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Synthesis of α-arylalkylferrocenes through cesium fluoride-promoted coupling of arylboronic acids with *N*-tosylhydrazones

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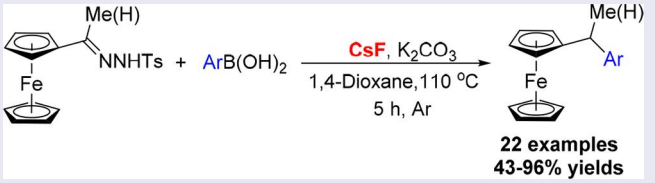
ABSTRACT

A cesium fluoride-promoted reductive coupling reaction of acylferrocene tosylhydrazones with arylboronic acids has been developed, producing highly substituted α-arylalkylferrocenes in moderate to excellent yields. The reaction employs anionic fluorine to facilitate the cleavage of C–B bond. The developed methodology demonstrates a wide substrate scope and high functional groups tolerance. Moreover, the α-arylalkylferrocenes compounds were also obtained on a multi-gram scale.

GRAPHICAL ABSTRACT



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KEYWORDS
α-Arylalkylferrocene; Boronic acid; synthesis; tosylhydrazones

Introduction

Ferrocene and its derivatives are well-known compounds that have been applied to a wide range of scientific and technological areas, such as electrochemistry,[1] materials science,[2] pharmaceuticals,[3] and bioorganometallic chemistry.[4] In particular, α-arylalkylferrocenes have attracted interest due to potential applications as asymmetric catalysts[5] and as anticancer drugs.[3b] Over the years, several useful synthetic strategies for α-arylalkylferrocenes have been developed. In generally, α-arylalkylferrocenes can be accessed through Friedel-Crafts alkylation[3,a] of ferrocenes with α-aryl alcohols or α-aryl halides catalyzed by Brønsted or Lewis acids such as CF_3CO_2H or $ZnCl_2$ (Scheme 1a). Similarly, α-aminoalkylferrocenes or α-hydroxylalkylferrocenes can also be transformed into α-arylalkylferrocenes via direct substitution of the hydroxyl or the amino groups by treatment with Lewis acids[7] (Scheme 1b). In addition, Fukuzawa et al. reported a method for the synthesis of α-arylalkylferrocenes through substitution of the α-dimethylamino group by dialkylzinc in chiral benzylferrocene[8] (Scheme 1c). Although the synthetic strategies

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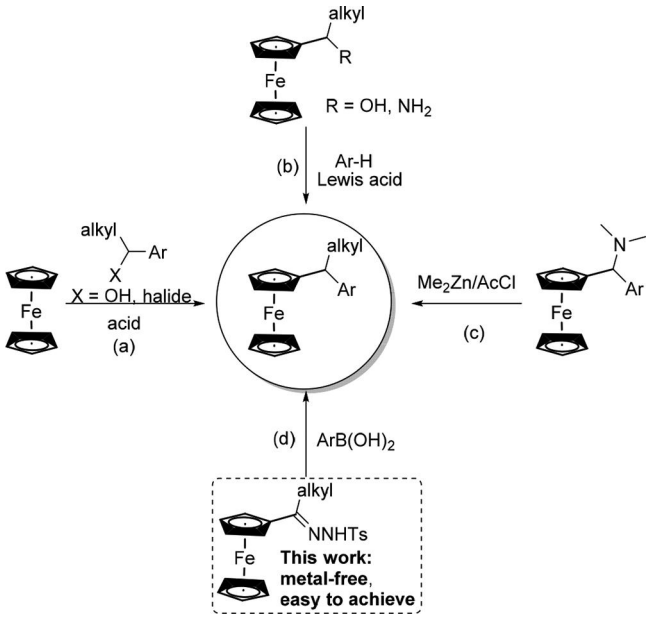


Scheme 1. Synthesis strategies for α-arylalkylferrocenes.

mentioned above have proved useful for synthesizing α-arylalkylferrocenes, these strategies face shortfalls including the need for expensive or toxic catalysts, the production of complicated byproducts, starting material unavailability, and poor functional group tolerance.

