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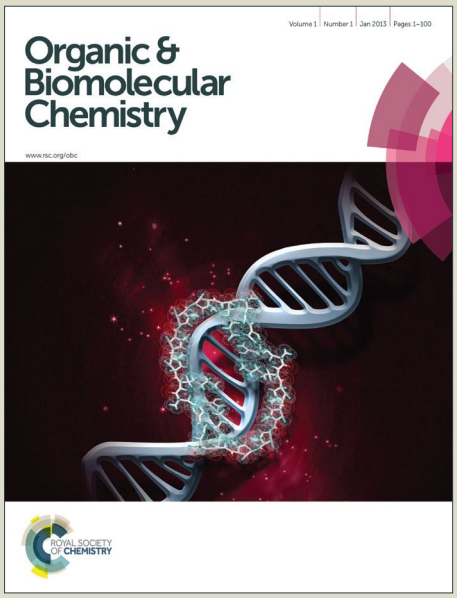

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ARTICLE

A Unprecedented Pd-catalyzed Decarboxylative Coupling Reaction of Aromatic Carboxylic Acids in Aqueous Medium under Air: Synthesis of 3-Aryl-imidazo[1,2-a]pyridines from Aryl Chlorides

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An efficient and practical protocol for palladium-catalyzed decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acids with aryl chlorides has been developed. Note that the reaction could proceed smoothly without the additive in aqueous medium under ambient atmosphere, and the addition of H_2O could effectively promote the decarboxylative arylation. Particularly noteworthy is that these results represent the first examples of Pd-catalyzed decarboxylative coupling reactions of (hetero) aromatic carboxylic acids in aqueous medium under air, and the first successful examples of the synthesis of 3-aryl-imidazo[1,2-a]pyridines using cheap, diverse aryl chlorides and heteroaryl chlorides as the starting materials.

Introduction

Imidazo[1,2-a]pyridines are one of the most important classes of organic compounds due to the abundance of the imidazo[1,2-a]pyridine structural motif in agrochemical,[1] functional materials,[2] and pharmaceutical products.[3] In particular, 3-arylimidazo[1,2-a]pyridines show excellent antiinflammatory,[4] anticancer,[5] antiprotozonal,[6] antibacterial,[7] antiulcer,[8] antiviral,[9] and antifungal activities.[10] Owing to the attractive biological properties of 3-arylimidazo[1,2-a]pyridine derivatives, a variety of synthetic strategies have been developed for the construction of 3-arylimidazo[1,2-a]pyridine scaffolds. The traditional route to 3-arylimidazo[1,2-a]pyridines such as the condensation between 2-aminopyridines and 2-bromo-1,2-diarylethanone,[11-14] and oxidative coupling of 2-aminopyridine with nitroalkenes[15]/alkyne[16]/chalcone[17], usually suffers from the prior preparation of original materials and the limited substrate scope, thus restraining the applications of these methodologies. Additionally Suzuki-type cross-coupling between 3-halo-2-arylimidazo[1,2-a]pyridines and arylboronic acid, is also important strategy for the synthesis of these derivatives.[18-22] However, the reaction usually need the preactivation of organoboron nucleophiles and aryl iodides/aryl bromides that are often not commercially available and severe environmental problems. Very recently, a more streamlined and attractive strategy is established in which the reaction can proceed via C-H arylations of imidazo[1,2-a]pyridines at C-3,[23] but these reactions were usually performed efficiently in dry organic solvents under nitrogen atmosphere, and the substrate scope is mainly limited to aryl iodides/bromides or C2-substituted imidazo[1,2-a]pyridines.[24-29]

In the past few years, a rapidly growing number of the decarboxylative coupling reactions as a new synthetic strategy have been reported that give access to various valuable product classes,[30-33] since carboxylic acids have distinguishing features of solid-state without pungent smell, non-toxicity, low cost, ready availability, easy storage, transport and handle.[34-37] However, Pd-catalyzed decarboxylative coupling reactions of (hetero) aromatic carboxylic acids in aqueous medium under air have not been reported, as far as we know. Therefore, Pd-catalyzed decarboxylative coupling reactions in aqueous solvent would be rich in challenges. To the best of our knowledge, the decarboxylative coupling of imidazo[1,2-a]pyridine-3-carboxylic acids with aryl halides was only reported by Lee on the syntheses of 3-arylimidazo[1,2-a]pyridine derivatives.[38] The method suffers from significant moisture and air sensitivity, and the substrate scope is mainly limited to arylbromides.

