One-Pot Procedures for the Formation of Secondary Aryl Amines from Nitro Aryls

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Abstract: Strategies for the one-pot formation of secondary aryl amines from the corresponding nitro aryls by utilizing reductive amination procedures are discussed. The extension of this chemistry where a Suzuki–Miyaura cross-coupling is conducted between a boronic acid and bromonitrobenzene prior to the reductive amination in one-pot is also presented.

Key words: one pot, Suzuki–Miyaura cross-coupling, reductive monoalkylation, biaryl, secondary amine

Selective synthesis of secondary amines in high yield can be a challenge with various degrees of overalkylation to the tertiary amine taking place.[1] This is often a problem when alkyl halides are utilized as the alkylation agent, and to a lesser extent when aldehydes are used as the alkyl source where first the corresponding imine is formed followed by a reduction of the imine, thus forming the secondary amine. A range of secondary aromatic amines are present in biological active compounds,[1] pharmaceuticals,[1,2] intermediates for drug synthesis,[1] and dyes[3] (Figure 1). Due to that fact, there is an interest in generating new efficient strategies for the selective preparation of these types of amines.

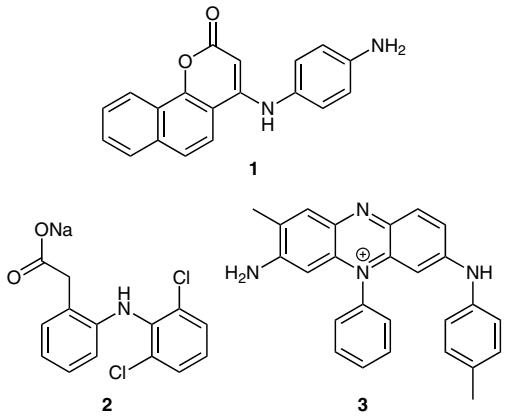

Figure 1 Example of a biological active compound {4-[(4′-aminophenyl)amino]-2*H*-benzo[*h*]chromen-2-one (**1**)},[4] pharmaceutical [Voltaren (**2**)],[2] and dye [Mauveine A (**3**)][3] containing a secondary aryl amine moiety in its structure

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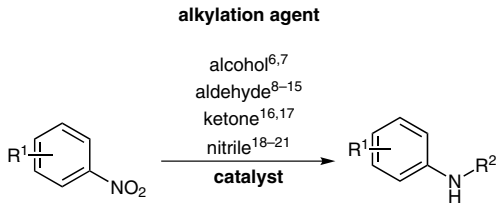
Magne O. Sydnes (right) was born in Oslo, Norway in 1973. He received his MSc degree in synthetic organic chemistry from the University of Oslo in 1998. After a short stint in industry he commenced his PhD studies in 2001 at the Australian National University, Canberra, under the guidance of Professor Banwell. Since earning his PhD in 2004 he has been working as a postdoctoral fellow both in Australia and Japan, including two years as a JSPS postdoctoral fellow in Professor Isobe's group at Nagoya University, Japan. In 2009 he joined International Research Institute of Stavanger, Norway, as a researcher. Since December 2011 he has been an associate professor at the University of Stavanger, Norway. His research interests include catalysis, natural product synthesis, and chemical biology.

Nitro aryls, which can easily be prepared from the corresponding aryls,[5] are excellent starting materials for the formation of the corresponding secondary aryl amines. Traditionally, nitro aryls have been transformed into the corresponding secondary amine in a two-step process. First reduction of the nitro group to the primary amine followed by alkylation.[1] Lately a range of strategies have been reported where nitro aryls have been converted into the corresponding secondary amines by using one-pot reductive monoalkylation strategies (Scheme 1). These reactions have utilized alcohols,[6,7] aldehydes,[8–15] ketones,[16,17] and nitriles[18–21] as the alkyl source together with a range of catalysts. With a few exceptions the catalysts used in these reactions were palladium on solid supports and hydrogen gas as the hydrogen source.

Nitro aryls have also been converted into their corresponding carbamates (Boc and CO_2Et) in one pot utilizing Boc_2O or $ClCO_2Et$, respectively, Sn and NH_4Cl in methanol under ultrasound conditions.[22] The method represents an excellent strategy for the formation of protected primary amines.