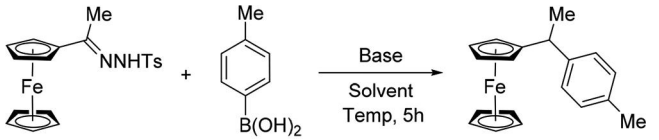
Boronic acids are highly versatile synthetic intermediates that have attracted considerable attention due to stability, low toxicity, and commercial availability.[9] Consequently, extensive investigations of boronic acids and their derivatives have been reported during the past few decades.[10] Notably, a series of coupling reactions between boronic acids and diazo compounds or diazo precursors[10c,11] such as *N*-tosylhydrazones have been developed. Initially, Kabalka first reported a facile metal-free alkylation of aryl aldehyde tosylhydrazones with trialkylboranes.[12] In 2009, Barluenga et al. provided a metal-free C–C bond formation reaction between *N*-tosylhydrazones and boronic acids to construct biarylmethane moieties.[13] Subsequently, this methodology was further developed to prepare drug fragment-like,[14] saturated cycle-containing molecules.[15] Recently, we also developed a series of protocols for the synthesis of 9-arylfluorenes, triarylmethanes, and substituted 1(or 2)-(1-phenylethyl)naphthalenes through three-component, two-step reactions of arylboronic acids and the corresponding *in situ* generated *N*-tosylhydrazones.[16] Herein, based on our previous work, we describe an efficient synthesis of α-arylalkylferrocenes through a cesium fluoride-promoted coupling reaction of acylferrocene tosylhydrazones with arylboronic acids (Scheme 1d). The synthetic method described will not only mitigate the disadvantages described above synthetic methods for α-arylalkylferrocenes, but will also broaden the substrate scope and improve functional group tolerance.

Results and discussion

Initially, we investigated the reaction of acetylferrocene tosylhydrazone (**1a**) and *p*-tolylboronic acid (**2a**) in the presence of K_2CO_3 in 1,4-dioxane in air at 110 °C. Gratifyingly,

the desired product (**3a**) was isolated in a moderate yield (Table 1, Entry 1). Encouraged by this initial result, a solvent screen was performed using toluene, DMF, and DMSO (Table 1, entries 2–4). Toluene proved to be optimal. Literature precedence indicates that the base plays a crucial role in these types of reactions to promote the formation of the diazomethane intermediate. NaOH gave lower yield (Table 1, entry 5); Et_3N was ineffective (Table 1, entry 6); however, Cs_2CO_3 prove to be a suitable base, affording **3a** in good yield (Table 1, entry 7). Vinylferrocene was the primary observed byproduct in the reaction, which was attributed to the decomposition of *N*-tosylhydrazone[17] (**3a**). Because the fluorine anion is known to facilitate the cleavage of C–B bond,[15a,15c,18] a series of experiments were conducted in the presence of fluorine sources (entries 8–14). We found that the addition of TBAF as fluorine source led to a decrease in yield, probably due to the decomposition of TBAF at high temperature (Table 1, entries 8–9). However, in the presence of fluorine anion, using toluene as a solvent and Cs_2CO_3 as a base proved detrimental to the reaction (Table 1, entries 10–12). Interestingly, when only 0.5 equivalent of CsF was added in 1,4-dioxane in the presence of K_2CO_3, the yield dramatically increased to 90% (Table 1, entry 13). In addition, when the reaction was operated under an Ar atmosphere, the yield slightly increased to 95% (Table 1, entry 15). Finally, it was confirmed that decreasing the loading of boronic acid and removing CsF under an Ar atmosphere produced lower yields (Table 1, entries 16 and 17). In summary, the optimized reaction conditions were established as follows: tosylhydrazone (0.5 mmol), boronic acid (0.75 mmol), K_2CO_3 (0.75 mmol), CsF (0.25 mmol), 1,4-dioxane (5 mL), 110 °C for 5 h under an argon atmosphere.

Table 1. Conditions screening.[a]



