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ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · MARCH 2014

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C–H Functionalization

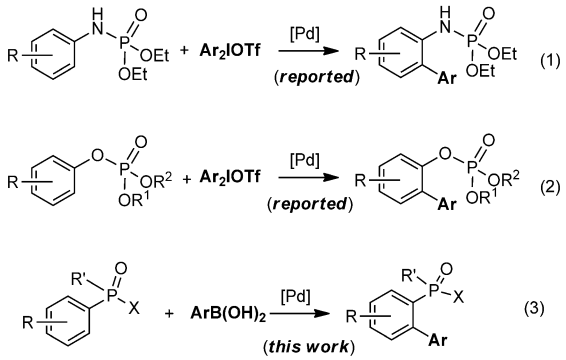
Pd^{II}-Catalyzed Mild C–H *ortho* Arylation and Intramolecular Amination Oriented by a Phosphinamide Group

Jing Guan,[a, b] Guo-Jie Wu,[c] and Fu-She Han*[a, d]

Abstract: A novel protocol for the Pd-catalyzed *ortho*-arylation of aryl phosphinamide with boronic acid is reported. By using phosphinamide as a new directing group, the reaction proceeds efficiently under mild conditions at 40 °C. Mechanistic studies reveal that the reaction proceeds via a Pd^{II} to Pd^{0} cycle. The phosphinamide group is also shown to be an effective orienting group for direct C–H amination.

The aryl phosphino compounds, that is, the aryl C–P bond-containing derivatives, are valuable structural motifs in a wide variety of areas such as naturally occurring and designed bioactive compounds,[1] functional materials,[2] and catalysis.[3] Conventionally, aryl C–P bond formation has relied mainly on the transition-metal-catalyzed cross-coupling of aryl (pseudo)-halides with $H(O)PR_2$ or HPR_2.[4,5] In addition, the nucleophilic displacement of aryl metallic reagents to $X(O)PR_2$ or XPR_2 has also been frequently used.[6]

With the major advances in transition-metal-catalyzed direct C–H functionalization,[7] direct C–H phosphorylation,[8] particularly the recent success on the intermolecular phosphorylation of azoles by Li et al.[9] and on 2-arylpyridyl derivatives by Yu et al.,[10] have appeared to provide a promising approach for the construction of aryl phosphino derivatives. As another appealing option for the synthesis of aryl phosphino compounds, the direct C–H functionalization by using the readily affordable phosphino chemicals as substrates should be a far more efficient strategy. Such a strategy takes advantage of using the phosphino functionality as a directing group, and thereby, avoiding the trouble of removing directing groups after functionalization. However, this chemistry has been rarely investigated. Very recently, a few papers have appeared in which the Pd-[11] or Rh-catalyzed[12] olefination using phosphonic acid as a directing group is reported. In addition, the Pd-catalyzed arylation of phosphoramidate [Eq. (1)][13] or phosphate [Eq. (2)][14] with high-valent diaryliodonium triflates has also been presented. However, the P-containing groups in these reactions contained a nitrogen or oxygen atom between the aryl carbon and phosphorus atom. Consequently, these methods cannot be used for the synthesis of aryl phosphino compounds. As such, protocols for the synthesis of aryl phosphino derivatives through the direct C–H functionalization of the substrates containing aryl C–P bonds are relatively unknown [Eq. (3)].



On the other hand, in cross-coupling reactions, the use of organoboron reagents takes advantage of the ready availability, broad functional group tolerance, low toxicity, and the ease of separating the boron-containing by-products.[15] Motivated by our extensive experiences in transition-metal-catalyzed couplings of boron reagents[16] as well as the interest in the development of new methods for the construction of aryl C–P bonds,[17] we recently initiated a study aimed at achieving the direct C–H functionalization of aryl phosphino substrates with boron reagents. The successful demonstration of this protocol is presented herein through the C–H *ortho* arylation of aryl phosphinamides with boronic acids. Moreover, the detailed mechanism is also clarified. In addition, we have also elaborated that the phosphinamide group can be an effective directing group for the C–H activation/C–N bond forming reaction. These novel results presented herein provide some new methods for the direct C–H functionalization and the versatile synthesis of aryl phosphino compounds.

