Organic LETTERS

Letter

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# Palladium-Catalyzed Formylation of Aryl Halides with *tert*-Butyl Isocyanide

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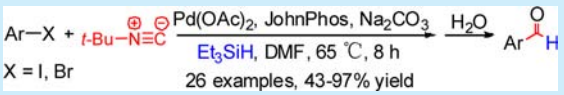
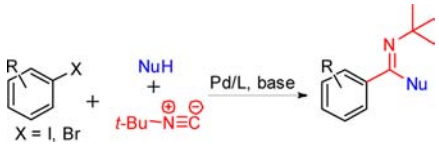
Supporting Information

**ABSTRACT:** A novel palladium-catalyzed formylation of aryl halides with isocyanide in the presence of $Et_3SiH$ has been demonstrated, which provides a strategy toward important aldehydes with moderate to excellent yield. The advantage of this reaction includes milder conditions, convenient operation, lower toxicity, and wide functional group tolerance.




Isocyanides have been versatile $C_1$ building blocks in organic synthesis. In the past decades, isocyanide insertion has offered widespread application in the synthesis of nitrogen compounds among all types of reactions involving isocyanides, such as electrophilic and nucleophilic reactions, imidoylative reactions, oxidation, etc.[1] In the case of palladium-catalyzed isocyanide insertion into C–X bonds[2] to form amidines and (thio)imidates, C-, N-, O-, and S-containing nucleophiles are generally used (Scheme 1). In order to achieve carboxide, further hydrolysis by losing *tert*-butylamine is sometimes needed. Delightfully, our group has successfully built C–O and C–C bonds to form the skeleton of isocounmarins, phthalides,[2i] and alkynones[2l] through isocyanide insertion into C–X bonds. Instead of carbon, oxygen, or nitrogen nucleophiles, we speculated that the hydride ion could be introduced to deliver valuable aldehydes, which would expand the application of isocyanide insertion.

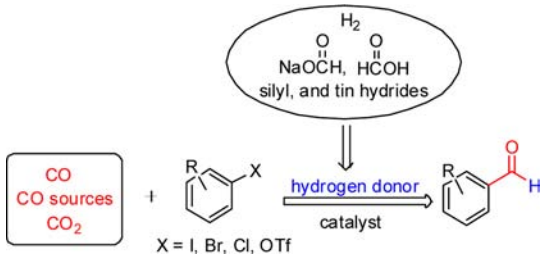
**Scheme 1. Catalytic Synthesis of Amidine or (Thio)Imidate**




Aromatic aldehydes are an important class of compounds widely used as an active formyl group for further transformations, such as C–C, C–N, and C–S coupling reactions, which can be readily employed in fine and pharmaceutical chemicals, agricultural chemicals, perfumery, and dyestuff industries.[3] Conventional methods for synthesizing aromatic aldehydes include Gattermann–Koch, Reimer–Tiemann, Vilsmeier–Haag, Duff, and Rieche reactions;[4] the reduction[5] of carboxylic acids, chloride, esters, acylamide, or nitrile; and the oxidation[6] of benzyl alcohol. Unfortunately, these reactions suffer from poor selectivity, low yield, harsh reaction conditions, use of an environmentally hazardous reagent, and production of significant quantities of waste.

Classical direct formylation of aryl halides involves a halogen/metal exchange with *n*BuLi and subsequent formylation agents (e.g., DMF) added at low temperatures.[7] Clearly, the scope of functional groups are limited by tough experimental conditions. Since the pioneering work of Heck,[8a] many explorations for palladium-catalyzed synthesis of aldehydes from aryl halides, which employs toxic CO, or CO sources as a formyl source, hydrogen, formate salt, or silyl, and tin hydrides as a reducing agent, have been reported[8] (Scheme 2). However, the conditions of high pressure, high toxicity, difficult operation of CO, instability of formylating agents, and limited functional group tolerance restricted their applications.

**Scheme 2. Palladium-Catalyzed Formylation of Aryl Halides**




Thus, a more eco-benign, efficient procedure for their construction will be greatly appreciated. As part of our interest in isocyanide as a surrogate for toxic CO, herein, we provide a new protocol for the synthesis of aldehyde via palladium-catalyzed formylation of aryl halides with silane, an economical, environmental, and high-activity hydrogen donor, following *tert*-butyl isocyanide insertion into a carbon–halogen bond (Scheme 3).

