air. The mixture was fiercely stirred at 100 °C for 5 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (15 mL) and then filtered through a pad of Celite and washed by ethyl acetate (50 mL). The organic solvent was evaporated under vacuum and the crude product was purified by column chromatograph using silica gel with *n*-hexane/ethyl acetate (v/v 1:2) as eluent to providing the corresponding product **3aa** (156.5 mg) in 80% yield.

3aa: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(s, 3H), 1.32(s, 6H), 1.91(s, 2H), 3.43(t, *J* = 11.0 Hz, 1H), 3.53(d, *J* = 10.5 Hz, 1H), 3.68(s, 3H). 4.34(s, 2H), 4.57(s, 2H), 5.06(s, 1H), 6.67(d, *J* = 7.5 Hz, 2H), 7.03(d, *J* = 7.5 Hz, 2H), 7.66(s, 2H), 7.72(s, 2H), 7.79(s, 1H), 7.91(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.0, 29.8, 31.0, 33.7, 34.2, 51.5, 55.1, 55.2, 113.9, 123.4, 124.0, 128.6, 129.9, 131.6, 134.1, 158.3, 167.8, 169.1; HRMS (ESI) m/z calcd for $C_{27}H_{31}N_5O_4$ $[M]^+$ 489.2449; found 489.2467.

3ab: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 6.5 Hz, 3H), 1.33(s, 6H), 1.92(s, 2H), 3.41(dd, J_1 = 13.5 Hz, J_2 = 10.5 Hz, 1H), 3.60(dd, J_1 = 13.5 Hz, J_2 = 4.5 Hz, 1H), 3.74(s, 3H), 4.35(t, *J* = 7.5 Hz, 2H), 4.61(s, 2H), 5.26(dd, J_1 = 10.5 Hz, J_2 = 5.5 Hz, 1H), 6.69(t, *J* = 7.0 Hz, 1H), 6.75(d, *J* = 7.5 Hz, 1H), 6.98(d, *J* = 6.0 Hz, 1H), 7.12(t, *J* = 8.0 Hz, 2H), 7.68(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 3H), 7.75(t, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.0, 30.4, 31.1, 34.8, 51.0, 52.4, 55.2, 110.2, 120.5, 123.3, 125.0, 128.5, 130.9, 131.7, 134.0, 157.5, 167.8, 169.2; HRMS (ESI) m/z calcd for $C_{27}H_{31}N_5O_4$ $[M]^+$ 489.2449; found 489.2459.

3ac: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 7.0 Hz, 3H), 1.30-1.35(m, 9H), 1.88(t, *J* = 7.0 Hz, 2H), 3.43-3.54(m, 2H), 3.88-3.93(m, 2H), 4.30(t, *J* = 7.5 Hz, 2H), 4.47-4.56(m, 2H), 5.08(dd, J_1 = 11.0 Hz, J_2 = 6.0 Hz, 1H), 6.68(d, *J* = 8.5 Hz, 2H). 7.03(d, *J* = 8.5 Hz, 2H), 7.13(t, *J* = 5.5 Hz, 1H), 7.56(s, 1H), 7.68(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.7, 22.4, 26.1, 30.1, 31.1, 33.9, 35.1, 50.6, 55.5, 63.3, 114.6, 122.6, 123.5, 128.4, 129.9, 131.5, 134.2, 144.2, 157.8, 167.9, 168.8; HRMS (ESI) m/z calcd for $C_{28}H_{33}N_5O_4$ $[M]^+$ 503.2605; found 503.2627.

3ad: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 6.5 Hz, 3H), 1.31(s, 6H), 1.86(dd, J_1 = 13.5 Hz, J_2 = 7.0 Hz, 2H), 3.49-3.62(m, 2H), 4.27(t, *J* = 7.5 Hz, 2H), 4.50(s, 2H). 5.12(q, *J* = 5.5 Hz, 1H), 7.10-7.16(m, 5H), 7.25(s, 1H), 7.58(s, 1H), 7.66(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H), 7.73(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.0, 31.1, 34.6, 51.0, 52.3, 123.4, 126.8, 128.5, 128.9, 131.6, 134.1, 136.8, 167.8, 168.9; HRMS (ESI) m/z calcd for $C_{26}H_{29}N_5O_3$ $[M]^+$ 459.2343; found 459.2320.