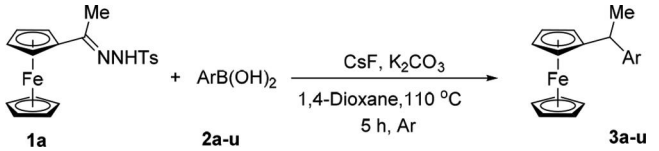
1a **2a** **3a**

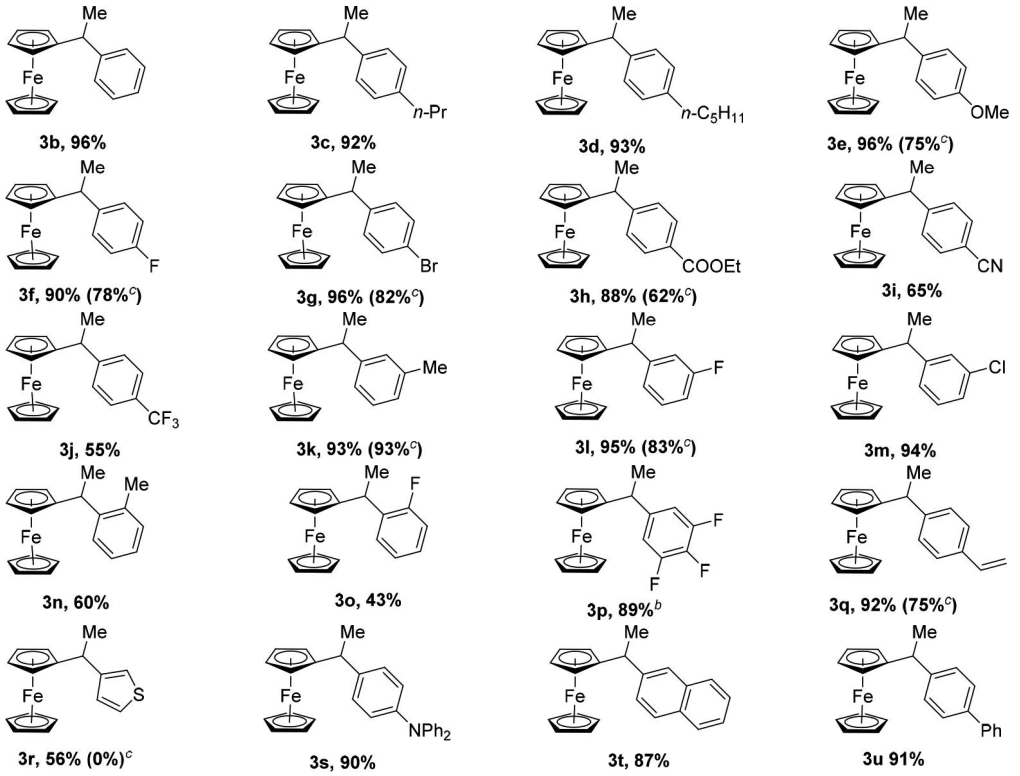
Entry	Base	Solvent	Atmosphere	Additive	Yield (%)[b]
1	K_2CO_3	1,4-Dioxane	Air	None	58
2	K_2CO_3	Toluene	Air	None	74
3	K_2CO_3	DMF	Air	None	16
4	K_2CO_3	DMSO	Air	None	10
5	NaOH	Toluene	Air	None	56
6	Et_3N	Toluene	Air	None	0
7	Cs_2CO_3	Toluene	Air	None	84
8	Cs_2CO_3	Toluene	Air	TBAF	22
9	Cs_2CO_3	1,4-Dioxane	Air	TBAF	18
10	Cs_2CO_3	Toluene	Air	CsF	78
11	K_2CO_3	Toluene	Air	CsF	75
12	Cs_2CO_3	1,4-Dioxane	Air	CsF	15
13	K_2CO_3	1,4-Dioxane	Air	CsF	90
14	none	1,4-Dioxane	Air	CsF	34
15	**K_2CO_3**	**1,4-Dioxane**	**Ar**	**CsF**	**95**
16	K_2CO_3	1,4-Dioxane	Ar	None	78
17 [c]	K_2CO_3	1,4-Dioxane	Ar	CsF	73

The significance for bold values are that the yield is the best under the reaction condition.
[a]General reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), base (0.75 mmol), solvent (5 mL), temperature (110 °C), 5 h. If additive was used the amount is 0.25 mmol (TBAF, tetrabutylammonium fluoride).
[b]Yields of isolated products.
[c]0.6 mmol **2a** was employed.