In our initial study, the arylation of several diphenyl phosphino derivatives **1a–e** was extensively screened by varying the palladium catalysts, solvents, and temperature (Table 1). We

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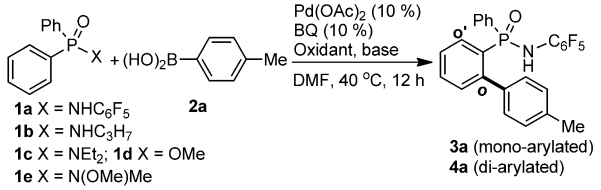
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303056.

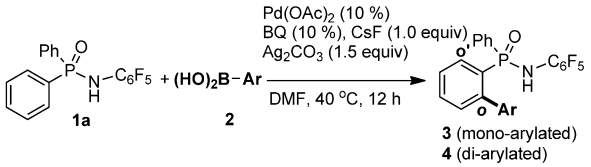
Table 1. Optimization of the reaction conditions.[a]

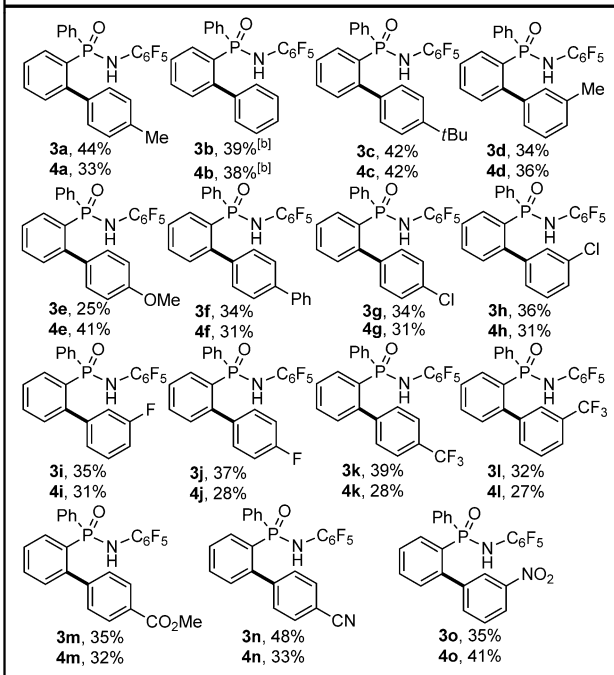


Entry	Oxidant (equiv)	Base (equiv)	**3a**/**4a**	Yield [%][b]
1	Ag_2CO_3 (1.5)	CsF (1.0)	1:0.74	77
2	Ag_2O (1.5)	CsF (1.0)	–	trace[c]
3	AgOAc (3.0)	CsF (1.0)	–	19
4	$AgBF_4$ (3.0)	CsF (1.0)	–	n.r.[d]
5	$AgNO_3$ (3.0)	CsF (1.0)	–	n.r.
6	Ag_2CO_3 (1.5)	K_3PO_4 (1.0)	1:1.1	77
7	Ag_2CO_3 (1.5)	K_2CO_3 (1.0)	–	6
8	Ag_2CO_3 (1.5)	KF (1.0)	1:1.4	61
9	Ag_2CO_3 (1.5)	Na_2CO_3 (1.0)	1:0.7	63
10	Ag_2CO_3 (1.5)	CsF (1.0)	1:0.42	76[e]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 equiv), Ag salts (*x* equiv), base (1.0 equiv), 10 mol% of $Pd(OAc)_2$, 10 mol% of BQ under nitrogen in DMF (3 mL) at 40 °C for 12 h; [b] **3a** and **4a** were separated by column chromatography, the yields were calculated based on **1a**; [c] monitored by TLC; [d] no reaction; [e] 50 mol% of BQ was used.

Table 2. Arylation of **1a** with various boronic acids.[a]





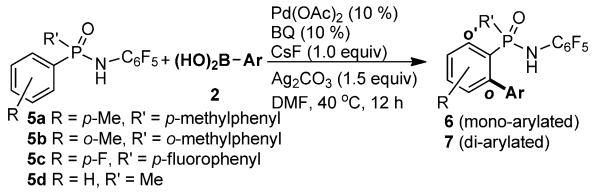
[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), Ag_2CO_3 (1.5 equiv), CsF (1.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (10 mol%) under nitrogen in DMF (3 mL) at 40 °C for 12 h; isolated yield. [b] The reaction was run at 80 °C.

