Arylation

International Edition: DOI: 10.1002/anie.201610666
German Edition: DOI: 10.1002/ange.201610666

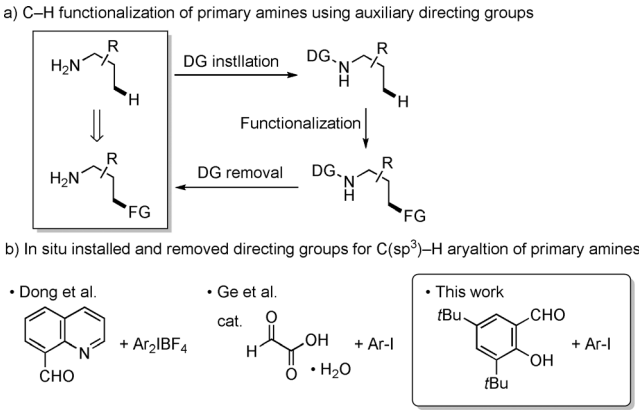
Buttressing Salicylaldehydes: Multipurpose Directing Group for C(sp^3)–H Bond Activation

*Akira Yada, Wenqing Liao, Yuta Sato, and Masahiro Murakami**

Dedicated to Professor Tamejiro Hiyama on the occasion of his 70th birthday

Abstract: *A palladium-catalyzed reaction of primary amines with iodoarenes produces γ-arylated primary amines. A bulky salicylaldehyde, which is marked as easily available, installable, removable, and recoverable, plays a key role in directing palladium to site-selectively activate the C–H bond located γ to the amino group.*

Amines constitute an important and vast class of organic compounds, and it ranges from biologically active compounds to organic functional materials. It presents a valuable synthetic maneuver if a functionality is installed selectively at a specific site of an amine.[1] An amino group itself or a nitrogen functionality derived thereof can coordinate to a metal, thus acting as the directing group, as a complex-induced proximity effect[2] arises between the metal and a specific C–H bond of the amine. In fact, specific C(sp^2)–H bonds of primary[3] and secondary[4] amines are amenable to transition metal catalyzed functionalization. It is much more difficult, however, to activate C(sp^3)–H bonds than C(sp^2)–H bonds,[5] and thus, there are no examples reported so far for the direct functionalization of C(sp^3)–H bonds of primary amines. In contrast, various auxiliary directing groups have been devised for this purpose.[6] They are installed on the nitrogen atom prior to a metal-catalyzed functionalization reaction and followed by an isolation/purification procedure. The auxiliary directing groups are finally removed after the functionalization reaction, and is again followed by an isolation/purification procedure (Scheme 1a). It would dramatically augment the synthetic usefulness if a directing group is easily installed and removed in the same reaction vessel with that for the desired functionalization reaction without intervention of an isolation/purification procedure.[7] It would further increase the synthetic value from a practical viewpoint if the directing group was readily available from commercial sources, and could be recovered from the reaction mixture.



Scheme 1. Palladium-catalyzed C–H bond functionalization using auxiliary directing groups. DG = directing group, FG = functional group.

The dehydration process of a primary amine with an aldehyde to produce an aldimine is fascinating because it is a reversible process and the equilibrium can be shifted in either direction by setting appropriate reaction conditions. There have appeared reports in which either an imine or an oxime is used as an *exo*-directing group for C–H bond functionalization of primary amines.[8,9] Recently, a palladium-catalyzed C(sp^3)–H bond arylation reaction of primary amines was reported by two groups. Dong et al. used 8-formylquinoline as a directing group which was installed in situ,[10] and Ge et al. used a catalytic amount of glyocylic acid as a transient directing group (Scheme 1b).[11] We directed our attention to salicylaldehyde and its derivatives, which are readily available from commercial sources and easily synthesized and derivatized in a laboratory. They convert primary amines into the corresponding salicylaldimines, which are also called phenoxy-imines. Upon treatment with metals, salicylaldimines chelate at the phenoxy group and the imino group, instantly in most cases, to form six-membered ring complexes. Once a chelate complex is formed, the rigid backbone of the bidentate ligand places the metal in proximity of a specific site of an amine for its activation.[12] Thus, we examined various salicylaldehydes, which are sterically modified, as a directing group for a palladium-catalyzed C–C bond-forming reaction of primary amines. Herein, we report that arylation with an iodoarene successfully takes place to produce the corresponding γ-arylated primary amine and a buttressing salicylaldehyde[13] acts as the multipurpose, that is, easily available, installable, removable, and recoverable, directing group for palladium.[14]