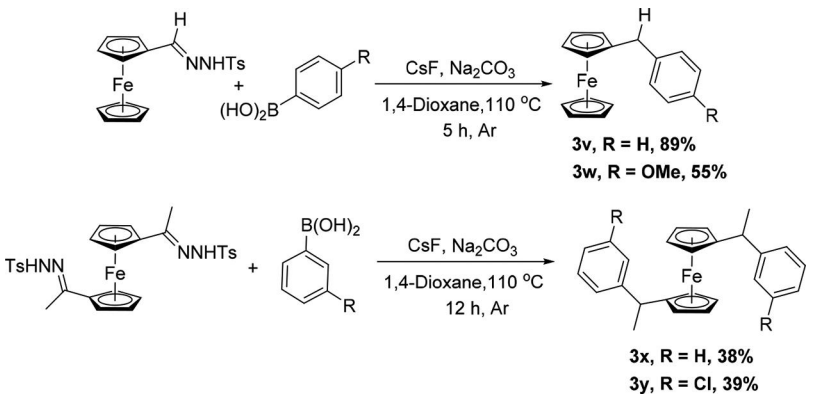
After optimizing the reaction conditions, we investigated the substrate scope for this reductive coupling reaction. As shown in Table 2, the *para*-substituted arylboronic acid substrates bearing either electron-withdrawing or electron-donating groups afford desired products **3b–3h** in good to excellent yields (88–96%). However, substrates with strong electron-withdrawing groups such as CN and CF_3 produced lower yields for products **3i** and **3j** (65 and 55%, respectively). Next, the coupling reactions of *meta*-substituted arylboronic acids were investigated. The electronic properties of the substrates showed no significant influence on the coupling reaction, affording the coupling products **3k–3m** in excellent yields (93–95%). To further ascertain the applicable scope of the methodology, various *ortho*-substituted arylboronic acids were studied. Steric hindrance of the substrates had an significant influence on the coupling reaction, producing desired products **3n** and **3o** in moderate yields (60 and 43%, respectively). To our delight, (3,4,5-trifluorophenyl)boronic acid showed good reactivity, providing product **3p** in 89% yield.

Table 2. Reductive coupling of acylferrocene sulfonylhydrazones with boronic acids.[a]





[a]Reaction conditions: Tosylhydrazone (0.5 mmol), arylboronic acid (0.75 mmol), K_2CO_3 (0.75 mmol), 1,4-dioxane (5 mL), CsF (0.25 mmol), Ar, 5 h. Yields of isolated products.
[b]9 h.
[c]Yields in parentheses were obtained under air atmosphere.



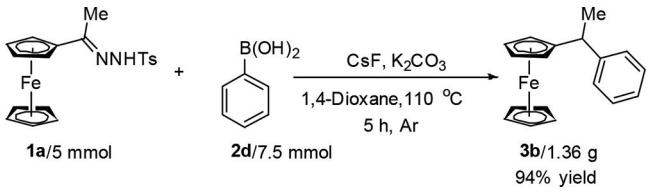
Scheme 2. Reductive coupling of others ferrocene sulfonylhydrazone with arylboronic acids.

Notably, (4-vinylphenyl)boronic acid was also successfully coupled to produce product **3q** in 92% yield. Thiophen-3-yl boronic acid was employed as a coupling partner to obtain desired product **3r** in 56% yield. In addition, the coupling reactions of (4-(diphenylamino)phenyl)boronic acid, naphthalen-2-ylboronic acid and [1,1′-biphenyl]-4-ylboronic acid successfully provided coupling products **3s–3u** in excellent yield (87–91%). To further confirm the effect of the Ar atmosphere, the reaction was conducted in air for several of the arylboronic acids. As expected, most of the desired product yields decreased compared to the previous results obtained under an Ar atmosphere (Table 2, yields in parentheses).[19] In particular, under an air atmosphere the cross-coupling reaction of thiophen-3-yl boronic acid and acetylferrocene tosylhydrazone failed to provide the product **3r**.

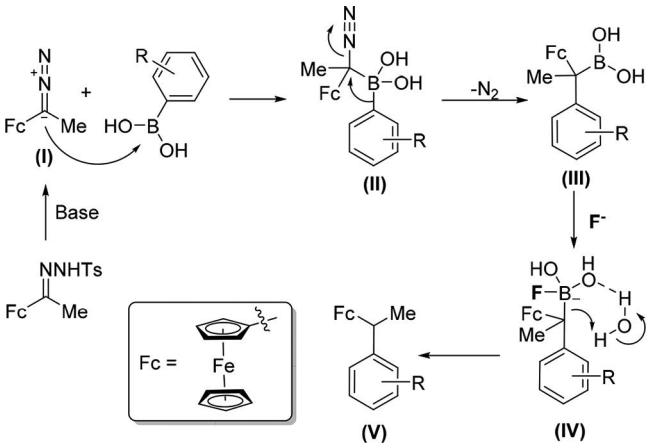
Meanwhile, we tested the reaction of arylboronic acids with *N*-tosylhydrazone derived from aryl aldehyde. The results showed that formylferrocene tosylhydrazone could also be transformed to the respective coupling products **3v** and **3w** using Na_2CO_3 as base. Moreover, the corresponding *N*-tosylhydrazone of 1,1′-diacetylferrocene was also successfully coupled to produce the desired product **3x** and **3y** (Scheme 2).