Scheme 1 Alkylation agents used for reductive monalkylation of nitro aryls

Our entry into this type of chemistry was by coincidence due to a byproduct (secondary amine **4**) formed during reduction of the corresponding nitro aryl [ethyl (4-methoxy-3-nitrophenyl)acetate] to the corresponding primary amine under an atmosphere of hydrogen gas over Pd/C (10%) at room temperature in ethanol.[23] The primary amine was needed for the formation of the corresponding aryl azide which was used for photochemistry studies.[24] The formation of secondary ethyl amine **4** was possible due to small quantities of acetaldehyde formed via oxidative addition of palladium to the alcohol followed by β-hydride elimination.[25,26] The equilibrium for this formation was far towards ethanol, however, due to the presence of the primary amine functioning as a trapping agent for the aldehyde a relatively large yield (41%) of the secondary amine could be isolated after 48 hours.[23] No trace of the corresponding diethyl tertiary amine could be found in the product mixture.

We thought we could take advantage of the fact that the tertiary amine was not formed under these conditions and see if we could develop a useful reaction by adding the alkylation agent, viz. the aldehyde to the reaction mixture. And indeed, when ethyl (4-methoxy-3-nitrophenyl)acetate was stirred under an atmosphere of hydrogen gas over Pd/C (10%) in the presence of 1.1 equivalents of acetaldehyde at room temperature the corresponding secondary ethyl amine was formed in 98% isolated yield in the course of three hours.[23] A range of secondary amines could be formed by utilizing this procedure (Figure 2).

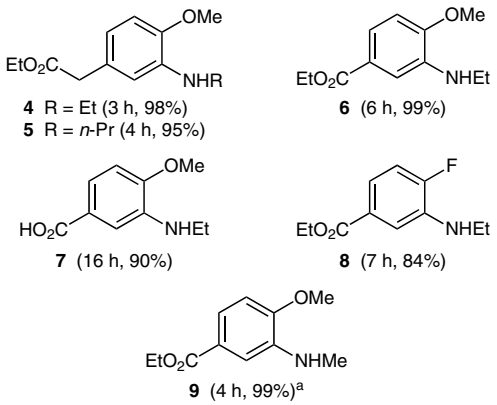


Figure 2 Examples of some secondary aryl amines prepared by one-pot reductive monoalkylation of the corresponding nitro aryl (reaction time and isolated yields in parentheses). [a] Formaldehyde solution (37 wt% in H_2O) was used. Reaction conditions for the formation of compounds **4**–**8**: nitro aryl and aldehyde (1.1–1.7 equiv) in EtOH was stirred under H_2 (1 atm) over Pd/C (10%) at r.t. for 3–16 h.

Only when one equivalent of formaldehyde (37 wt% in water) was used as the alkylation agent during the reductive monoalkylation of ethyl (4-methoxy-3-nitrophenyl)acetate was some (16%) of the corresponding tertiary amine formed together with 61% of the desired product. In addition 17% of the primary amine were also isolated. However, by altering the reaction conditions slightly, namely conducting the imine formation under an atmosphere of air followed by reduction with hydrogen gas over Pd/C (10%) the secondary amine **9** could be isolated in 99% yield.[23]

The synthetic strategy utilized for the latter synthesis of secondary amine **9** could also be used in order to prepare some benzyl-protected amines.[26] This was possible despite the fact that deprotection of benzyl-protected amine is conducted by hydrogenation over palladium on solid support, most often palladium on activated charcoal.[27] However, the final hydrogenation, namely reduction of the imine, had to be fine-tuned for each substrate. It was also absolutely necessary to keep the exposure time for the substrate to hydrogen to a minimum in order to avoid deprotection. By utilizing this strategy it was only possible to obtain a few benzyl-protected amines in good yield (Figure 3). The outcome could be improved by utilizing the strategy reported by Sajiki and Hirota where a nitrogen-containing base was added to the reaction mixture as a catalyst poison in order to improve the chemoselectivity for the hydrogenolysis reaction.[28] In our case triethylamine was added prior to the final reduction of the imine with hydrogen gas over Pd/C (10%).[26] This strategy facilitates the direct formation of some benzyl-protected primary amines and represents an addition to Chandrasekhar and co-workers' direct formation of Boc-protected amines.[22] Utilizing this strategy it was also possible to generate secondary amines with substitution on the benzyl group albeit in mixed yields.[26]