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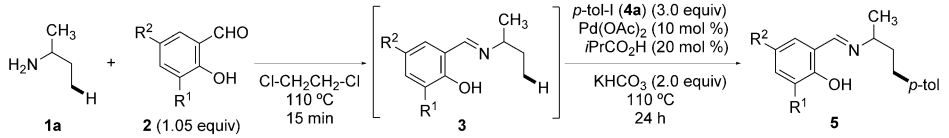
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201610666.

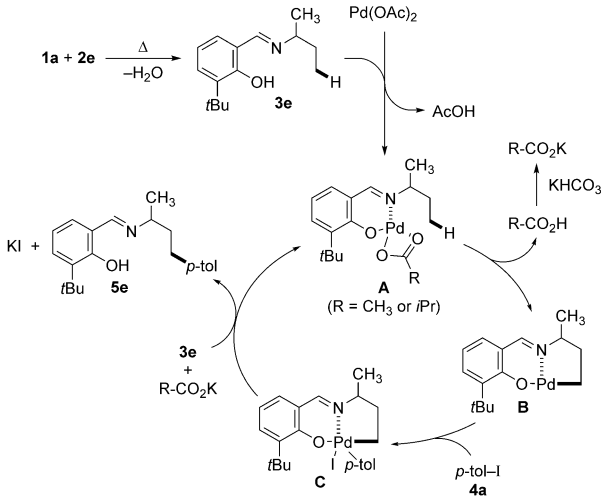
Table 1: Screening of salicylaldehydes (**2**).



2	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**
NMR yield of **5** [%]	0	0	0	0	78	81	0

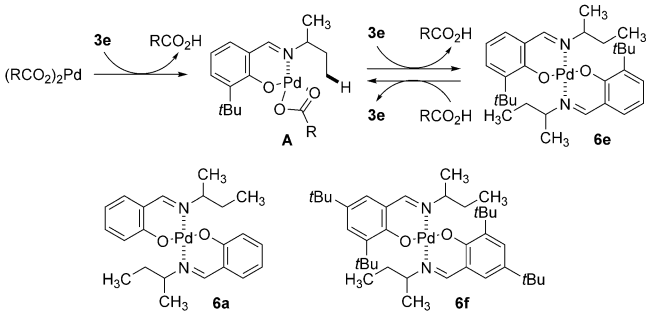
Our investigation set out with the examination of various salicylaldehydes (**2**) for an arylation reaction of *sec*-butylamine (**1a**; Table 1). Initially, salicylaldehyde (**2a**, 0.21 mmol) was treated with **1a** (0.20 mmol) at 110 °C in 1,2-dichloroethane. Dehydration was complete after 15 minutes to deliver the salicylaldimine **3a** quantitatively. Then, 4-iodotoluene (**4a**; 0.60 mmol), $Pd(OAc)_2$ (10 mol %), isobutyric acid (20 mol %), and $KHCO_3$ (0.40 mmol) were added to the reaction vessel, and the resulting mixture was stirred at 110 °C. After 24 hours, however, no formation of an arylated product was observed and **3a** was recovered. 3,5-Dimethylsalicylaldehyde (**2b**), 3,5-dichlorosalicylaldehyde (**2c**), and 5-*tert*-butysalicylaldehyde (**2d**) all failed to afford an arylated product. To our surprise, a contrasting result was obtained when the *tert*-butyl group of **2d** was relocated from the 5-position to the 3-position (**2e**). The γ-arylated imine **5e** was obtained in 78 % yield along with 4 % of the γ bis(arylation) product. The more-space-demanding 3,5-di-*tert*-butylsalicylaldehyde (**2f**) attained the best yield of 81 %. These results signify the importance of the *tert*-butyl group located at the 3-position. In contrast, the arylation reaction shut down when we used the methyl ether **2g** where the hydroxy group of **2f** was methylated. Thus, the hydroxy group is also indispensable for the arylation to occur.