3ae: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 5.5 Hz, 3H), 1.33(s, 6H), 1.90(s, 2H), 3.47-3.59(m, 2H), 4.32(t, *J* = 7.0 Hz, 2H), 4.54(s, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 6.84(t, *J* = 8.0 Hz, 2H), 7.10(dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 2H), 7.60(s, 1H), 7.70(t, *J* = 4.0 Hz, 2H), 7.75(t, *J* = 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.1, 30.2, 31.1, 34.1, 35.3, 50.4, 55.2, 120.9, 122.2, 123.6, 130.6, 131.4, 131.8, 134.3, 135.9, 144.2, 167.8, 168.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.75; HRMS (ESI) m/z calcd for $C_{26}H_{28}FN_5O_3$ $[M]^+$ 477.2249; found 477.2267.

3af: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 6.5 Hz, 3H), 1.33(s, 6H), 1.92(t, *J* = 7.0 Hz, 2H), 3.47-3.60(m, 2H), 4.35(t, *J* = 7.0 Hz, 2H), 4.52-4.62(m, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 7.08(d, *J* = 8.5 Hz, 2H), 7.12(t, *J* = 8.5 Hz, 2H), 7.54(s, 1H), 7.67(s, 1H), 7.70(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.76(dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 29.9, 31.0, 33.9, 34.6, 51.2, 55.0, 123.3, 123.6, 128.7, 130.3, 131.5, 132.7, 134.4, 135.2, 143.6, 167.7, 168.6; HRMS (ESI) m/z calcd for $C_{26}H_{28}ClN_5O_3$ $[M]^+$ 493.1953; found 493.1939.

3ag: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 6.0 Hz, 3H), 1.31(s, 6H), 1.86(s, 2H), 3.48-3.58(m, 2H), 4.27(t, *J* = 6.5 Hz, 2H), 4.47(s, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 7.01(d, *J* = 8.5 Hz, 2H), 7.26(s, 1H), 7.52(s, 1H), 7.56(s, 1H), 7.68(t, *J* = 3.0 Hz, 2H), 7.73(t, *J* = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.1, 30.1, 31.1, 34.1, 35.1, 50.5, 55.0, 120.8, 123.5, 130.6, 131.4, 131.6, 134.2, 135.8, 167.7, 168.4; HRMS (ESI) m/z calcd for $C_{26}H_{28}BrN_5O_3$ $[M]^+$ 537.1448; found 537.1451.

3ah: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 5.5 Hz, 3H), 1.32(s, 6H), 1.87(s, 2H), 3.50-3.61(m, 2H), 4.28(t, *J* = 7.0 Hz, 2H), 4.50(dd, J_1 = 6.0 Hz, J_2 = 1.5 Hz, 2H). 5.12(dd, J_1 = 11.5 Hz, J_2 = 6.0 Hz, 1H), 6.98(t, *J* = 8.0 Hz, 2H), 7.06(dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.12(dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1H), 7.53(s, 1H), 7.71(dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz, 2H), 7.78(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.2, 28.4, 30.2, 31.2, 35.3, 50.5, 53.6, 119.0, 119.3, 122.3, 123.6, 127.5, 131.5, 132.3, 132.4, 134.4, 167.6, 168.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ -114.56; HRMS (ESI) m/z calcd for $C_{26}H_{27}BrFN_5O_3$ $[M]^+$ 555.1354; found 555.1365.

3ai: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 6.0 Hz, 3H), 1.32(s, 6H), 1.86(s, 2H), 3.65-3.74(m, 2H), 4.26(t, *J* = 7.0 Hz, 2H), 4.48(s, 2H). 5.16(d, *J* = 7.5 Hz, 1H), 7.33(d, *J* = 8.5 Hz, 2H), 7.56(s, 2H), 7.70(s, 2H), 7.73(s, 2H), 8.02(d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.5, 26.1, 30.2, 31.2, 34.6, 35.2, 50.7, 54.7, 123.7, 123.8, 129.9, 131.4, 134.6, 144.8, 147.1, 167.7, 168.0; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2186.