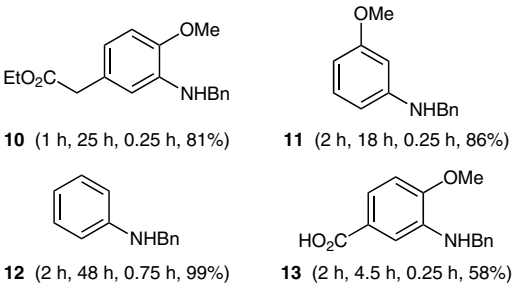
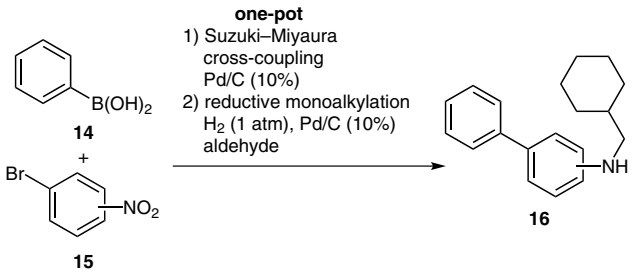


Figure 3 Examples of some benzyl-protected amines generated by reductive monoalkylation of the corresponding nitro compounds (reaction time and isolated yields in parentheses). *Reagents and conditions*: nitro aryl in EtOH was stirred under H_2 (1 atm) over Pd/C (10%) at r.t. for 1–2 h; benzaldehyde (1.4 equiv) was added, and the reaction mixture was stirred at r.t. under an atmosphere of air for 4.5–48 h; H_2 (1 atm) at r.t. for 0.25–0.75 h.

Inspired by the early work of Sajiki and co-workers using ligand-free Pd/C in Suzuki–Miyaura cross-coupling reactions[29,30] we were wondering if it was possible to conduct a cross-coupling with a boronic acid on to a haloni-

trobenzene prior to the previously developed reductive monoalkylation in one pot (Scheme 2). And indeed, upon optimization of the reaction conditions it was possible to obtain secondary biaryl amine **16a** in 89% isolated yield after column chromatography (Figure 4).[31] The optimized conditions utilized ethanol–water (12:1) as the solvent system and the Suzuki–Miyaura cross-coupling was conducted at reflux followed by cooling the reaction mixture to room temperature. Addition of 10 equivalents of aldehyde and stirring the reaction mixture at room temperature under an atmosphere of hydrogen gas resulted in smooth reductive monoalkylation of the nitrobiaryl in predominantly good yields.



Scheme 2 One-pot reaction sequence with 1-bromo-4-nitrobenzene (**15a**) and 1-bromo-3-nitrobenzene (**15b**)

The conditions also facilitated the formation of the secondary amine **16b** when 1-bromo-3-nitrobenzene (**15b**) was used as the cross-coupling partner (Table 1, entry 2). However, when 1-bromo-2-nitrobenzene (**15c**) was utilized in the reaction the desired cross-coupling reaction did not take place in the course of 24 hours at reflux (Table 1, entry 3).

Although the conditions recently reported gave predominantly good yields for saturated aldehydes (Figure 4[31] and Table 1, entry 2). The fact that 10 equivalents of the aldehyde were required in order for the reaction to reach completion within one to two days at room temperature was limiting the practicality of the chemistry (Table 1, entries 1 and 2). In an effort to improve the reaction on this point we set out to further optimize the reaction conditions. The optimization work was carried out utilizing phenylboronic acid (**14**) and 1-bromo-4-nitrobenzene (**15a**) as cross-coupling partner and cyclohexanecarboxaldehyde as the alkylation agent.