In addition, the reductive cross-coupling of *N*-tosylhydrazones with arylboronic acids could be scaled up to gram-scale, affording desired product **3b** in 94% isolated yield after column chromatography (Scheme 3).

Based on the reports in the literature[18] and our experimental results, Scheme 4 illustrates a possible reaction mechanism. First, under basic conditions, the diazo species is generated through hydrazone decomposition (**I**). Then, the diazo compound (**I**) reacts with the arylboronic acid via boronate species (**II**), to produce boronic acid (**III**). Finally, protodeboronation of (**IV**) provides the final product (**V**).



Scheme 3. A gram-scale synthesis of product **3b**.



Scheme 4. CsF-promoted coupling reaction mechanism.

Experimental section

Materials and instruments

Chemicals were obtained commercially and used as received. NMR spectra were recorded on a Bruker DPX-400 spectrometer using TMS as the internal standard. EI-Mass spectrum was measured on a LC/Q-TOF MS (Micromass, England). All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. Acylferrocene and its derivatives, and arylboronic acids were of analytical grade quality, purchased from Adamas-beta Pharmaceuticals, Inc.

General procedure for the CsF-promoted couping reaction of acylferrocene sulfonylhydrazones and arylboronic acids

A Schlenk tube (20 mL) was charged with acylferrocene sulfonylhydrazones (0.5 mmol), boronic acid (0.75 mmol), K_2CO_3 (0.75 mmol), and CsF (0.25 mmol). The tube was degassed for 30 s, and then was filled with argon. This operation was repeated for three times. After 1,4-dioxane (5 mL) was added under argon atmosphere, the resulting reaction mixture was stirred at 110 °C for 5 h. After the completion of the reaction, the reaction mixture was allowed to cool to room temperature. Ethyl acetate (5 mL) and a saturated solution of NaCl (5 mL) were added and the layers were separated. The aqueous phase was extracted three times with ethyl acetate (5 mL × 3). Then the organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude mixture was purified by chromatography on silica gel to obtain the desired products.

Conclusion

In conclusion, a procedure employing CsF under Ar conditions was developed for mediating the cross-coupling between acylferrocene sulfonylhydrazones and arylboronic acids. The efficient and scalable conditions offer a method to prepare α-arylalkylferrocenes. This methodology exhibits a broad substrate scope, good functional group tolerance, and good yields, complementing the classical synthesis strategies that produce α-arylalkylferrocenes.

Conflict of interest

We state that none of the authors have any conflict of interest in the context of this communication.

Funding

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References

[1] (a) Zhao, H.; Chen, M.; Zhu, X.; Chen, S.; Bian, Z. *Res. Chem. Intermed.* **2015**, *41*, 3971–3980; (b) Qu, F.; Zhang, Y.; Rasooly, A.; Yang, M., *Anal. Chem.* **2014**, *86*, 973–976; (c) Peng, L.; Feng, A.; Huo, M.; Yuan, J. *Chem. Commun.* **2014**, *50*, 13005–13014; (d) Camurlu, P.; Bicil, Z.; Gültekin, C.; Karagoren, N. *Electrochim. Acta* **2012**, *63*, 245–250; (e) Gagne, R. R.; Koval, C. A.; Lisensky, G. C. *Inorg. Chem.* **1980**, *19*, 2854–2855.

[2] (a) Bui-Thi-Tuyet, V.; Trippé-Allard, G.; Ghilane, J.; Randriamahazaka, H. *ACS Appl. Mater. Interfaces* **2016**, *8*, 28316–28324; (b) Sun, R.; Wang, L.; Yu, H.; Abdin, Z.-u.; Chen, Y.; Huang, J.; Tong, R. *Organometallics* **2014**, *33*, 4560–4573; (c) Hardy, C. G.; Ren, L. X.; Tamboue, T. C.; Tang, C. B., *J. Polym. Sci. A Polym. Chem.* **2011**, *49*, 1409–1420; (d) Yuan, W. Z.; Mao, Y.; Zhao, H.; Sun, J. Z.; Xu, H. P.; Jin, J. K.; Zheng, Q.; Tang, B. Z., *Macromolecules* **2008**, *41*, 701–707; (e) Tamura, K.; Akutagawa, N.; Satoh, M.; Wada, J.; Masuda, T. *Macromol. Rapid Commun.* **2008**, *29*, 1944–1949; (f) Geiger, W. E., *Organometallics* **2007**, *26*, 5738–5765; (g) Wilbert, G.; Zentel, R. *Macromol. Chem. Phys.* **1996**, *197*, 3259–3268.