Therefore, a catalyst system which allows the construction of C2-unsubstituted 3-arylimidazo[1,2-a]pyridine derivatives in aqueous medium under air, and makes the coupling partner more economical and practical is still in demand since such

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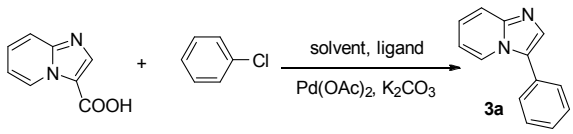
Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Solvent	Temp (°C)	Yield (%) [b]
1 [d, e]	PCy_3	DMA	160	91 [c]
2 [e]	PCy_3	DMA	160	52
3 [d]	PCy_3	DMA	160	61
4	PCy_3	DMA	160	70
5	PCy_3	DMA	150	26
6	PCy_3	DMF	150	20
7	PCy_3	DMSO	150	Trace
8	PCy_3	Dioxane	110	Trace
9	PCy_3	DMA/H_2O (40/1)	150	67
10	PCy_3	DMA/H_2O (3/1)	150	5
11	PCy_3	Xylene/H_2O (1/1)	120	NR
12	S-Phos	DMA/H_2O (40/1)	150	81
13[f]	S-Phos	DMA/H_2O (40/1)	150	100 (96 [c])
14[f]	X-Phos	DMA/H_2O (40/1)	150	59
15[f]	Ru-Phos	DMA/H_2O (40/1)	150	30
16[f]	S-Phos	DMA/H_2O (40/1)	140	11

[a] Reaction conditions: 0.3 mmol of imdazol[1,2-a]pyridine-3-carboxylic acid, 0.9 mmol of chlorobenzene, 0.9 mmol of K_2CO_3, 5 mol% of $Pd(OAc)_2$, 6 mol% of ligand, and 4 mL of solvent under air for 24 h. [b] GC yields. [c] Isolated yields.
[d] 0.15mmol of Cu_2O. [e] 4 mL of dry DMA, 200 mg of 4 Å molecular sieve, under nitrogen. [f] 7.5 mol% of ligand.

catalyst system has the potential to be used in industrial process. In continuing our former works on palladium-catalyzed decarboxylative cross-coupling reactions,[39] herein, we attempt to develop a convenient and efficient protocol for the synthesis of 3-aryl-imidazo[1,2-a]pyridines in aqueous medium under air via palladium-catalyzed decarboxylative coupling of imidazo[1,2-a]pyridine-3-carboxylic acids with cheap aryl/heteroaryl chlorides.

Results and discussion

The decarboxylative cross-coupling reaction of imidazo[1,2-a]pyridine-3-carboxylic acid with chlorobenzene was chosen as model reaction to optimize the reaction conditions as shown in Table 1. To make our present methodology more convenient and practical, we initiated our studies by examining the influence of moisture and air on the conversion. First, we performed the reaction in dry DMA under nitrogen in the presence of 0.5 equiv of Cu_2O at 160 °C, and the desired product was obtained in 91% isolated yield (entry 1). With the same reaction conditions above, only 52% GC yield was obtained in the absence of Cu_2O (entry 2). Then, we carried out the reaction in DMA under air at 160 °C with Cu_2O, and the desired coupling product was obtained in 61% yields (entry 3). However, the yields increased slightly without Cu_2O in 70% yield, indicating that the addition of Cu_2O is not necessary under air (entry 4). Lowering the reaction temperature to 150