A proposed reaction mechanism is depicted in Scheme 2. Dehydration from the amine **1a** and the salicylaldehyde **2e** forms the salicylaldimene **3e**. It acts as the bidentate chelating ligand to replace the acetate ligands of $Pd(OAc)_2$. The generated chelate complex **A** possesses a planar core, to which a tertiary butyl substituent as well as a secondary butyl substituent appended. The sterically demanding tertiary butyl group on the benzene ring exercises a buttressing effect, as it blocks an open space which would otherwise be available for the other pendant secondary butyl chain, and places it a conformation for metalation, through a concerted metalation deprotonation (CMD) mechanism.[15] Oxidative addition of the iodoarene **4a** occurs on the resulting palladabicycle **B**. The following reductive elimination forms a new C–C bond and exchange of the chelating salicylaldimine and iodide ligands releases the arylated salicylaldimine **5e**. Thus, **A** is regenerated for the next catalytic cycle. It has been reported that **A** possibly reacts with another molecule of the phenoxyimine **3e** to form the bis(imine)/Pd complex **6e**. The complex **6e** lacks a carboxylate ligand, and therefore, is unable to metalate the C–H bond through a CMD mechanism (Scheme 3). We assume that the secondary and tertiary butyl groups located on the periphery of the central flat core of **6e** would buttress against each other. Thus, the repulsive interaction arising between the peripheral butyl groups would disfavor **6e**, and instead, would induce its dissociation into the mechanistically active **A**, thus mitigating the repulsive interaction.



Scheme 2. Plausible reaction mechanism.

Next, we carried out a control experiment. The diimine-palladium complexes **6a** and **6f** (Scheme 3) were prepared

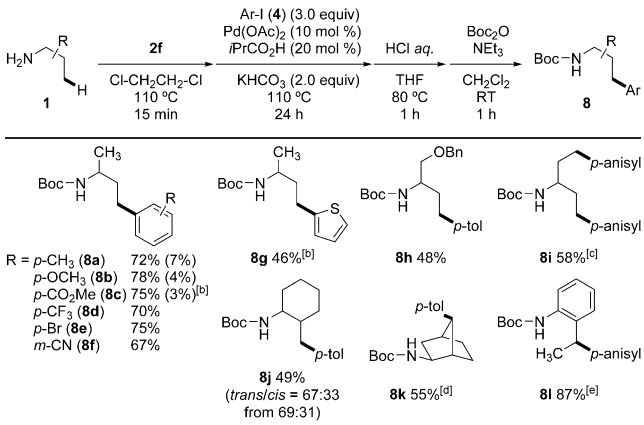


Scheme 3. Formation of the bis(phenoxy-imine)palladium complex **6e**.

from **2a** and **2f**, respectively, and their catalytic activities were compared in the arylation reaction of **3f**. The *tert*-butyl-substituted **6f** worked well as the catalyst to afford **5f** in good yield whereas the reaction using nonsubstituted **6a** was sluggish, even in the presence of an excess amount of **3f**. These contrasting results are consistent with the mechanistic interpretation mentioned above.

We took advantage of the facile reversibility of the imine-forming step to increase the practical usefulness. All the steps, including hydrolysis of **5**, were all executed in one reaction vessel (Table 2). After the palladium-catalyzed reaction of **1a** with **4a** was complete in 24 hours, conc. HCl and THF were simply added to the same reaction vessel. The aqueous acidic conditions allowed hydrolysis of the imino group at 80 °C. The resulting **2f** was separated from the reaction mixture into an organic phase by extraction, and recovered in 99%. The remaining aqueous acidic layer was basified, and the following extractive workup afforded the γ-arylated primary amine **7a** (4-(*p*-tolyl)-2-butylamine), which was directly subjected to a standard procedure for Boc protection. Chromatographic purification furnished the Boc-protected amine **8a** in 72% yield [bis(arylation) product **8a′** in 7%].

Table 2: Arylation of primary amines (**1**) with aryl iodides (**4**).[a]



[a] Yield of diarylated product is given within parentheses. [b] AcOH used instead of aq. HCl. [c] 15% of monoarylated product. [d] Arylation run at 120 °C. [e] CsOAc used instead of $KHCO_3$ in chlorobenzene. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.

