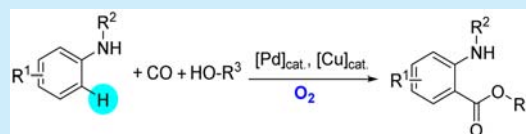


Palladium/Copper-Catalyzed Aerobic Oxidative C–H Carbonylation for the Synthesis of *o*-AminobenzoatesWu Li,[†] Zhengli Duan,[†] Ru Jiang,[†] and Aiwen Lei^{*,†,‡}[†]College of Chemistry and Molecular Sciences, the Institute for Advanced Studies (IAS), Wuhan University, Wuhan, Hubei 430072, P. R. China[‡]National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, Jiangxi, P. R. China

Supporting Information

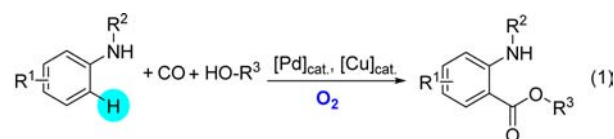
ABSTRACT: The palladium/copper-catalyzed aerobic oxidative C–H carbonylation for the synthesis of *o*-aminobenzoates is described. Molecular oxygen is used as the terminal oxidant. This methodology proceeds with a wide range of *N*-substituted anilines and alcohols and gives straightforward access to valuable *o*-aminobenzoates.



Palladium-catalyzed oxidative carbonylations apply different organic nucleophiles in the presence of CO and oxidation reagents to prepare various carbonyl-containing compounds, which have been recognized as a powerful approach to carboxylic acids and their derivatives.¹ In the last decades, considerable efforts have been made in this area, and much work has been carried out by Gabriele's group on the oxidative carbonylation of alkynes (simple and functionalized), amines, alcohols, diols, and amino alcohols.² The oxidative C–H carbonylation of simple nucleophiles such as C–H or Y–H (Y = O, N, etc.) has become a hot topic in organic synthesis, and much progress has been made in this field.³ However, in this aspect, most examples have been achieved by using stoichiometric amounts of copper(II) salts, silver(I) salts, and peroxide as the oxidants. Molecular oxygen is one of the ideal oxidants in oxidative transformations. Oxidative carbonylation using O₂ as the oxidant is an attractive synthetic goal and great challenges still remain. Several reports have been demonstrated in oxidative C–H carbonylation with O₂ as the terminal oxidant.⁴

Anilines are important basic chemical feedstocks and represent an important class of reagents with broad utility in the fields of chemical, pharmaceutical, and material sciences. Although anilines have been widely utilized in organic synthesis, the *ortho*-selective C–H functionalization of anilines still remains an outstanding challenge.⁵ This may be because anilines are easily decomposed under aerobic conditions or in the presence of powerful oxidants at high temperature. Indeed, the development of an effective catalytic protocol for carbonylation using CO by palladium-catalyzed C–H activation under aerobic conditions has long been recognized as being difficult. To the best of our knowledge, oxidative C–H carbonylation of *N*-substituted anilines under O₂ atmosphere has never been achieved. *O*-Aminobenzoates and their derivatives represent a highly important class of compounds, and they not only exist in numerous biologically active molecules and natural products but also serve as useful synthetic intermediates in organic synthesis.⁶ Therefore, the

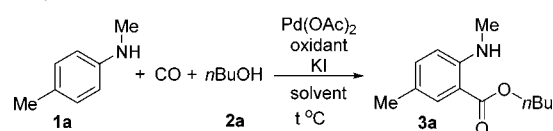
development of efficient synthetic methodologies to construct *o*-aminobenzoates is of broad interest. Herein, we communicate a palladium-catalyzed amino group *o*-C–H carbonylation of commercially available *N*-substituted anilines with O₂ as the terminal oxidant for the synthesis of *o*-aminobenzoates (eq 1).⁷