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°C led to poor substrate conversion (entry 4 vs entry 5). Subsequently, the effects of different solvents were tested at 150 °C, and no improvement of the yield was observed (entries 6-8).To our delight, the yields significantly changed with the addition of H_2O to these catalytic systems (entry 9). However, when the reaction was conducted in DMA/H_2O (3:1), only trace amounts of product 3a were detected (entry 10). Obviously, DMA/H_2O (40:1) as the solvent is best choice for this reaction (entries 5-11). Then, a variety of bases were investigated, such as K_2CO_3, Na_2CO_3, KOAc, $K_3PO_4·7H_2O$, Cs_2CO_3 and KO^{t}Bu (see Table S1 in Supporting Information). K_2CO_3 was identified as the best base. Other ligands such as S-Phos, X-Phos, Ru-Phos were also screened (Figure 2), and obviously, S-phos was more effective than the other ligands in this reaction affording a 96% isolated yield (entries 12-15). Finally, the replacement of $Pd(OAc)_2$ with $PdCl_2$, $Pd_2(dba)_3$, $Pd(acac)_2$ or $Pd(CF_3CO_2)_2$ leads to a drop in yield (see Table S1 in Supporting Information).

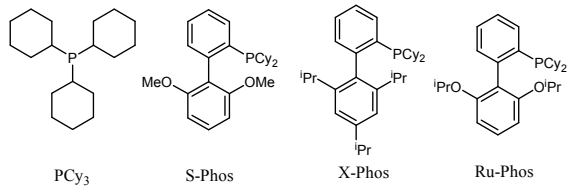
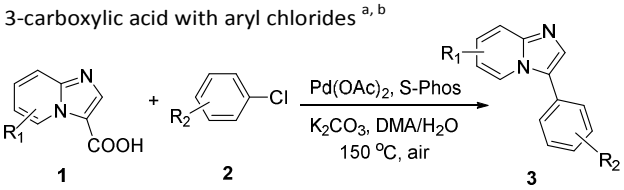
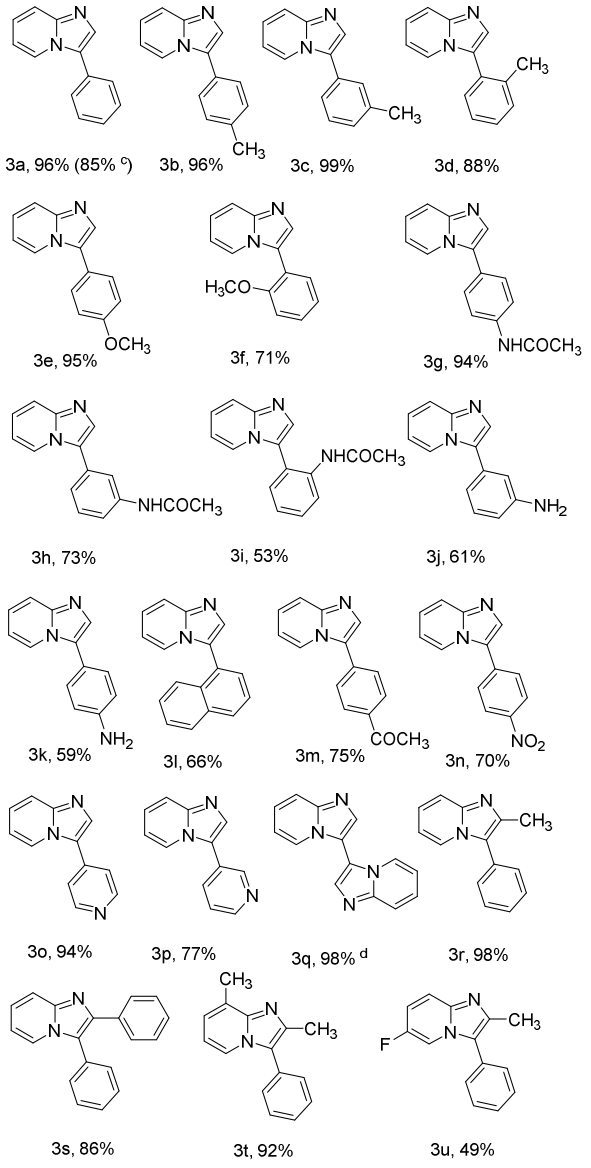