Initial investigations were carried out using 4-methoxyiodobenzene as a model substrate in the presence of $Pd(OAc)_2$, DPPB, $Na_2CO_3$, *tert*-butyl isocyanide, and $Et_3SiH$ (2 equiv) in DMF for 8 h, and the desired 4-methoxybenzaldehyde was

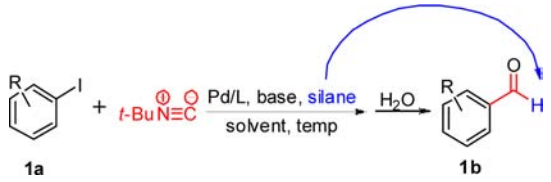
**Received:** May 18, 2014
**Published:** June 23, 2014





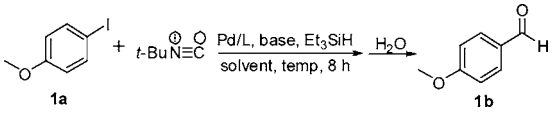
dx.doi.org/10.1021/ol5014262 | *Org. Lett.* 2014, 16, 3492–3495

**Scheme 3. Palladium-Catalyzed Formylation Strategy toward Aldehyde from Aryl Halides**




obtained in 61% yield (Table 1, entry 1). Compared with other solvents (Table 1, entries 2–5), DMF was optimal for this reaction. $Na_2CO_3$ was clearly superior to other bases (Table 1, entries 6–9). Lowering the temperature led to an increase in the yield (Table 1, entries 10 and 11). Switching to other catalysts, such as $PdCl_2$ and $Pd_3(dba)_2$, resulted in a lower yield (Table 1, entries 12 and 13). Ligand screening showed that $PCy_3$ could also be used but less efficiently than JohnPhos (Table 1, entries 14–22).

**Table 1. Optimization of Reaction Conditions**[a]

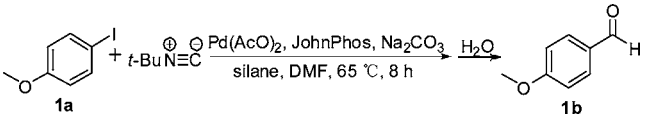



| entry | catalyst/ligand | base | solvent | temp (°C) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | DMF | 85 | 61 |
| 2 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | DMSO | 85 | 38 |
| 3 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | toluene | 85 | trace |
| 4 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | THF | 85 | trace |
| 5 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | MeCN | 85 | 0 |
| 6 | $Pd(OAc)_2$/DPPB | $Cs_2CO_3$ | DMF | 85 | 42 |
| 7 | $Pd(OAc)_2$/DPPB | $K_2CO_3$ | DMF | 85 | 46 |
| 8 | $Pd(OAc)_2$/DPPB | NaOAc | DMF | 85 | 55 |
| 9 | $Pd(OAc)_2$/DPPB | $NaHCO_3$ | DMF | 85 | 40 |
| 10 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | DMF | 100 | 44 |
| 11 | $Pd(OAc)_2$/DPPB | $Na_2CO_3$ | DMF | 65 | 68 |
| 12 | $PdCl_2$/DPPB | $Na_2CO_3$ | DMF | 65 | 41 |
| 13 | $Pd_3(dba)_2$/DPPB | $Na_2CO_3$ | DMF | 65 | 30 |
| 14 | $Pd(OAc)_2$/DPEPhos | $Na_2CO_3$ | DMF | 65 | 40 |
| 15 | $Pd(OAc)_2$/(*R*)-BINAP | $Na_2CO_3$ | DMF | 65 | 51 |
| 16 | $Pd(OAc)_2$/DPPF | $Na_2CO_3$ | DMF | 65 | 59 |
| 17 | $Pd(OAc)_2$/$PPh_3$ | $Na_2CO_3$ | DMF | 65 | 23 |
| 18 | $Pd(OAc)_2$/$PCy_3$ | $Na_2CO_3$ | DMF | 65 | 78 |
| 19 | $Pd(OAc)_2$/JohnPhos | $Na_2CO_3$ | DMF | 65 | 81 |
| 20 | $Pd(OAc)_2$/TFP | $Na_2CO_3$ | DMF | 65 | 35 |
| 21 | $Pd(OAc)_2$/SPhos | $Na_2CO_3$ | DMF | 65 | 65 |
| 22 | $Pd(OAc)_2$/XPhos | $Na_2CO_3$ | DMF | 65 | 53 |

[a]Conditions: All reactions were performed with **1a** (0.7 mmol), *tert*-butyl isocyanide (1.2 equiv), catalyst (3 mol %), ligand (4.5 mol %), base (1 equiv), $Et_3SiH$ (2 equiv), and 2.0 mL of solvent under nitrogen for 8 h in a sealed tube unless otherwise noted. DPPB = 1,4-bis(diphenylphosphino)butane, DPEPhos = bis[(2-diphenylphosphino)phenyl]ether, (*R*)-BINAP = (R)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, $PPh_3$ = triphenylphosphine, $PCy_3$ = tricyclohexylphosphine, JohnPhos =2-(dicyclohexylphosphino)biphenyl, TFP = tri(2-furyl)phosphine, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl, XPhos =2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [b]Isolated yield.