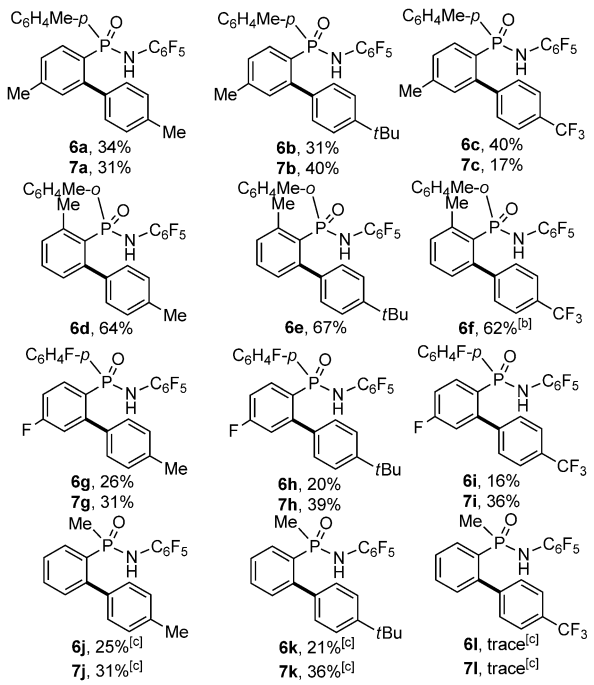
found that among the five derivatives, only phosphinamide **1a** reacted with boronic acid **2a** to afford a mixture of mono- and di-*ortho* arylated products **3a** and **4a** in 77% total yield under the roughly optimized conditions, that is, $Pd(OAc)_2$ (10 mol%), 1,4-benzoquinone (BQ; 10 mol%), Ag_2CO_3 (1.5 equiv), and CsF (1.0 equiv) in DMF at 40 °C for 12 h (entry 1). These preliminary results indicate that pentafluorophenyl-substituted phosphinamide group is a promising directing group for the C–H arylation. Notably, the reaction could proceed under mild conditions at 40 °C. Indeed, the polyfluorophenyl group has been also well demonstrated by Yu et al.[18] to be a powerful directing group in the C–H functionalization of aryl carboxylic amides, that is, the $ArCONHC_6F_4X$ (X = F, CN, or CF_3) derivatives.

Having optimized the directing group and established the basic conditions for the arylation, we improved the reaction conditions (Table 1). An extensive screening of the oxidants showed that Ag_2CO_3 was suitable (entries 1–5). In addition, an evaluation of the base showed that CsF (entry 1) and K_3PO_4 (entry 6) were the most effective bases although KF and Na_2CO_3 also afforded the product in fairly good yields (entries 8 and 9). Finally, it should be mentioned that although the selectivity for the mono- or diarylation might be improved by tuning the amount of BQ (entry 10) or the ratio of **1a** to **2a** (roughly, 56% of mono- and 64% of diarylated products could be obtained, respectively, when the ratio of **1a** to **2a** was 2:1 and 1:4. Only a trace amount of di- and monoarylated products was detected in each case), further optimization was not executed herein because the mono- and diarylated products can be separated easily by flash column chromatography. Thus, for a rapid preparation of both mono- and diarylated products, we chose the conditions in entry 1 as the appropriate conditions to examine the generality of the newly developed protocol.