3aj: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88(t, *J* = 7.5 Hz, 3H), 1.29(s, 6H), 1.83(t, *J* = 6.5 Hz, 2H), 3.63-3.78(m, 2H), 4.24(t, *J* = 7.0 Hz, 2H), 4.43(t, *J* = 5.0 Hz, 2H). 5.15(q, *J* = 5.5 Hz, 1H), 7.34(t, *J* = 7.5 Hz, 1H), 7.50(d, *J* = 7.0 Hz, 1H), 7.51(s, 1H), 7.66(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.71(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.97(dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1H), 8.02(s, 1H), 8.05(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.1, 31.1, 34.3, 34.8, 50.7, 54.7, 122.0, 123.5, 123.9, 129.5, 131.4, 134.3, 135.2, 139.3, 148.2, 167.7, 168.1; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2217.

3ak: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, *J* = 6.5 Hz, 3H), 1.32(s, 6H), 1.89(t, *J* = 5.5 Hz, 2H), 3.67-3.73(m, 1H), 4.05(dd, J_1 = 14.5 Hz, J_2 = 4.5 Hz, 1H), 4.30(t, *J* = 7.5 Hz, 2H), 4.54(d, *J* = 5.5 Hz, 2H), 5.31(dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz, 1H), 6.90(s, 1H), 7.21(dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1H), 7.33-7.35(m, 2H), 7.57(s, 1H), 7.71(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 7.77(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 8.00 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, , 22.4, 26.1, 30.1, 31.1, 32.6, 35.2, 50.53, 53.5, 122.6, 123.4, 125.4, 128.3, 131.5, 132.8, 132.9, 133.3, 134.2, 149.0, 167.7, 168.0; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2170.

3al: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 6.5 Hz, 3H), 1.30(s, 6H), 1.85(s, 2H), 2.49(s, 3H), 3.59-3.68(m, 2H), 4.25(t, *J* = 7.5 Hz, 2H), 4.46(t, *J* = 15.0 Hz, 2H), 5.15(q, *J* = 5.5 Hz, 1H), 7.23(d, *J* = 7.5 Hz, 2H), 7.55(s, 2H), 7.66(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.71(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H), 7.74(d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 26.5, 30.1, 31.1, 34.6, 35.1, 50.4, 54.8, 123.5, 128.6, 129.1, 131.4, 134.2, 135.8, 142.6, 167.8, 168.3, 197.7; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_5O_4$ $[M]^+$ 501.2449; found 501.2465.

3am: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 6.5 Hz, 3H), 1.32(s, 6H), 1.87(t, *J* = 7.0 Hz, 2H), 3.59-3.69(m, 2H), 4.27(t, *J* = 7.0 Hz, 2H), 4.49(t, *J* = 5.0 Hz, 2H), 5.15(q, *J* = 5.5 Hz, 1H), 7.26(s,

1H), 7.32(s, 1H), 7.42(d, J = 8.0 Hz, 2H), 7.54(s, 1H), 7.69(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.1, 31.1, 34.4, 35.1, 50.4, 54.9, 123.5, 123.7, 128.2, 128.5, 129.2, 131.4, 134.3, 134.5, 167.8, 168.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ -62.99; HRMS (ESI) m/z calcd for $C_{27}H_{28}F_3N_5O_3$ $[M]^+$ 527.2217; found 527.2234.

3an: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87(t, J = 6.5 Hz, 3H), 1.27(s, 6H), 1.80(s, 2H), 3.56-3.68(m, 2H), 3.80(s, 3H), 4.18(t, J = 7.5 Hz, 2H), 4.38(s, 2H), 5.13(dd, J_1 = 11.0 Hz, J_2 = 5.0 Hz, 1H), 7.17(d, J = 8.5 Hz, 2H), 7.54(s, 1H), 7.60(t, J = 4.0 Hz, 2H), 7.65(t, J = 4.0 Hz, 2H), 7.78(d, J = 8.0 Hz, 2H), 8.07(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.3, 26.1, 30.0, 31.1, 34.6, 35.0, 50.4, 51.9, 54.8, 122.7, 123.3, 128.7, 128.9, 129.7, 131.5, 134.0, 142.5, 144.4, 166.7, 167.7, 168.3; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_5O_5$ $[M]^+$ 517.2398; found 517.2399.