An investigation of hydrogen donors was also performed, and 3 equiv of $Et_3SiH$ resulted in a satisfactory reaction with a 92% yield under the established conditions (Table 2, entries 1–5).

**Table 2. Influence of Hydrogen Donors**[a]




| entry | silane | equiv | yield[b] (%) |
|---|---|---|---|
| 1 | $Et_3SiH$ | 1 | 53 |
| 2 | $Et_3SiH$ | 1.5 | 65 |
| 3 | $Et_3SiH$ | 3 | 92 |
| 4 | $PhSiH_3$ | 3 | 60 |
| 5 | $(Me_2SiH)_2O$ | 2 | 87 |

[a]Conditions: All reactions were performed with **1a** (0.7 mmol), *tert*-butyl isocyanide (1.2 equiv), $Pd(OAc)_2$ (3 mol %), JohnPhos (4.5 mol %), $Na_2CO_3$ (1 equiv), silane, and 2.0 mL of DMF under nitrogen at 65 °C for 8 h in a sealed tube unless otherwise noted. [b]Isolated yield.

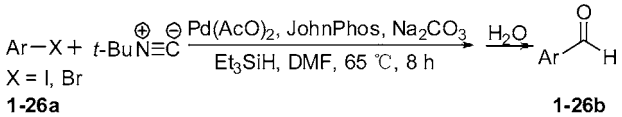
With the optimal conditions, namely treatment of aryl halide, *tert*-butyl isocyanide (1.2 equiv), $Pd(OAc)_2$ (3 mol %), JohnPhos (4.5 mol %), $Na_2CO_3$ (1 equiv), and $Et_3SiH$ (2.1 mmol, 3 equiv) in DMF (2.0 mL) at 65 °C, in hand, we explored the scope of the reaction. As shown in Scheme 4, moderate to excellent yields were obtained. Electron-rich phenyl halides (Scheme 4, **1b–4b**, **10b**, **16b**, **18b**, and **19b**) afforded higher yields than the electron-poor phenyl halides (Scheme 4, **5b–9b**, **11b**, **14b**, **15b**, and **17b**). Steric hindrance has a slight effect on the reaction (Scheme 4, **2b**, and **3b**). The reaction tolerates a variety of functional groups, such as halogen, nitryl, ketone, ester, ether, and hydroxy (Scheme 4, **5b–7b** and **14b–19b**), affording the corresponding aldehydes in moderate to good yields. A low yield of **17b** was obtained (Scheme 4, **17b**), which resulted from the sensitivity of isocyanide to the acidity of phenolic hydroxyl group. Notably, 4-iodobiphenyl and 1- and 2-naphthyl halides could not be converted totally under our standard conditions. Satisfactory results were obtained by a slight change of increasing the amount of *tert*-butyl isocyanide (2 equiv), $Pd(OAc)_2$ (6 mol %), JohnPhos (9 mol %), and $Na_2CO_3$ (2 equiv) (Scheme 4, **8b**, **12b**, and **20b**). Meanwhile, sterically hindered 9-bromoanthracene was converted to the desired product in 65% yield. Heteroaromatic halides are suitable for this transformation as well, giving moderate to good yields (Scheme 4, **13b**, **22b–24b**, and **26b**). Interestingly, an 88% yield of cinnamaldehyde was obtained by using our standard condition (Scheme 4, **25b**).