Figure 1. Various ligands used in Pd-catalyzed decarboxylative arylation

With the optimized conditions in hand, the scope of the coupling of aryl chlorides with imidazo[1,2-a]pyridine-3-carboxylic acid is summarized in Scheme 1. The para-substituted aryl chlorides such as 4-chlorotoluene, 4-chloroanisole or 4-chloroacetanilide gave the corresponding products in 94-96% yields (products 3b, 3e and 3g). Electron-deficient aryl chlorides such as 4-chloroacetophenone or 4-chloronitrobenzene gave the coupling product in 75 and 70% yields, respectively (products 3m and 3n). 4-Chloroaniline and 1-chloronaphthalene was also found to be suitable coupling partner, and gave the product in 59% and 66% yields, respectively (products 3k, 3l). For meta or ortho-substituted aryl chlorides such as 2-chloroanisole, 3-chloroacetanilide, 2-chloroacetanilide or 3-chloroaniline, products 3f, 3h-j were obtained in slightly lower yields of 53-73%. Notably, the sterically hindered 2-chlorotoluene and 3-chlorotoluene also proceeded smoothly, giving the desired arylation products 3d and 3c in 88% and 99% yields, respectively. Moreover, heteroaromatic chlorides such as 4-chloropyridine and 3-chloropyridine were also reactive partners in this coupling to give the product in 94 and 77% yields, respectively (products 3o and 3p). Subsequently, the scope of imidazo[1,2-a]pyridine-3-carboxylic acids was also explored, and the results are summarized in Scheme 1. For example, 2-methyl, 2-phenyl and 2,8-dimethyl imidazo[1,2-a]pyridine-3-carboxylic acids could be efficiently converted into the corresponding products in good yields (products 3r-3t). However, 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid had a relatively lower reactivity,

Scheme 1. Decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid with aryl chlorides [a, b]





[a] Reaction conditions: 0.3 mmol of imdazol[1,2-a]pyridine-3-carboxylic acid, 0.9 mmol of aryl chlorides, 0.9 mmol of K_2CO_3, 5 mol% of $Pd(OAc)_2$, 7.5 mol% of S-Phos, 4 mL of DMA, and 0.1 mL of H_2O at 150 °C under air for 24 h. [b] Isolated yields. [c] 6.2 mmol (1.0 g) of imdazol[1,2-a]pyridine-3-carboxylic acid. [d] Without aryl chlorides.

only affording the product in moderate yield (product 3u). To

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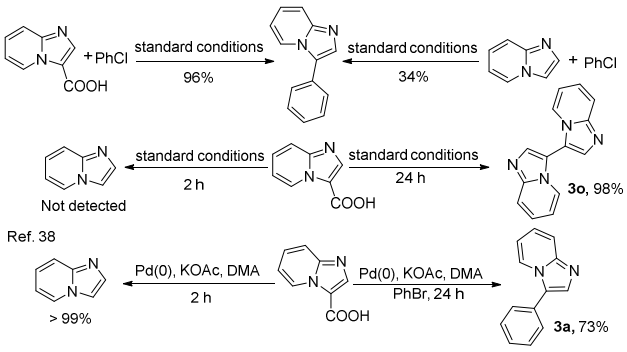
demonstrate the scalability of the reaction, we chose the decarboxylative reaction of imidazo[1,2-a]pyridine-3-carboxylic acid with chlorobenzene on a 1.0 g scale. The desired product was isolated in 85% yield (product 3a).