3ao: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91(t, J = 6.5 Hz, 3H), 1.35(s, 6H), 1.99(s, 2H), 3.52(t, J = 11.0 Hz, 1H), 3.70(dd, J_1 = 13.0 Hz, J_2 = 4.5 Hz, 1H), 4.46(d, J = 6.0 Hz, 2H), 4.69(d, J = 13.0 Hz, 1H), 4.79(d, J = 13.0 Hz, 1H), 5.20(dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz, 1H), 7.22(d, J = 8.0 Hz, 2H), 7.30(t, J = 7.5 Hz, 1H), 7.36-7.40(m, 4H), 7.48(d, J = 7.5 Hz, 2H), 7.66(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 8.03(s, 1H), 8.38(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.2, 30.1, 31.1, 34.3, 35.1, 50.6, 55.3, 122.7, 123.5, 126.9, 127.2, 128.7, 129.3, 131.5, 134.2, 135.8, 139.6, 140.5, 144.2, 167.8, 168.7; HRMS (ESI) m/z calcd for $C_{32}H_{33}N_5O_3$ $[M]^+$ 535.2656; found 535.2663.

3ap: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.5 Hz, 3H), 1.30(s, 6H), 1.83(t, J = 7.5 Hz, 2H), 3.84(dd, J_1 = 15.0 Hz, J_2 = 11.0 Hz, 1H), 4.18-4.24(m, 2H), 4.40-4.50(m, 2H). 5.30(dd, J_1 = 10.5 Hz, J_2 = 5.0 Hz, 1H), 7.15(t, J = 3.0 Hz, 2H), 7.43-7.53(m, 4H), 7.61-7.67(m, 5H), 7.78(d, J = 7.5 Hz, 1H), 8.09(d, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 25.9, 29.6, 30.0, 31.7, 33.5, 52.5, 54.1, 123.2, 123.4, 125.1, 125.8, 126.4, 127.3, 127.8, 128.9, 131.6, 132.9, 133.8, 134.1, 167.7, 169.3; HRMS (ESI) m/z calcd for $C_{30}H_{31}N_5O_3$ $[M]^+$ 509.2500; found 509.2510.

3bj: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(dd, J_1 = 10.0 Hz, J_2 = 6.5 Hz, 3H), 1.30(d, J = 10.0 Hz, 6H), 1.83(s, 3H), 1.86(d, J = 9.0 Hz, 2H), 3.40-3.64(m, 1H), 3.89-4.03(m, 1H), 4.12-4.28(m, 3H), 4.35-4.42(m, 1H), 7.30-7.37(m, 1H), 7.54-7.61(m, 3H), 7.65-7.68(m, 3H), 7.69-7.86(m, 1H), 8.00-8.04(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 24.8, 26.1, 30.1, 31.2, 34.9, 39.7, 40.5, 50.4, 122.3, 123.0, 123.1, 125.6, 129.0, 131.4, 134.0, 134.3, 136.9, 148.0, 168.5, 168.9; HRMS (ESI) m/z calcd for $C_{27}H_{30}N_6O_5$ $[M]^+$ 518.2350; found 518.2363.

3cg: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 7.0 Hz, 3H), 1.34(t, J = 5.5 Hz, 6H), 1.90(s, 2H), 2.83(dd, J_1 = 13.0 Hz, J_2 = 4.0 Hz, 1H), 3.02(dd, J_1 = 14.0 Hz, J_2 = 10.0 Hz, 1H), 3.11(s, 1H), 3.83(dd, J_1 = 14.0 Hz, J_2 = 5.0 Hz, 1H), 3.96(dd, J_1 = 14.0 Hz, J_2 = 7.5 Hz, 1H), 4.44(d, J = 6.5 Hz, 4H), 7.10(d, J = 7.5 Hz, 2H), 7.31(d, J = 8.5 Hz, 2H), 7.69(q, J = 3.0 Hz, 3H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 25.9, 29.5, 31.0, 32.3, 35.6, 40.0, 47.0, 53.3, 120.2, 123.3, 130.9, 131.4, 131.9, 134.1, 137.3, 168.4, 173.1; HRMS (ESI) m/z calcd for $C_{27}H_{30}BrN_5O_3$ $[M]^+$ 551.1604; found 551.1608.

Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (No. 20702051), the Natural Science Foundation of Zhejiang Province (LY13B020017) and the Key Innovation Team of Science and Technology in Zhejiang Province (No. 2010R50018).

Notes and references

[a] *College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014. People's Republic of China*
Fax/Tel: (+86)-571-88320147; E-mail: dingcr@zjut.edu.cn;
[b] *School of Public Health, Central South University, Changsha 410078, People's Republic of China.*

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

1 (a) S. V. Bhat, B. A. Nagasampagi, M. Sivakumar, *Chemistry of Natural Products*, Springer: Berlin, 2005; (b) A. B. Hughes. *Amino Acids, Peptides and Proteins in Organic Chemistry,* Wiley-VCH, Weinheim, 2009.

2 (a) G. Chen, T. Shigenari, P. Jain, Z.-P. Zhang, Z. Jin, J. He, S.-H. Li, C. Mapelli, M. M. Miller, M. A. Poss, P. M. Scola, K.-S. Yeung, and J.-Q. Yu, *J. Am. Chem. Soc.,* 2015, **137**, 3338; (b) L. Chu, K.-J. Xiao and J.-Q. Yu, *Science,* 2014, **346**, 451; (c) W. Gong, G.-F. Zhang, T. Liu, Ramesh Giri and J.-Q. Yu, *J. Am. Chem. Soc.,* 2014, **136**, 16940; (d) K.-J. Xiao, D.-W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.,* 2014, **136**, 8138; (e) J. He, S.-H. Li, Y.-Q. Deng, H.-Y. Fu, B. N. Laforteza, J. E. Spangler, A. Homs and J.-Q. Yu, *Science,* 2014, **343**, 1216.

3 (a) J.-Q. Yu and Z.-J. Shi, *Topics in Current Chemistry,* Springer: Heidelberg, 2010; (b) L. Ackermann, *Modern Arylation Methods,* Wiley-VCH: Weinheim, 2009.

4 For recent reviews on C(sp^2)-H activation, see: (a) F.-Z. Zhang and D. R. Spring, *Chem. Soc. Rev*., 2014, **43**, 6906; (b) M. Zhang, Y.-F. Zhang, X.-M. Jie, H.-Q. Zhao, G. Li and W.-P. Su, *Org. Chem. Front*., 2014, **1**, 843; (c) R. Giri, S. Thapa and A. Kafle, *Adv. Synth. Catal*., 2014, **7**, 1395; (d) G.-F. Shi and Y.-H. Zhang, *Adv. Synth. Catal*., 2014, **7**, 1419; (e) S. D. Sarkar, W.-P. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal*., 2014, **7**, 1461; (f) A. Ros, R. Fernandez and J. M. Lassaletta, *Chem. Soc. Rev*., 2014, **43**, 3229; (g) Q.-Z. Zheng and N. Jiao, *Tetrehedron Lett.,* 2014, **55**, 1121; (h) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.,* 2013, **42**, 5744; (i) D. Li, C. He, H. Cai and G.-W. Wang, *Chin. J. Org. Chem.,* 2013, **33**, 203; (j) J. WencelDelord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev*., 2011, **40**, 4740; (k) C. Liu, H. Zhang, W. Shi and A.-W. Lei, *Chem. Rev*., 2011, **111**, 1780; (l) C. S. Yeung and V. M. Dong, *Chem. Rev*., 2011, **111**, 1215; (m) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624; (n) T. W. Lyons and M. S. Sanford, *Chem. Rev*., 2010, **110**, 1147; (o) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed*., 2009, **48**, 9792; (p) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed*., 2009, **48**, 5094; (q) B.-J. Li, S.-D. Yang and Z.-J. Shi, *Synlett,* 2008, 949; (r) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev*., 2007, **107**, 174; (s) L. C. Campeau and K. Fagnou, *Chem. Commun*., 2006, **42**, 1253.