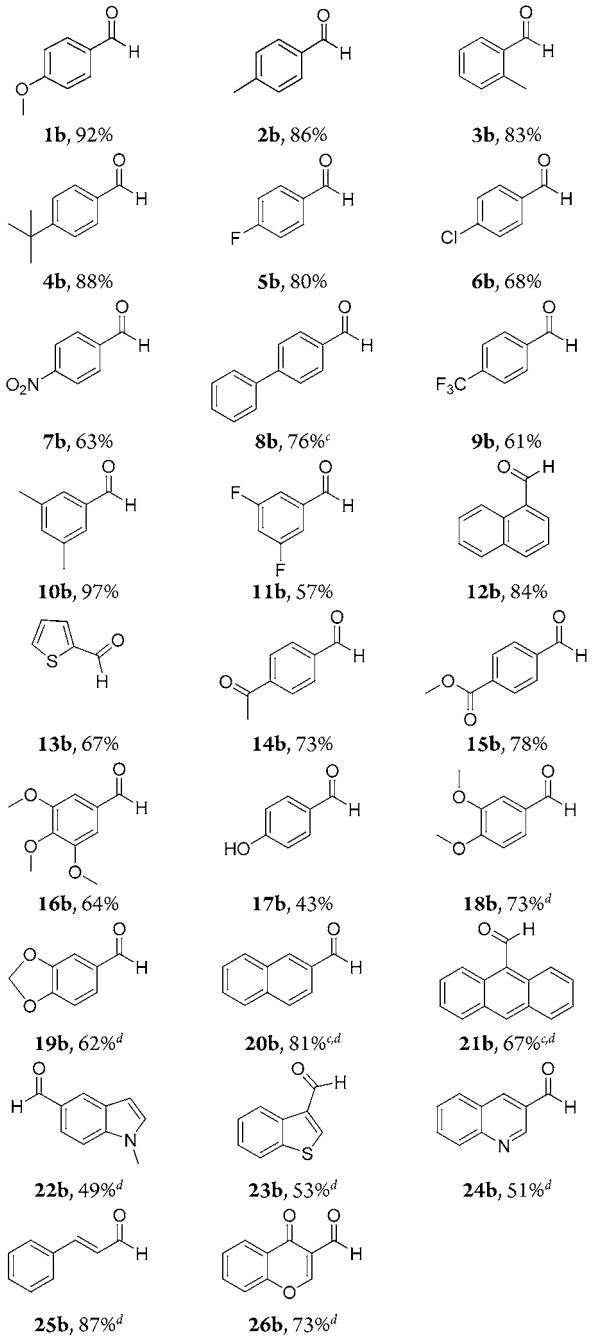
Amide was generated as the main product without a hydrogen donor ($Et_3SiH$) under our standard conditions, which is in accordance with the report of Huang.[2g] And there was no amide for our reaction. We speculate that palladium-catalyzed hydride ion transfer is prior to the replacement of halogen by hydroxyl. A plausible mechanism is depicted in Scheme 5. Oxidative addition of ary halides to the Pd(0) catalyst leads to a palladium complex **3**, followed by *tert*-butyl isocyanide insertion to form palladium(II) species **4**. **4** could be trapped by silane, and the desired aldehyde **1b** is achieved via palladium-catalyzed hydride transfer and subsequent reductive elimination.

In summary, an efficient palladium-catalyzed method for synthesizing aromatic aldehydes involving isocyanide insertion


dx.doi.org/10.1021/ol5014262 | *Org. Lett.* 2014, 16, 3492–3495

**Scheme 4. Palladium-Catalyzed Formylation of Aryl Halides**[a,b]

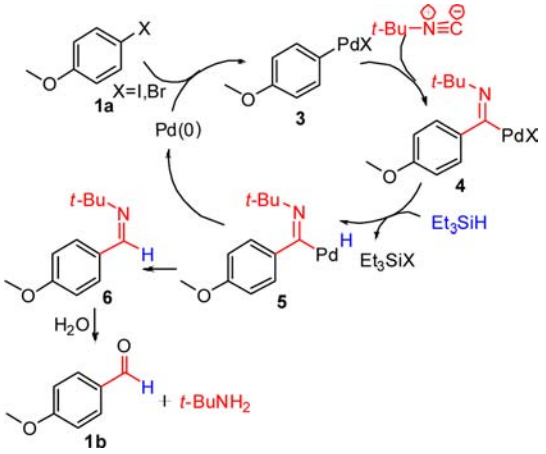



[a]Conditions: All reactions were performed with aryl iodide (0.7 mmol), *tert*-butyl isocyanide (1.2 equiv), $Pd(OAc)_2$ (3 mol %), JohnPhos (4.5 mol %), $Na_2CO_3$ (1 equiv), $Et_3SiH$ (3 equiv) and DMF (2.0 mL) under nitrogen at 65 °C for 8 h in a sealed tube unless otherwise noted. [b] Isolated yield. [c] *tert*-butyl isocyanide (2 equiv), $Pd(OAc)_2$ (6 mol %), JohnPhos (9 mol %), $Na_2CO_3$ (2 equiv). [d] Aryl bromide.

and formylation has been developed. The functional group can be applied to this powerful approach, affording moderate to excellent yields. Compared to other reactions, the procedure is more mild, general, and efficient. Furthermore, this new perspective can expand the application of palladium-catalyzed isocyanide insertion.

**Scheme 5. Plausible Mechanism**




## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support by PAPD (A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions) and NSFC (National Nature Science Foundation of China, No. 21172162).

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