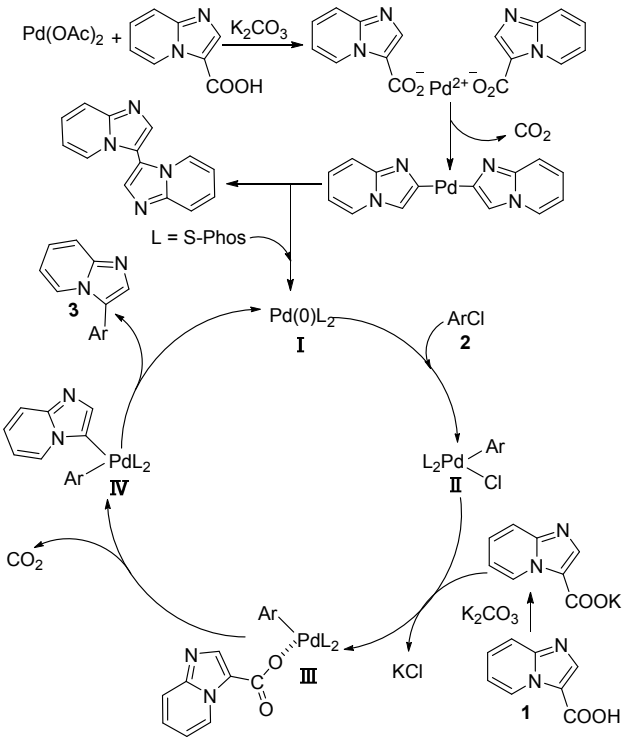
Scheme 2. Comparative experiments of different reaction conditions



Finally, the investigation was aimed at revealing the decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid as shown in Scheme 2. With the optimized conditions, the decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid with chlorobenzene gave the product in 96% yield, but the direct arylation of imidazo[1,2-a]pyridine with chlorobenzene was still very sluggish, affording only a 34% GC yield of the arylation product. Under the same conditions without added aryl chlorides, imidazo[1,2-a]pyridine from hydrodecarboxylation of imidazo[1,2-a]pyridine-3-carboxylic acid was not also detected for 2 h, and decarboxylative homocoupling of imidazo[1,2-a]pyridine-3-carboxylic acid was proformed in 98% yield for 24 h. On the basis of the previous reports, [38] the decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid with bromobenzene gave the product in 73% yield for 24 h, and without added aryl chlorides imidazo[1,2-a]pyridine from hydrodecarboxylation of imidazo[1,2-a]pyridine-3-carboxylic acid was afforded in high yield of 99% for 2 h. The results indicated that the arylation products of imidazo[1,2-a]pyridine-3-carboxylic acid were generated not by the hydrodecarboxylation in our catalytic system.

On the basis of the above-mentioned results, a possible mechanism of palladium-catalyzed decarboxylative arylation is outlined in Scheme 3. The first step would be the release of Pd(0) species from $Pd(OAc)_2$, which is possibly through ligand-exchange of imidazo[1,2-a]pyridine-3-carboxylic acid with acetic acid anion followed by the decarboxylative reaction and reductive elimination to afford the homocoupling product and the catalytically active $Pd(0)L_2$ (I) with the assist of phosphine ligand. Then, the oxidative addition of aryl chloride (2) to $Pd(0)L_2$ would take place to form the intermediate II. Subsequently, the ligand-exchange reaction between intermediate II and carboxylic acid anion which was generated by the reaction of carboxylic acid and K_2CO_3 could occur to afford intermediate III. After the intermediate III underwent the decarboxylative reaction to release one molecular CO_2 to form the intermediate IV, the reductive elimination of the intermediate IV would afford the corresponding products (3) and regenerate the catalytically active catalyst $Pd(0)L_2$ to fulfill the catalytic cycle.

Scheme 3. Proposed mechanism of palladium-catalyzed decarboxylative arylation



Experimental

General Procedure for Palladium-catalyzed decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid with aryl chlorides

Imidazo[1,2-a]pyridine-3-carboxylic acid (0.3 mmol), aryl chloride (0.9 mmol, 3 equiv), K_2CO_3 (0.9 mmol, 3 equiv), $Pd(OAc)_2$ (5 mol %) and S-phos (7.5 mol %) were added to a 10 mL round-bottomed flask, and then a mixed solvent of 4.0 mL of DMA and 0.1 mL of H_2O was added. The mixture was stirred at 150 °C for 24 h under air. After the reaction was complete, the mixture was washed with water and extracted with ethyl acetate three times. The combined organic layer was dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using ethyl acetate or hexane/ethyl acetate as the eluent to give the pure product.