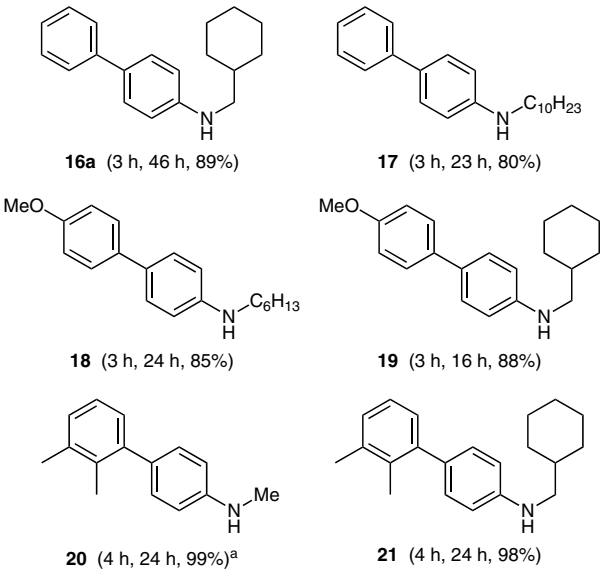


Figure 4 Examples of some secondary biaryl amines formed in one-pot utilizing 1-bromo-4-nitrobenzene [**15a**; reaction time (Suzuki–Miyaura cross-coupling, reductive monoalkylation) and isolated yields in brackets]. [a] Formaldehyde solution (37 wt% in H_2O) was used. *Reagents and conditions*: boronic acid/1-bromo-4-nitrobenzene (1:1), Pd/C (10%), and $Na_2CO_3 \cdot 10H_2O$ (1.6 equiv) at reflux for 3–4 h; aldehyde (10 equiv), H_2 (1 atm) at r.t. for 16–46 h.

As an initial experiment in the optimization process the Suzuki–Miyaura cross-coupling was conducted at reflux as in the previous work.[31] In addition, the reductive monoalkylation sequence was also conducted at reflux utilizing 1.5 equivalents of cyclohexanecarboxaldehyde as alkylation agent (Table 2, entry 1). After 22 hours at reflux under an atmosphere of hydrogen an 85% yield of azo compound **22** (Figure 5) could be isolated by flash chromatography in addition to small amounts (14%) of the corresponding hydrazine **23**. No trace of the desired secondary amine **16a** could be found. The formation of compounds **22** and **23** was puzzling; however, its origin had to come from incomplete reduction of the nitrobiaryl. It is known that both azo compounds and hydrazines are intermediates during the reduction of nitrobenzenes with hydrogen over Pd/C.[32] Occasionally, it is possible to isolate a few percent of these compounds, but seldom in large yields. Since this product had not been observed in our previous work[31] it was thought that the fact that the reduction of the nitro group was conducted at reflux resulted in

Table 1 Expanding the Scope with Respect to the Bromonitrobenzene (**15**)[a]

Entry	Compd	Cyclohexanecarboxaldehyde	Time (h)[b]	Product	Yield (%)
1	**15a**	10 equiv	3, 46	**16a**	89
2	**15b**	10 equiv	5, 43	**16b**	83
3[c]	**15c**	–	24, –	**16c**	–

[a] Solvent (EtOH–H_2O = 12:1), Suzuki–Miyaura cross-coupling conducted at reflux, and the reductive monoalkylation sequence was conducted at r.t.
[b] The times given refer to the following reactions: Suzuki–Miyaura cross-coupling, reductive monoalkylation.
[c] The Suzuki–Miyaura cross-coupling did not proceed in the course of 24 h at reflux.

incomplete reduction of the nitro functionality. However, how temperature influences the reduction reaction is at this stage not known.