We first examined the scope and limitation of this protocol by varying the aryl boronic acids (Table 2). A range of aryl boronic acids **2** reacted effectively with diphenyl phosphinamide **1a** to afford a mixture of mono- and di-*ortho* arylated product **3** and **4** in high overall yields in which the phenyl ring of the substituent was either unsubstituted (**3b** and **4b**) or decorated by electron-rich (**3a**, **4a**, **3c**–**3e** and **4c**–**4e**) and electron-deficient groups (**3f**–**3o** and **4f**–**4o**). Interestingly, the diarylation occurred exclusively in the same aryl ring as confirmed by NMR analysis and a X-ray single crystal structure of **10b** derived from **4c** (Figure 1b and Table 4). The exact origin of such selectivity is unclear, but increased acidity of the aryl proton due to the enlarged aromatic system after the first arylation seems to be the most reasonable explanation. Notably, the mild reaction conditions allowed a flexible incorporation of various labile functionalities such as OMe, Cl, F, CF_3, CO_2Me, CN, and NO_2 groups into the biaryls. The Cl, F, CN, and NO_2 groups, which are potential leaving groups in transition-metal-catalyzed cross-couplings, were particularly well tolerated. The

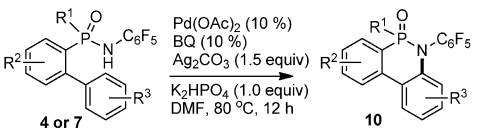
Table 3. Arylation of various phosphinamides with boronic acids.[a]

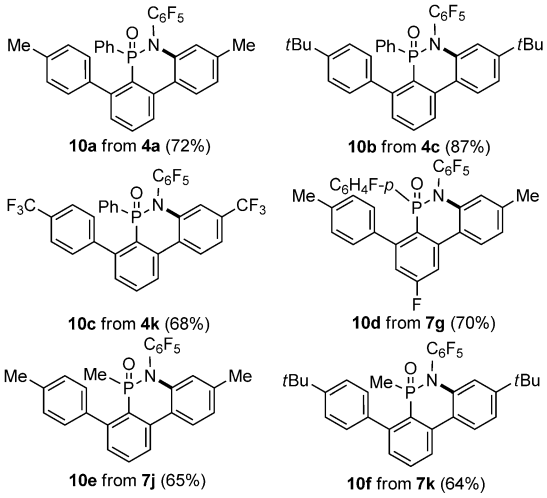




[a] Reaction conditions: **5** (0.25 mmol), **2** (0.5 mmol), Ag_2CO_3 (1.5 equiv), CsF (1.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (10 mol%) under nitrogen in DMF (3 mL) at 40 °C for 12 h; isolated yield. [b] The reaction was run for 22 h. [c] The reaction was run at 80 °C.

Table 4. Direct intramolecular C–H amination.[a]





[a] Reaction conditions: **4** or **7** (0.25 mmol), Ag_2CO_3 (1.5 equiv), K_2HPO_4 (1.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (10 mol%) under nitrogen in DMF (3 mL) at 80 °C for 12 h; isolated yield.

survival of these functionalities enables one to further modify the biaryl or triaryl systems.

The reaction efficacy of a range of aryl phosphinamides (**5a–d**) was also inspected (Table 3). For the diaryl phosphinamides whose aryl ring was modified by an electron-donating Me (**5a** and **5b**) or an electron-withdrawing F group (**5c**), the arylation proceeded smoothly with various types of boronic acids such as the electron-rich Me- and *t*Bu-, or the electron-deficient CF_3-substituted aryl boronic acids (**6a–i**, **7a–c**, and **7g–i**, respectively). Of note, only monoarylated products **6d–f** were afforded for the di-*ortho*-methylphenyl phosphinamide **5b**. The reactivity of alkyl aryl phosphinamdes such as **5d** was somewhat lowered. Moderately high yields of **6j** and **6k**, as well as **7j** and **7k** were afforded when **5d** was allowed to react with the electron-rich boronic acids. In contrast only trace amounts of **6l** and **7l** were observed in reactions with the electron-deficient boronic acids.

Since phosphino and fluoro groups have been widely demonstrated to be important functionalities in many bioactive aryl compounds,[1,19] the synthesized polyaryl phosphinamides **3**, **4**, **6**, and **7**, whose structures feature phosphino and pentafluorophenyl moieties, are anticipated to have interesting biological activities, which we are currently investigating. Compounds **3**, **4**, **6**, and **7** are thus considered to be important substrates for further transformation, for example, C–H activaton/C–N formation (vide infra). In addition, the phosphinamides can be used as Brønsted acid catalysts or precursors for the preparation of novel biaryl or triaryl phosphine ligands.