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The products were characterized by ^{1}H NMR, ^{13}C NMR, m.p., MS and HRMS.

Conclusions

In conclusion, we have developed an efficient and facile protocol for the synthesis of 3-aryl-imidazo[1,2-a]pyridines via palladium-catalyzed decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acids with aryl chlorides. It is worth noting that the reaction proceeded smoothly without the additive in aqueous medium under ambient atmosphere, and the scope of the substrate could be extended to electron-poor, electron-neutral, electron-rich, even sterically hindered aryl chlorides and aromatic heterocyclic chlorides. Remarkably, the decarboxylative arylation was quite effectively promoted by the addition of H_2O. This economical and practical synthetic protocol for 3-arylimidazo[1,2-a]pyridines may have wide applications to the industrial process in the future.

Acknowledgements

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References

1 U. Egner, K. P. Gerbling, G. A. Hoyer, G. Krüger and P. Wegner, *Pestic. Sci*., 1996, **47**, 145.
2 J. S. Bae, D. W. Lee, D. H. Lee and D. S. Jeong, *PCT Int. Appl*., WO2007011163A1, 2007.
3 G. C. Moraski, L. D. Markley, P. A. Hipskind, H. Boshoff, S. Cho, S. G. Franzblau and M. J. Miller, *ACS Med. Chem. Lett*., 2011, **2**, 466.
4 R. B. Lacerda, C. K. de Lima, L. L. da Silva, N. C. Romeiro, A. L. Miranda, E. J. Barreiro and C. A. Fraga, *Bioorg. Med. Chem*., 2009, **17**, 74.
5 W. M. El-Sayed, W. A. Hussin, Y. S. Al-Faiyz and M. A. Ismail, *Eur. J. Pharmacol*., 2013, **715**, 212.
6 M. A. Ismail, R. K. Arafa, T. Wenzler, R. Brun, F. A. Tanious, W. D. Wilson and D. W. Boykin, *Bioorg. Med. Chem*., 2008, **16**, 683.
7 N. M. Shukla, D. B. Salunke, E. Yoo, C. A. Mutz, R. Balakrishna and S. A. David, *Bioorg. Med. Chem*., 2012, **20**, 5850.
8 J. J. Kaminski and A. M. Doweyko, *J. Med. Chem*., 1997, **40**, 427.
9 J. B. Véron, H. Allouchi, C. Enguehard-Gueiffier, R. Snoeck, G. Andrei, E. De Clercq and A. Gueiffier, *Bioorg. Med. Chem*., 2008, **16**, 9536.
10 Y. Rival, G. Grassy, A. Taudon and R. Ecalle, *Eur. J. Med. Chem*., 1991, **26**, 13.
11 C. Enguehard-Gueiffier, S. Musiu, N. Henry, J. B. Véron, S. Mavel, J. Neyts, P. Leyssen, J. Paeshuyse and A. Gueiffier, *Eur. J. Med. Chem*., 2013, **64**, 448.
12 J. G. Kettle, S. Brown, C. Crafter, B. R. Davies, P. Dudley, G. Fairley, P. Faulder, S. Fillery, H. Greenwood, J. Hawkins, M. James, K. Johnson, C. D. Lane, M. Pass, J. H. Pink, H. Plant and S. C. Cosulich, *J. Med. Chem*., 2012, **55**, 1261.
13 L. Yin, F. Erdmann and J. Liebscher, *J. Heterocycl. Chem*., 2005, **42**, 1369.