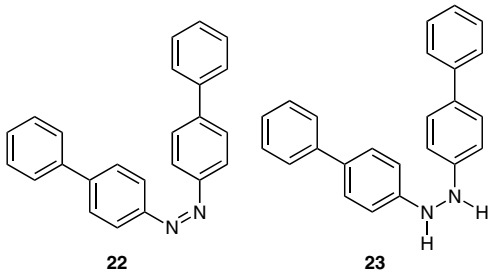


Figure 5 Structures of azo compound **22** and hydrazine **23**

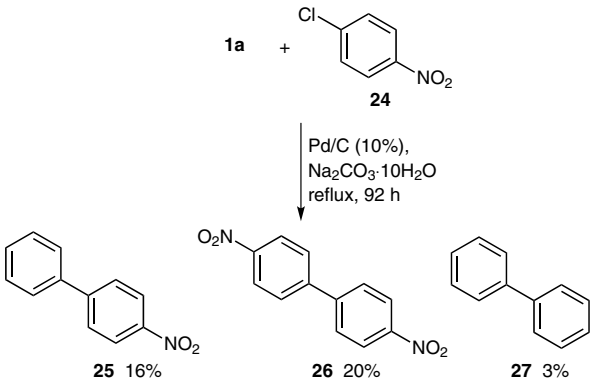
A revised procedure was then attempted where the reduction of the nitro group was conducted at room temperature for three hours without the presence of aldehyde. Under these conditions the nitro group was fully converted into the primary amine, and the aldehyde (cyclohexanecarboxaldehyde) was added to the reaction mixture. The reaction mixture was then stirred at reflux under an atmosphere of hydrogen in order to facilitate the alkylation. This improved the outcome, and the desired secondary amine **16a** was formed as the only product in 93% yield when 3.0 equivalents of aldehyde were used (Table 2, entry 2). Attempts to further reduce the number of equivalents of aldehyde added (Table 2, entries 3 and 4) and keeping the same reaction time or shorter only resulted in lower isolated yields of the desired product.

Table 2 Optimization of the Reaction Conditions Utilizing Phenylboronic Acid and 1-Bromo-4-nitrobenzene in the Cross-Coupling Reaction and Cyclohexanecarboxaldehyde as Alkylation Agent

Entry	Aldehyde (equiv)	Time (h)	Yield of **16a** (%)
1	1.5	3, 22[a]	–[b]
2	3.0	3, 3, 7.5[c]	93
3	1.2	3, 3, 7.5[c]	65[d]
4	1.5	3, 3, 3	60[d]

[a] Suzuki–Miyaura cross-coupling 3 h at reflux, reductive monoalkylation at reflux for 22 h.
[b] Azo compound **22** was isolated in 85%, and hydrazine **23** was isolated in 14% yield.
[c] Suzuki–Miyaura cross-coupling 3 h at reflux, reduction of the nitro group to the amine 3 h at r.t., alkylation and reduction conducted at reflux (see Table [2] for reaction time).
[d] Primary amine and imine were observed by TLC when the reaction was worked up.

Finally, it was attempted to utilize 1-chloro-4-nitrobenzene in the cross-coupling reaction with the aim to establish conditions that could facilitate the use of chloronitrobenzene in the one-pot reaction. Upon prolonged heating at reflux (92 h) it was possible to isolate a 16% yield of the desired nitrobiphenyl **25** together with two other cross-coupling products (homocoupling products **26** and **27**) in addition to starting material **24** (Scheme 3). Switching solvent to solvents with higher boiling point (toluene and xylene) did not improve the outcome of the cross-coupling reaction. Further one-pot work with 1-chloro-4-nitrobenzene was abandoned since the cross-coupling reaction with this analogue did not perform to expectation under our reaction conditions.



Scheme 3 Cross-coupling of 1-chloro-4-nitrobenzene with phenylboronic acid

In conclusion, we have broadened the scope of the one-pot reductive monoalkylation reaction by introducing a Suzuki–Miyaura cross-coupling reaction prior to the alkylation sequence. By such means a range of secondary biaryl amines can be generated in one pot from the corresponding bromonitroaryl. The cross-coupling chemistry should also work well with other boronic acids then the once utilized thus far by us. This chemistry should therefore facilitate the formation of a broad range of substituted secondary aryl amines.

Acknowledgment

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References

(1) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.
(2) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112.
(3) Perkin, W. H. *J. Chem. Soc., Trans.* **1879**, *35*, 717.
(4) Dong, Y.; Nakagawa-Goto, K.; Lai, C.-Y.; Morris-Natschke, S. L.; Bastow, K. F.; Kim, Y.; Lee, E. Y.-H. P.; Lee, K.-H. *J. Nat. Prod.* **2012**, *75*, 370.
(5) Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley: New York, **2001**, 170.