Having extensively investigated the substrate scope and limitation of the protocol, we shifted our attention to the mechanistic studies. Treatment of **1a** with 1.0 equivalent of $Pd(OAc)_2$ produced a stable arylpalladated Pd^{II} complex **8** with the incorporation of one DMF molecule [Eq. (4)]. The structure of **8** was confirmed by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, and X-ray crystallography (Figure 1a).[20] In the single-crystal structure, the DMF molecule was replaced by two H_2O molecules, since **8** was crystallized from a mixture of acetone and H_2O.

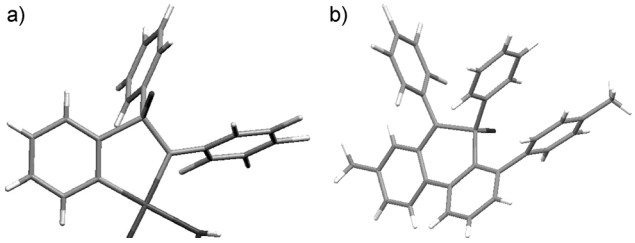
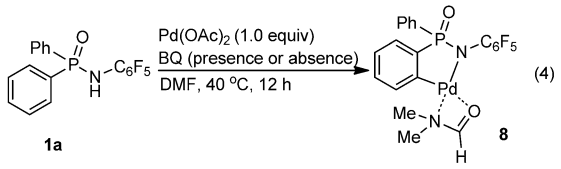
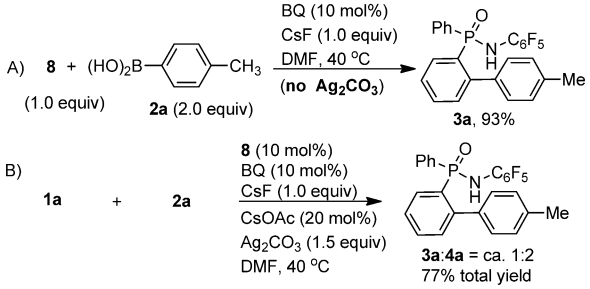


Figure 1. Single crystal structures of a) **8** (DMF was replaced by two H_2O molecules), and b) **10b**.



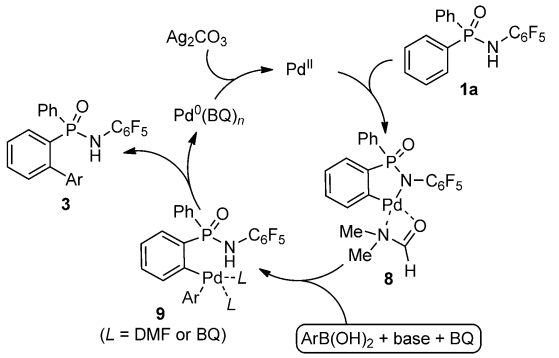
The reaction of 1.0 equivalent of Pd^{II} complex **8** with 2.0 equivalent of boronic acid **2a** in the absence of Ag_2CO_3 afforded exclusively the monoarylated product **3a** in excellent isolated yield (Scheme 1A, 93%). The palladium black was apparently precipitated out from the reaction system. In comparison, when a catalytic amount of **8** (10 mol%) was used to catalyze the reaction of **1a** and **2a** in the presence of Ag_2CO_3 (Scheme 1B), both the monoarylated **3a** and the diarylated **4a** were produced in an approximate 1:2 ratio in 77% overall yield. These results clearly imply that the reaction proceeds via a Pd^{II} to Pd^0 cycle, wherein **8** is the catalytically active metal species and Ag_2CO_3 serves as the oxidant to oxidize Pd^0 to Pd^{II}, which brings the reaction to the next cycle.



Scheme 1. Reaction of palladium complex **8** with boronic acid **2a**.