Our initial efforts focused on the C–H carbonylation of *N*-methyl-4-methylaniline (**1a**) and butan-1-ol (**2a**) (Table 1). We were pleased to observe the desired product under the combination conditions of Pd(OAc)₂ and Cu(OPiv)₂ in a mixed solvent of DMSO/toluene at 100 °C under 1 atm CO using O₂ as the terminal oxidant and KI as the effective additive (Table 1, entry 1).^{1d,e,8} Under these reaction conditions, a 69% yield (determined by NMR spectroscopy) of **3a** was obtained in 12 h. After preliminary optimization, we found fewer side products were detected when *N*-methyl-4-methylaniline was used as the substrate. Replacing Cu(OPiv)₂ with Cu(OAc)₂ resulted in loss of reactivity (Table 1, entry 2). Actually, palladium-catalyzed oxidative carbonylation uses anilines as the substrate, and *N*-acetylation of anilines may be generated when Cu(OAc)₂ is used as the oxidant. The acylation of substrate could completely be inhibited when replacing Cu(OAc)₂ with Cu(OPiv)₂. Furthermore, the solubility of Cu(OPiv)₂ is better compared to that of other copper(II) salts such as Cu(OAc)₂ in organic solvents, which could be considered as another promotion to the reactions.^{3j,1} While screening further oxidants, we observed that other oxidants such as CuBr₂, CuCl₂, and Ag₂O were totally ineffective (Table 1, entries 3–5). No desired product was detected when Cu(OPiv)₂ was removed

Received: January 21, 2015

Published: March 4, 2015

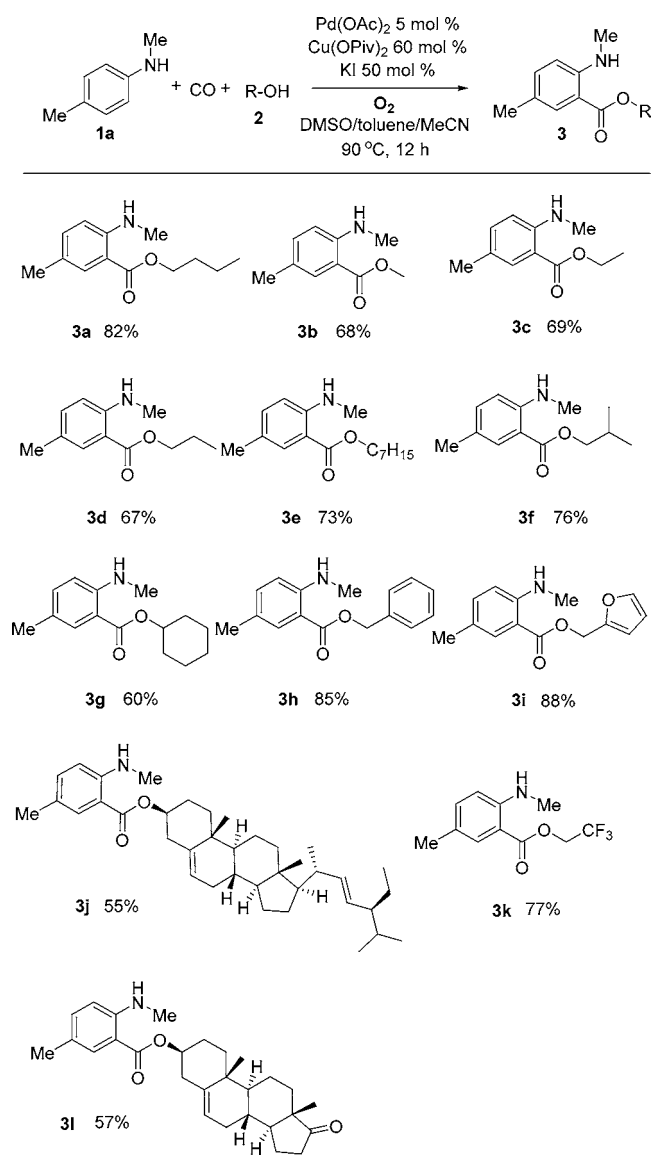
Table 1. Reaction Optimization for the C–H Carbonylation^a


entry	oxidant	solvent	yield ^b (%)
1	Cu(OPiv) ₂	DMSO/tol	69
2	Cu(OAc) ₂	DMSO/tol	30
3	CuBr ₂	DMSO/tol	0
4	CuCl ₂	DMSO/tol	0
5	Ag ₂ O	DMSO/tol	0
6	O ₂	DMSO/tol	0
7	Cu(OPiv) ₂	DMSO/tol	trace ^c
8	Cu(OPiv) ₂	DMSO/tol	53 ^d
9	Cu(OPiv) ₂	DMSO/MeCN	trace
10	Cu(OPiv) ₂	MeCN/tol	trace
11	Cu(OPiv) ₂	DMSO/tol/MeCN	80
12	Cu(OPiv) ₂	DMSO/tol/MeCN	84 ^e (82) ^f