(6) Xiaojian, Z.; Zuwang, W.; Li, L.; Guijuan, W.; Jiaping, L. *Dyes Pigm.* **1998**, *36*, 365.
(7) Lee, C.-C.; Liu, S.-T. *Chem. Commun.* **2011**, *47*, 6981.
(8) (a) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C.-O. M.; Yoon, C. M. *Chem. Commun.* **2000**, 1857. (b) The chemistry described in ref. 8a was later expanded upon by Yoon and co-workers in order to prepare tertiary aromatic amines incorporating two different alkyl groups, see: Jung, Y. J.; Bae, J. W.; Park, E. S.; Chang, Y. M.; Yoon, C. M. *Tetrahedron* **2003**, *59*, 10331.
(9) Byun, E.; De Castro, K. A.; Lim, M.; Rhee, H. *J. Org. Chem.* **2007**, *72*, 9815.
(10) Dell'Anna, M. M.; Mastrorilli, P.; Rizzuti, A.; Leonelli, C. *Appl. Catal., A* **2011**, *401*, 134.
(11) del Pozo, C.; Corma, A.; Iglesias, M.; Sánchez, F. *J. Catal.* **2012**, *291*, 110.
(12) Li, H.; Dong, Z.; Wang, P.; Zhang, F.; Ma, J. *React. Kinet., Mech. Catal.* **2013**, *108*, 107.
(13) Li, L.; Niu, Z.; Cai, S.; Zhi, Y.; Li, H.; Rong, H.; Liu, L.; Liu, L.; He, W.; Li, Y. *Chem. Commun.* **2013**, *49*, 6843.
(14) Pintado-Sierra, M.; Rasero-Almansa, A. M.; Corma, A.; Iglesias, M. *J. Catal.* **2013**, *299*, 137.
(15) Sreedhar, B.; Rawat, V. S. *Synth. Commun.* **2012**, *42*, 2490.
(16) Wahba, A. E.; Hamann, M. T. *J. Org. Chem.* **2012**, *77*, 4578.
(17) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 1692.
(18) (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977. (b) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Process Res. Dev.* **2005**, *9*, 219.
(19) (a) Nacario, R.; Kotakonda, S.; Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Org. Lett.* **2005**, *7*, 471. (b) Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Synthesis* **2005**, 17.
(20) Reddy, C. R.; Vijeender, K.; Bhusan, P. B.; Madhavi, P. P.; Chandrasekhar, S. *Tetrahedron Lett.* **2007**, *48*, 2765.
(21) Ikawa, T.; Fujita, Y.; Mizusaki, T.; Betsuin, S.; Takamatsu, H.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Org. Biomol. Chem.* **2012**, *10*, 293.
(22) Chandrasekhar, S.; Narsihmulu, C.; Jagadeshwar, V. *Synlett* **2002**, 771.
(23) Sydnes, M. O.; Isobe, M. *Tetrahedron Lett.* **2008**, *49*, 1199.
(24) Sydnes, M. O.; Doi, I.; Ohishi, A.; Kuse, M.; Isobe, M. *Chem. Asian. J.* **2008**, *3*, 102.
(25) Esaki, H.; Ohtaki, R.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *J. Org. Chem.* **2007**, *72*, 2143.
(26) Sydnes, M. O.; Kuse, M.; Isobe, M. *Tetrahedron* **2008**, *64*, 6406.
(27) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, **1999**, 3rd ed., 579–580.
(28) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981.
(29) (a) Kitamura, Y.; Sako, S.; Udzu, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Commun.* **2007**, 5069. (b) Maegawa, T.; Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Endo, K.; Bora, U.; Kurita, T.; Kozaki, A.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* **2007**, *13*, 5937. (c) Kitamura, Y.; Sakurai, A.; Udzu, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2007**, *63*, 10596. (d) Kitamura, Y.; Sako, S.; Tsutsui, A.; Monguchi, Y.; Maegawa, T.; Kitade, Y.; Sajiki, H. *Adv. Synth. Catal.* **2010**, *352*, 718. (e) Monguchi, Y.; Fujita, Y.; Hashimoto, S.; Ina, M.; Takahashi, T.; Ito, R.; Nozaki, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2011**, *67*, 8628.
(30) For reviews discussing heterogeneous palladium-catalyzed Suzuki–Miyaura cross-coupling reactions, see: (a) Lamblin, M.; Nassar-Hardy, L.; Hierso, J.-C.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2010**, *352*, 33. (b) Sydnes, M. O. *Curr. Org. Synth.* **2011**, *8*, 881. (c) Mora, M.; Jiménez-Sanchidrián, C.; Ruiz, J. R. *Curr. Org. Chem.* **2012**, *16*, 1128.
(31) Pedersen, L.; Mady, M. F.; Sydnes, M. O. *Tetrahedron Lett.* **2013**, *54*, 4772.
(32) Figueras, F.; Coq, B. *J. Mol. Catal. A: Chem.* **2001**, *173*, 223.