14 H. S. Patel, J. A. Linn, D. H. Drewry, D. A. Hillesheim, W. J. Zuercher and W. J. Hoekstra, *Tetrahedron Lett*., 2003, **44**, 4077.
15 K. Monir, A. K. Bagdi, M. Ghosh and A. Hajra, *Org. Lett*., 2014, **16**, 4630.
16 J. Zeng, Y. J. Tan, M. L. Leow and X. W. Liu, *Org. Lett*., 2012, **14**, 4386.
17 K. Monir, A. Bagdi, S. Mishra, A. Majee and A. Hajra, *Adv. Synth. Catal*., 2014, **356**, 1105.
18 S. C. Goodacre, L. J. Street, D. J. Hallett, J. M. Crawforth, S. Kelly, A. P. Owens, W. P. Blackaby, R. T. Lewis, J. Stanley, A. J. Smith, P. Ferris, B. Sohal, S. M. Cook, A. Pike, N. Brown, K. A. Wafford, G. Marshall, J. L. Castro and J. R. Atack, *J. Med. Chem*., 2006, **49**, 35.
19 C. Enguehard, J. L. Renou, V. Collot, M. Hervet, S. Rault and A.Gueiffier, *J. Org. Chem*., 2000, **65**, 6572.
20 J. M. Crawforth, S. C. Goodacre, D. J. Hallett, T. Harrison, A. P. Owens, M. Rowley and M. R. Teall, *PCT Int. Appl*., WO 2001038326 A2, 2001.
21 M. T. Bilodeau, M. E. Fraley and Z. Wu. *PCT Int. Appl*., WO 2003092595 A2, 2003.
22 N. Masuda, S. Miyamoto, S. Kikuchi, K. Samizu, F. Sato, Y. Shiina, W. Hamaguchi, R. Seo and T. Mihara, *PCT Int. Appl*., WO 2012133607 A1, 2012
23 J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed*., 2012, **51**, 8960.
24 J. Lee, J. Chung, S. M. Byun, B. M. Kim and C. Lee, Tetrahedron, 2013, **69**, 5660.
25 H. Y. Fu, L. Chen and H. Doucet, *J. Org. Chem*., 2012, **77**, 4473.
26 H. Cao, H. Y. Zhan, Y. G. Lin, X. L. Lin, Z. D. Du and H. F. Jiang, *Org. Lett*., 2012, **14**, 1688.
27 S. Marhadour, M. A. Bazin and P. Marchand, *Tetrahedron Lett*., 2012, **53**, 297.
28 H. Cao, Y. G. Lin, H. Y. Zhan, Z. D. Du, X. L. Lin, Q. M. Liang and H. Zhang, *RSC Adv*., 2012, **2**, 5972.
29 P. Y. Choy, K. C. Luk, Y. N. Wu, C. M. So, L. L. Wang and F. Y. Kwong, *J. Org. Chem*., 2015, **80**, 1457.
30 L. J. Goossen, F. Collet and K. Goossen, *Isr. J. Chem*., 2010, **50**, 617.
31 K. Park and S. Lee, *RSC Adv*., 2013, **3**, 14165.
32 N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev*., 2011, **40**, 5030.
33 F. Bilodeau, M. C. Brochu, N. Guimond, K. H. Thesen and P. Forgione, *J. Org. Chem.*, 2010, **75**, 1550.
34 D. Yu and Y. Zhang, *Green Chem*., 2011, **13**, 1275.
35 X. Zhang, W. Z. Zhang, X. Ren, L. L. Zhang and X. B. Lu, *Org. Lett*., 2011, **13**, 2402.
36 L. J. Gooßen, N. Rodríguez, F. Manjolinho and P. P. Lange, *Adv. Synth. Catal*., 2010, **352**, 2913.
37 D. Yu, M. X. Tan and Y. Zhang, *Adv. Synth. Catal*., 2012, **354**, 969.
38 D. Nandi, Y. M. Jhou, J. Y. Lee, B. C. Kuo, C. Y. Liu, P. W. Huang and H. M. Lee, *J. Org. Chem*., 2012, **77**, 9384.
39 X. J. Li, D. P. Zou, F. Q. Leng, C. X. Sun, J. Y. Li, Y. J. Wu and Y. S. Wu, *Chem. Commun.*, 2013, **49**, 312.