^aStandard reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), Pd(OAc)₂ (0.01 mmol), Cu(OPiv)₂ (0.12 mmol), and solvent (1.0 mL) under 1 atm of CO at 100 °C for 24 h. ^bYields were determined by NMR using CH₂Br₂ (dibromomethane) as an internal standard. ^c0.20 mmol of Cu(OPiv)₂ was employed without O₂ atmosphere. ^d0.04 mmol of Cu(OPiv)₂ was employed. ^eThe reaction was performed at 90 °C. ^fIsolated yield. tol = toluene, OPiv = trimethyl acetate, DMSO = dimethyl sulfoxide.

and O₂ was used as the terminal oxidant (Table 1, entry 6). Only a trace amount of the desired carbonylation product was detected when Cu(OPiv)₂ was increased to a stoichiometric amount without O₂ (Table 1, entry 7). A smaller amount of Cu(OPiv)₂ reduced the reaction yield (Table 1, entry 8). Other cosolvents such as DMSO/MeCN and MeCN/toluene were not effective (Table 1, entries 9 and 10). Further optimization of the reaction conditions showed that the reaction was most productive when a mixed solvent of DMSO/toluene/MeCN (1:1:1) was used (Table 1, entry 11). Through further evaluation of the reaction conditions, we discovered that the yield was improved to 84% when the reaction was performed at 90 °C (Table 1, entry 12).

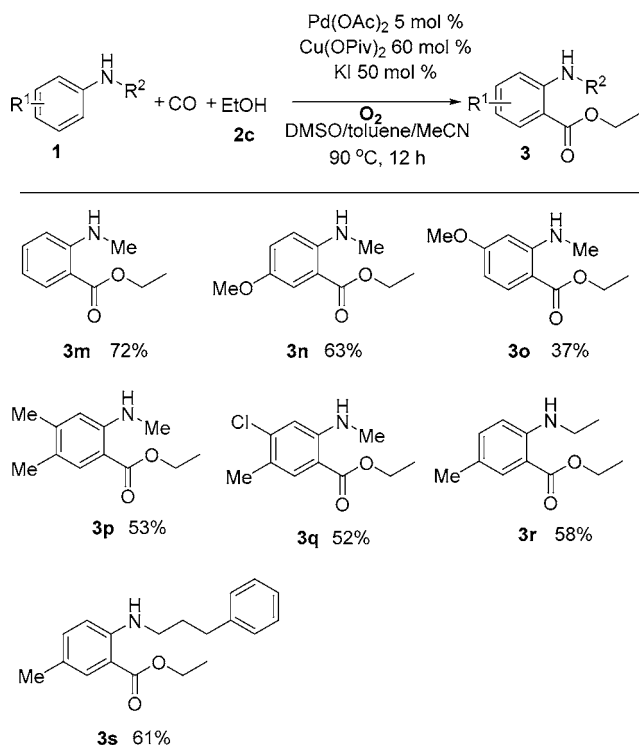
We next explored the substrate scope of the palladium-catalyzed aerobic oxidative C–H carbonylation reactions. The substrate scope of various aliphatic alcohols with **1a** was explored (Scheme 1). Delightfully, the results in Scheme 1 demonstrated a good functional-group tolerance for different aliphatic primary and secondary alcohols. Simple alcohols such as methanol, ethanol, and propanol were suitable for this transformation (**3b**, **3c**, and **3d**). When a long-chain alcohol such as *n*-heptanol was used as a substrate, 73% yield of **3e** was obtained. Branched alcohols such as isobutyl alcohol performed well under the standard conditions (**3f**). Secondary alcohols, such as cyclohexanol, which is vulnerable to oxidative systems, survived well under the aerobic oxidative conditions, giving the corresponding *o*-aminobenzoate in moderate yield (**3g**).⁹ Aromatic and heteroaromatic substituted methanols such as phenylmethanol and furan-2-ylmethanol proceeded smoothly to generate *o*-aminobenzoates in good yields (**3h** and **3i**). We did not observe the oxidation of alcohols in these reactions. To further demonstrate the utility of this new process for organic synthesis and to confirm its efficiency in the modification of complex molecules, we explored strategies to functionalize