5 For recent reviews on C(sp^3)-H activation, see: (a) G.-Y. Qiu and J. Wu, *Org. Chem. Front*., 2014, **2**, 1; (b) B. Zhang, H.-X. Guan, B. Liu, and B.-F. Shi, *Chin. J. Org. Chem.,* 2014, **34,** 1487; (c) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev*., 2012, **41**, 3464; (d) O. Baudoin, *Chem. Soc. Rev*., 2011, **40**, 4902; (e) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev*., 2011, **111**, 1293; (f) H. Li, B.-J. Li and Z.-J. Shi, *Catal. Sci. Technol*., 2011, **1**, 191; (g) W. R. Gutekunst and P. S. Baran, *Chem. Soc.*

Rev., 2011, **40**, 1976; (h) M. Wasa, K. M. Engle and J.-Q. Yu, *Isr. J. Chem*., 2010, **50**, 605; (i) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J*., 2010, **16**, 2654; (j) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (k) R. G. Bergman, *Nature*, 2007**, 446**, 391; (l) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234.

6 (a) L. D. Tran, J. Roane and O. Daugulis, *Angew. Chem., Int. Ed.,* 2013,**52**, 6043; (b) E. T. Nadres and O. Daugulis, *J. Am. Chem. Soc.,* 2012, **134**, 7; (c) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc*., 2012, **134**, 18237; (d) L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed*., 2012**, 51**, 5188; (e) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc*., 2010, **132**, 3965; (f) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154.

7 B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391.

8 (a) B. Wang, W. A. Nack, G. He, S.-Y. Zhang and G. Chen, *Chem. Sci.,* 2014, **5**, 3952; (b) G. He, S.-Y. Zhang, W. A. Nack, Q. Li and G. Chen, *Angew. Chem., Int. Ed.,* 2013, **52**, 11330; (c) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li and G. Chen, *J. Am. Chem. Soc*., 2013, **135**, 2124; (d) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.,* 2013, **135**, 12135; (e) G. He, Y. Zhao, S.-Y. Zhang, C. Lu and G. Chen, *J. Am. Chem. Soc.,* 2012, **134**, 3; (f) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack and G. Chen, *J. Am. Chem. Soc*., 2012, **134**, 7313; (g) G. He and G. Chen, *Angew. Chem., Int. Ed.,* 2011, **50**, 5192.

9 N. Rodriguez, J. A. Romero-Revilla, M. A. Fernandez-Ibanez, J. C. Carretero, *Chem. Sci.,* 2013, **4**, 175.

10 F.-M. Fan and D.-W. Ma, *Angew. Chem., Int. Ed.,* 2013, **52**, 12152.

11 (a) K. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.,* 2014, **53**, 11950; (b)K. Chen, S.-Q. Zhang, J.-W. Xu, F. Hu and B.-F. Shi, *Chem.Commun.*, 2014, **50**, 13924; (c) Q. Zhang, K. Chen, W.-H. Rao, Y. Zhang, F.-J. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.,* 2013, **52**, 13588; (d) K. Chen, F. Hu, S.-Q. Zhang and B.-F. Shi,. *Chem. Sci.,* 2013, **4**, 3906.

12 (a) Q. Gu, H. H. A. Mamari, K. Graczyk, E. Diers and L. Ackermann, *Angew. Chem., Int. Ed*., 2014, **53**, 3868; (b) X.-H. Ye and X.-D. Shi, *Org. Lett.,* 2014, **16**, 4448; (c) X.-H. Ye, Z.-R. He, T. Ahmed, K. Weise, N. J. Akhmedov, J. L. Petersena and X.-D. Shi, *Chem. Sci.,* 2013, **4**, 3712.

13 (a) G.-F. Zhang, Y.-X. Luan, X.-W. Han, Y. Wang, X. Wen and C.-R Ding, *Appl. Organometal. Chem.*, 2014, **28**, 332; (b) G.-F. Zhang, Y.-X. Luan, X.-W. Han, Y. Wang, X. Wen, C.-R Ding and J.-R. Gao, *Green Chem.,* 2013, **15**, 2081; (c) G.-F. Zhang, X.-W. Han, Y.-X. Luan, Y. Wang, X. Wen, L. Xu, C.-R Ding and J.-R. Gao, *RSC Adv*., 2013, **3**, 19255; (d) G.-F. Zhang, Y. Wang, X. Wen, C.-R Ding and Y. Li, *Chem. Commun*., 2012, **48**, 2979.