[3] (a) Hillard, E.; Vessières, A.; LeBideau, F.; Plażuk, D.; Spera, D.; Huché, M.; Jaouen, G. *Chem. Med. Chem.* **2006**, *1*, 551–559; (b) Ornelas, C. *New J. Chem.* **2011**, *35*, 1973–1985.

[4] van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931–5986.

[5] (a) Gomez Arrayas, R.; Adrio, J.; Carretero, J. C. *Angew Chem Int Ed Engl* **2006**, *45*, 7674–7715; (b) Atkinson, R. C.; Gibson, V. C.; Long, N. J. *Chem Soc Rev* **2004**, *33*, 313–328.

[6] (a) Plażuk, D.; Vessières, A.; Le Bideau, F.; Jaouen, G.; Zakrzewski, J. *Tetrahedron Lett.* **2004**, *45*, 5425–5427; (b) Neuse, E. W.; Trifan, D. S. *J. Am. Chem. Soc.* **1962**, *84*, 1850–1856; (c) Abdullah, R.; Chung, K.; Kim, Y.-W.; Hong, I. S. *Bull. Korean Chem. Soc.* **2015**, *36*, 32–35.

[7] (a) Zhou, M. G.; Zhang, W. Z.; Tian, S. K. *Chem. Commun.* **2014**, *50*, 14531–14534; (b) Xu, X.; Jiang, R.; Zhou, X.; Liu, Y.; Ji, S.; Zhang, Y. *Tetrahedron* **2009**, *65*, 877–882; (c) Vicennati, P.; Cozzi, P. G. *Eur. J. Org. Chem.* **2007**, *2007*, 2248–2253.

[8] Takahashi, T.; Konno, T.; Ogata, K.; Fukuzawa, S. *J. Org. Chem.* **2012**, *77*, 6638–6642.

[9] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *2004*, 2419–2440; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101.

[10] (a) Das, P.; Linert, W. *Coord. Chem. Rev.* **2016**, *311*, 1–23; (b) Maluenda, I.; Navarro, O. *Molecules* **2015**, *20*, 7528–7557; (c) Wang, J.; Li, H.; Zhang, Y., *Synthesis* **2013**, *45*, 3090–3098; (d) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193; (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473; (f) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (g) Zhu, C.; Falck, J. R. *Adv. Synth. Catal.* **2014**, *356*, 2395–2410.

[11] (a) Muller, S. T.; Wirth, T. *Chem. Sus. Chem.* **2015**, *8*, 245–250; (b) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500; (c) Xu, K.; Shen, C.; Shan, S. *Chin. J. Org. Chem.* **2015**, *35*, 294–308.

[12] (a) Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelley, S. W. *J. Org. Chem.* **1997**, *62*, 3688–3695; (b) Kabalka, G. W.; Maddox, J. T.; Bogas, E. *J. Org. Chem.* **1994**, *59*, 5530–5531.
[13] Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Nat. Chem.* **2009**, *1*, 494–499.
[14] Nakagawa, S.; Bainbridge, K. A.; Butcher, K.; Ellis, D.; Klute, W.; Ryckmans, T. *Chem. Med. Chem.* **2012**, *7*, 233–236.
[15] (a) Plaza, M.; Perez-Aguilar, M. C.; Valdes, C. *Chemistry (Easton)* **2016**, *22*, 6253–6257; (b) Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 328–338 (c) Perez-Aguilar, M. C.; Valdes, C. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 5953–5957.
[16] Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; He, L.; Dai, B., *RSC Adv.* **2015**, *5*, 63726–63731.
[17] Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735–4740.
[18] (a) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098; (b) Lozada, J.; Liu, Z.; Perrin, D. M. *J. Org. Chem.* **2014**, *79*, 5365–5368.
[19] (a) Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*(8), 3275–3332 (b) Sander, W. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*(4), 344–354; (c) Savino, T. G.; Senthilnathan, V. P.; Platz, M. S. *Tetrahedron* **1986**, *42*(8), 2167–2180.