Scheme 1. Scope of Alcohols^a


^aReaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Pd(OAc)₂ (0.01 mmol), Cu(OPiv)₂ (0.12 mmol), KI (0.10 mmol), CO/O₂ (1 atm), in toluene/DMSO/MeCN (0.3 mL/0.3 mL/0.3 mL) at 90 °C for 12 h. Yields are those of isolated and purified products.

natural product derivatives. Stigmasterol and dehydroepiandrosterone (DHEA), which widely exist in plants and animals, reacted smoothly with **1a** to provide the corresponding oxidative C–H carbonylation products in good yields (**3j** and **3l**), highlighting the broad substrate scope and the potential utility of this protocol. It is noteworthy that 2,2,2-trifluoroethanol-1-ol was also proved to be reactive (**3k**). In addition, we tried other alcohols such as *tert*-butyl alcohol, prop-2-en-1-ol, phenol, and quinolin-8-ol, but only a trace amount of the desired products was detected.

The scope of the reaction with respect to *N*-substituted anilines was investigated, too (Scheme 2). The sole product **3m** could be obtained in 72% yield by direct C–H carbonylation under the optimized conditions. *N*-Methylanilines bearing a methoxy group afforded the corresponding *o*-aminobenzoates **3n** and **3o** in 63% and 37% yields, respectively. 3,4-Disubstituted *N*-methylanilines were converted to the corre-

Scheme 2. Scope of *N*-Substituted Anilines^a

^aReaction conditions: **1** (0.20 mmol), **2c** (0.40 mmol), Pd(OAc)₂ (0.01 mmol), Cu(OPiv)₂ (0.12 mmol), KI (0.10 mmol), CO/O₂ (1 atm), in toluene/DMSO/MeCN (0.3 mL/0.3 mL/0.3 mL) at 90 °C for 12 h. Yields are those of isolated and purified products.

sponding products in moderate yields (**3p** and **3q**). Furthermore, *N*-ethyl-substituted aniline was also investigated and provided the desired product in moderate yield (**3r**). The 3-propylphenyl group survived well under the oxidative conditions, giving the corresponding product in moderate yields (**3s**).

Interestingly, when substrate 2-(methylamino)benzoic acid was employed under the standard conditions, the ethyl 2-(methylamino)benzoate was obtained in 72% yield (Table 2, eq 2). Control experiments indicated that no desired product was detected while removing the Pd(OAc)₂ or Cu(OPiv)₂ (Table 2, entries 1 and 2). Only 11% yield of *o*-aminobenzoate was detected when the KI was removed from the standard conditions (Table 2, entry 3). In addition, no desired product

Table 2. Control Experiments

entry	variation from the "standard conditions"	NMR yield ^a (%)
1	No Pd(OAc) ₂	0
2	No Cu(OPiv) ₂	0
3	No KI	11
4	No CO	0

^aYields were determined by NMR using CH₂Br₂ (dibromomethane) as an internal standard.

was detected when the reaction was carried out under N₂ atmosphere (Table 2, entry 4). Therefore, we propose that 2-(methylamino)benzoic acid should be a key intermediate in the reaction.

In summary, we have developed a palladium/copper-catalyzed aerobic oxidative C–H carbonylation and have given straightforward access to valuable *o*-aminobenzoates. O₂ was used as the terminal oxidant. The reaction tolerates a variety of primary and secondary alcohols, especially natural alcohols. Further substrate scope and mechanistic studies are ongoing in our laboratory and will be reported in the near future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and copies of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aiwenlei@whu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the 973 Program (2011CB808600, 2012CB725302), the National Natural Science Foundation of China (21390400, 21025206, 21272180, and 21302148), the Research Fund for the Doctoral Program of Higher Education of China (20120141130002), the Program for Changjiang Scholars and Innovative Research Team in University (IRT1030), and the Ministry of Science and Technology of China (2012YQ120060). The Program of Introducing Talents of Discipline to Universities of China (111Program) is also acknowledged.