We also examined the role of BQ in the transformation. Surprisingly, we found that when 1.0 equivalent of **8** and 2.0 equivalent of **2a** were allowed to react in the absence of BQ, almost no reaction was observed. Alternatively, when a catalytic amount of complex **8** (10 mol%) was used to catalyze the reaction of **1a** and **2a** in the presence of 1.0 equivalent of BQ and a catalytic amount of Ag_2CO_3 (10 mol%), only 14% of monoarylated **3a** was obtained. These results combined with those in Scheme 1 reveal that BQ functions neither as an oxidant to oxidize Pd^0 to Pd^{II} nor as a co-oxidant to oxidize Ag^0 in the reaction system. On the other hand, we have also demonstrated that the formation of palladium complex **8** was not affected by the presence or the absence of BQ [Eq. (4)]. Thus, it appears that BQ plays its critical role in the transmetalation or reductive elimination step. Indeed, previous reports have suggested that BQ could improve the reaction through promoting the reductive elimination in C–H activation/C–C bond formation reactions.[21]

On the basis of the NMR spectroscopic and X-ray single crystal studies, along with a series of control experiments, we propose a reaction mechanism for this transformation. As illustrated in Scheme 2 with **1a** as a model substrate, the reaction



Scheme 2. Proposed reaction mechanism.

starts with the aryl palladation of **1a** with Pd^{II} to give a Pd^{II} complex **8**. Transmetalation of **8** with the boronic acids affords the diaryl palladated intermediate **9**. Reductive elimination of **9** under the assistance of BQ generates the product **3** and Pd^0. Oxidation of Pd^0 by Ag_2CO_3 regenerates Pd^{II}, which brings the reaction to the next cycle. The formation of diarylated **4** should follow the same mechanism as the formation of **3** with the monoarylated **3** as reactants.

Finally, the facile and mild direct C–H arylation oriented by phosphinamide groups as well as the clarification of the reaction mechanism led us to investigate the phosphinamide group directed C–H activation/C–N bond forming reaction because aryl C–N formation is one of the most popular reactions in synthetic chemistry due to the ubiquity of aryl amino compounds. However, the methods for aryl amination by C–H activation have been far less investigated compared with those for the direct C–H activation/C–C bond formation.[22] Therefore, this reaction could provide a new pathway for the straightforward functionalization of aryl phosphino derivatives through a direct aryl C–H amination reaction. To demonstrate the feasibility of this unprecedented strategy, we first investigated the intramolecular reaction by using several representative compounds in Table 2 and Table 3 as substrates. On the basis of the extensive experience obtained from the above C–H arylation, we immediately found that the intramolecular amination could proceed smoothly under conditions similar to those for the arylation, the only differences being the CsF base was changed to K_2HPO_4 and the reaction temperature was elevated from 40 °C to 80 °C. As shown in Table 4, a range of substrates was aminated effectively to afford the cyclic polyaryl phosphinamides **10a–f** in high yields even though the conditions were not carefully optimized. The structure of the products was characterized by NMR spectroscopy and mass spectrometry. Compound **10b** was also determined by X-ray crystallography (Figure 1b).[20] Thus, we have shown that the phosphinamide group is also a powerful directing group for C–H amination. Most significantly, in some recent reports, derivatives with a core skeleton of a six-membered cyclic phosphinamide like compound **10** have been demonstrated to exhibit potential utility in a wide range of areas, such as the antiinflammatory and antiarthritic fields,[23] and optoelectronic and flam-retardant applications.[24].

In summary, we have achieved Pd-catalyzed direct C–H arylation and intramolecular amination using phosphinamide as a new directing group. These novel protocols are mild, straightforward, generally applicable, and efficient, and thereby, open new avenues not only for the direct C–H functionalization, but also for the straightforward synthesis of valuable biaryl phosphino compounds. Moreover, we have proposed a clear mechanism for the transformation. The results provide important information toward a deeper understanding of the direct C–H functionalization since, although C–H functionalization has been extensively studied, direct evidence for the reaction mechanism has not really been forthcoming. As such, the mechanism provided herein should prove useful for the design of more efficient catalysts or for the development of new reactions. Efforts towards improving the selectivity of mono- or diarylation reaction as well as achieving other types of direct C–H functionalization using phosphinamide as directing group are currently underway in our laboratory.

Experimental Section

Details are provided in the Supporting Information.

Acknowledgements

Financial support from the "Hundred Talent Program" of CAS, and State Key Laboratory of Fine Chemicals (KF1201) is acknowledged.

Keywords: amination · arylation · C–H functionalization · palladium · phosphinamide

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Received: August 2, 2013
Published online on February 23, 2014