The scope and limitations were studied in terms of iodoarenes and primary amines (alkyl-NH_2) using the one-pot procedure (Table 2). As for iodobenzenes, electron-donating and electron-withdrawing substituents were both tolerated on the benzene ring (**4b–f**). In the case of 1-bromo-4-iodobenzene (**4e**), coupling occurred selectively at the iodide moiety. 2-Iodothiophene (**4g**) also participated in the reaction. The arylation products **8h–j** were successfully obtained from primary amines having a secondary alkyl group (**1h–j**). In the case of 3-pentylamine (**1i**), the major product was the bis(arylated) amine **8i**. In contrast, propylamine (**1m**) failed to react. Neither 2-pentylamine (**1n**) nor 4-phenyl-2-butylamine (**1o**) gave arylation products (Figure 1). These results highlight the limitations that 1) the alkyl group on the nitrogen atom should be a secondary one, and 2) the γ C–H bond should be that of a methyl group. Substitution at the nitrogen atom by a secondary alkyl group would bear conformational constraints which are beneficial for the metalation by a CMD mechanism. A palladium carboxylate would be given better access in space to the C(sp^3)–H bond of a methyl group than to that of a methylene group.

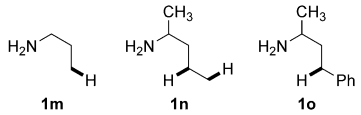
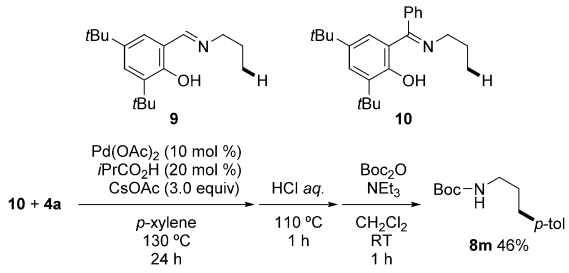


Figure 1. Other attempted primary alkyl amines.

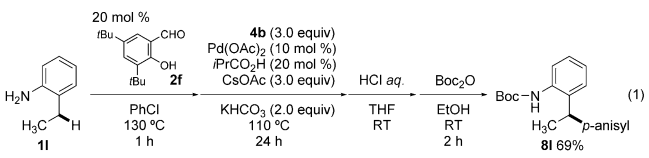
2-Aminonorbornane (**1k**) and 2-ethylaniline (**1l**), the carbon skeletons of which are conformationally less flexible than those of the primary amines **1h–j**, made exceptions with arylation of their methylene groups. The C(sp^3)–H bond of the bridging methylene group of **1k** was successfully arylated. The benzylic methylene group of **1l** was also amenable to the γ arylation.

For comparison, two phenoxy-imines, **9** and **10**, were prepared from propylamine and the corresponding carbonyl compounds, and their reactivities toward the γ-arylation were examined (Scheme 4). Whereas **9** furnished no arylation product, **10** gave the arylated amine **8m** in 46% yield, albeit under slightly modified reaction conditions (CsOAc in *p*-xylene at 130 °C). The additional phenyl group on the periphery of the chelate complex formed from **10** would generate an extra steric pressure and push the propyl substituent into the vicinity of the palladium to promote C–H activation.



Scheme 4. Arylation of the ketimine **10**.

Although the γ-arylation reaction studied above was catalytic in palladium, it used a stoichiometric amount of **2f**. If the facile reversibility of the imine formation is taken into account, however, turnover of **2f** was expected.[9–11,14,16] Thus, we carried out the arylation reaction of 2-ethylaniline (**1l**) using 20 mol% of **2f** as shown in Equation (1). The arylated product **8l** was obtained in 69% yield. This result suggested



that the tandem-type catalytic cycle, which is shown in the Supporting Information, could turnover more than three times, although it is yet to be improved.

To conclude, a substituted salicylaldehyde serves as an easily available, installable, removable, and even recoverable directing group for the C–H bond arylation reaction of primary amines.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (No. 22105005), Grant-in-Aid for Scientific Research (S) (No. 15H05756), and Challenging Exploratory Research (No. 26620083) from JSPS, and the ACT-C program of the JST.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · arylation · C–H activation · palladium · reaction mechanisms

[1] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; b) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W. Su, *Org. Chem. Front.* **2014**, *1*, 843.