■ REFERENCES

- (a) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788–10799. (b) Wu, X. F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229–241. (c) Wu, X. F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1–35. (d) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825–6839. (e) Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, *18*, 239–272.
- (a) Liu, Q.; Wu, L.; Jiao, H.; Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 8064–8068. (b) Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3371–3374. (c) Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 9429–9433. (d) Guan, Z.-H.; Lei, H.; Chen, M.; Ren, Z.-H.; Bai, Y.; Wang, Y.-Y. *Adv. Synth. Catal.* **2012**, *354*, 489–496. (e) Fini, F.; Beltrani, M.; Mancuso, R.; Gabriele, B.; Carfagna, C. *Adv. Synth. Catal.* **2015**, *357*, 177–184. (f) Gabriele, B.; Veltri, L.; Mancuso, R.; Carfagna, C. *Adv. Synth. Catal.* **2014**, *356*, 2547–2558. (g) Gabriele, B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G. *J. Org. Chem.* **2012**, *77*, 8657–8668. (h) Gabriele, B.; Veltri, L.; Salerno, G.; Mancuso, R.; Costa, M. *Adv. Synth. Catal.* **2010**, *352*, 3355–3363. (i) Della Ca, N.; Campanini, F.; Gabriele, B.; Salerno, G.; Massera, C.; Costa, M. *Adv. Synth. Catal.* **2009**, *351*, 2423–2432. (j) Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971–4977. (k) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319–3322. (l) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895–7898.

(3) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830–1833. (c) Giri, R.; Lam, J. K.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 686–693. (d) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967–971. (e) Guan, Z. H.; Chen, M.; Ren, Z. H. *J. Am. Chem. Soc.* **2012**, *134*, 17490–17493. (f) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902–9905. (g) Yu, J.-Q.; Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. *Synthesis* **2012**, *44*, 1778–1791. (h) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204–5207. (i) Chen, M.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 14196–14199. (j) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443–2446. (k) Wang, L.; Wang, Y.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5657–5661. (l) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1893–1896.

(4) (a) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 9581–9585. (b) Luo, S.; Luo, F. X.; Zhang, X. S.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10598–10601. (c) Shi, R.; Lu, L.; Zhang, H.; Chen, B.; Sha, Y.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10582–10585. (d) McNally, A.; Haffemayer, B.; Collins, B. S.; Gaunt, M. J. *Nature* **2014**, *510*, 129–133. (e) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312–315.

(5) (a) Zhang, Z. J.; Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Org. Lett.* **2014**, *16*, 3292–3295. (b) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895–11899. (c) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924–18927.

(6) (a) Deng, X.; Yang, Q.; Kwiatkowski, N.; Sim, T.; McDermott, U.; Settleman, J. E.; Lee, J.-D.; Gray, N. S. *ACS Med. Chem. Lett.* **2011**, *2*, 195–200. (b) Cheng, Y.-D.; Hwang, T.-L.; Wang, H.-H.; Pan, T.-L.; Wu, C.-C.; Chang, W.-Y.; Liu, Y.-T.; Chu, T.-C.; Hsieh, P.-W. *Org. Biomol. Chem.* **2011**, *9*, 7113–7125.

(7) During the preparation of this manuscript, Guan and co-workers reported the first palladium-catalyzed oxidative carbonylation of aromatic C–H bonds of *N*-alkylanilines with CO and alcohols. In their reaction, various aliphatic alcohols and phenol were tolerated, and stoichiometric amounts of Cu(OAc)₂ was used as the oxidant: Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *J. Org. Chem.* **2015**, *80*, 1258–1263.

(8) The use of KI as a promoter in oxidative carbonylation reactions has been extensively reported by Gabriele's group since 1992. (a) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1007–1008. (b) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84–88. (c) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613. (d) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601–604. (e) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, *346*, 351–358. (f) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219–228. (g) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. *Curr. Org. Chem.* **2004**, *8*, 919–946. (h) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468–2483.

(9) (a) Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 3236–3240. (b) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745. (c) Ooi, T.; Otsuka, H.; Miura, T.; Ichikawa, H.; Maruoka, K. *Org. Lett.* **2002**, *4*, 2669–2672.