[2] X. Chen, K. M. Engle, D. H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196.

[3] a) J. Vicente, I. Saura-Llamas, M. G. Palin, P. G. Jones, *J. Chem. Soc. Dalton Trans.* **1995**, 2535; b) J.-B. Sortais, N. Pannetier, A. Holuigue, L. Barloy, C. Sirlin, M. Pfeffer, N. Kyritsakas, *Organometallics* **2007**, *26*, 1856; c) A. Lazareva, O. Daugulis, *Org. Lett.* **2006**, *8*, 5211; d) H. He, W.-B. Liu, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2009**, *131*, 8346; e) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 3990.

[4] a) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342; b) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129; c) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009.

[5] O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902.

[6] Reviews on auxiliary-directed C–H bond functionalization reactions: a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; b) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053; c) R. K. Rit, M. R. Yadav, K. Ghosh, A. K. Sahoo, *Tetrahedron* **2015**, *71*, 4450; d) G. He, B. Wang, W. A. Nack, G. Chen, *Acc. Chem. Res.* **2016**, *49*, 635; Selected examples of auxiliary-directed C–H bond functionalization of primary amines: e) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; f) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; *Angew. Chem.* **2011**, *123*, 5298; g) N. Rodríguez, J. A. Romero-Revilla, M. Á. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2012**, *4*, 175; h) M. Fan, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12152; *Angew. Chem.* **2013**, *125*, 12374; i) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146; j) J. Han, Y. Zheng, C. Wang, Y. Zhu, D.-Q. Shi, R. Zeng, Z.-B. Huang, Y. Zhao, *J. Org. Chem.* **2015**, *80*, 9297; k) K. K. Pasunooti, B. Banerjee, T. Yap, Y. Jiang, C.-F. Liu, *Org. Lett.* **2015**, *17*, 6094; l) J. Li, S. Warratz, D. Zell, S. D. Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.* **2015**, *137*, 13894; Auxiliary directed C–H bond functionalization of secondary amines, see: m) J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford, *Nature* **2016**, *531*, 220.

[7] F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906.

[8] a) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856; b) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285; c) Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991.

[9] C–H bond arylation of ketones and aldehydes with transient imine directing groups: a) F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252; b) K. Yang, Q. Li, Y. Liu, G. Li, H. Ge, *J. Am. Chem. Soc.* **2016**, *138*, 12775.

[10] Y. Xu, M. C. Young, C. Wang, D. M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084; *Angew. Chem.* **2016**, *128*, 9230.

[11] Y. Liu, H. Ge, *Nat. Chem.* **2016**, DOI: 10.1038/nchem.2606.

[12] a) K. Hiraki, S. Ibaraki, M. Onishi, Y. Ono, J. K. Kawashima, M. Ando, *J. Organomet. Chem.* **1997**, *547*, 199; b) J. Dutta, M. G. Richmond, S. Bhattacharya, *Dalton Trans.* **2015**, *44*, 13615; c) Z. Ren, G. Dong, *Organometallics* **2016**, *35*, 1057.

[13] H. Makio, H. Terao, A. Iwashita, T. Fujita, *Chem. Rev.* **2011**, *111*, 2363.

[14] During preparation of this manuscript, a closely related work appeared: Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554.

[15] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118.

[16] Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222.

Manuscript received: November 1, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Arylation

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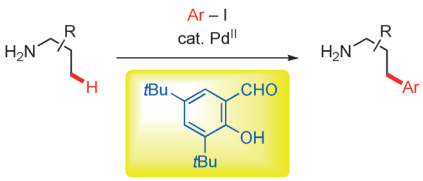
Buttressing Salicylaldehydes: Multipurpose Directing Group for C(sp^3)–H Bond Activation



Added bulk: A palladium-catalyzed reaction of primary amines with iodoarenes produces γ-arylated primary amines. A buttressing salicylaldehyde, which is marked as easily available, installable, removable, and recoverable, plays a key role in directing palladium to site-selectively activate the C–H bond located γ to the amino group.