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Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC = N-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction

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Abstract: The synthesis of NHC-$PdCl_2$-3-chloropyridine (NHC = N-heterocyclic carbene) complexes from readily available starting materials in air is described. The 2,6-diisopropylphenyl derivative was found to be highly catalytically active in alkyl–alkyl Suzuki and Negishi cross-coupling reactions. The synthesis, ease-of-use, and activity of this complex are substantial improvements over in situ catalyst generation and all current Pd–NHC complexes. The utilization of complex **4** led to the development of a reliable, easily employed Suzuki–Miyama protocol. Employing various reaction conditions allowed a large array of hindered biaryl and drug-like heteroaromatic compounds to be synthesized without difficulty.

Keywords: alkanes · C–C coupling · heterocycles · palladium

The use of N-heterocyclic carbenes (NHCs) as ligands has led to an array of exciting developments in Pd-catalyzed cross-coupling reactions.[1] The high sensitivity of isolated NHCs[2] necessitates handling under rigorously anhydrous conditions. In situ preparation of active Pd–NHC catalysts has been the dominant strategy to circumvent this problem.[3,4] Recently, we disclosed the first Negishi alkyl–alkyl cross-coupling protocol with a Pd–NHC catalyst prepared from the imidazolium salt **1** and common Pd sources, and proposed that the active catalyst is a monoligated Pd–NHC complex.[5] However, the uncertainty surrounding the stoichiometry and composition of the active species is a major drawback in mechanistic interpretation of the results.[6] Moreover, the rate and efficiency of catalyst formation is difficult to control under these conditions, possibly leading to waste of precious Pd metal and ligand precursor. The development of stable, easy-to-prepare-and-handle Pd–NHC complexes that are readily activated under the reaction conditions would increase the use of Pd–NHC catalysts in academic and industrial laboratories. Recently, the groups of Herrmann,[7] Nolan,[8] Beller,[9] and Sigman[10] have published an array of monoligated Pd–NHC complexes that show high levels of activity in Pd-catalyzed reactions. However, these catalysts were all prepared under rigorous anhydrous conditions even when the isolated carbene was not used. A major step forward, then, would be to develop a process for the preparation of Pd–NHC precatalysts in air, using readily available starting materials on a large scale. We envisioned stable, Pd^{II} species bearing one NHC ligand, two anionic ligands (e.g., Cl, Br, OAc) and a fourth, "throw-away" ligand. Even though a number of Pd complexes of NHC–pyridine bidentate chelating ligands have been prepared,[7a,11] analogues containing monodentate NHC and pyridine ligands are virtually unknown.[12] Hence, analogous to Grubbs et al.,[13a] we concluded that a suitably substituted pyridine would be an excellent candidate for the role of the throw-away ligand. Gratifyingly, heating of imidazolium salts **1**, **2**, or **3** with $PdCl_2$, and K_2CO_3 in neat 3-chloropyridine, in air (Scheme 1) led to the corresponding complexes **4–6** (Figure 1) in excellent yields by direct C–H insertion.[13b]

When we submitted complex **4** (1 mol%) to alkyl–alkyl Suzuki and Negishi cross-coupling reactions, rapid (Suzuki 5 minutes, Negishi 30 minutes) quantitative formation of **7**

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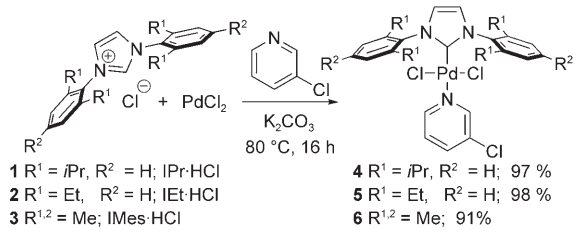
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains the preparation, characterization data, X-ray crystallography data for **4** and general procedures for all cross-coupling reactions.



Scheme 1. Synthesis of NHC-$PdCl_2$-3-chloropyridine complexes.

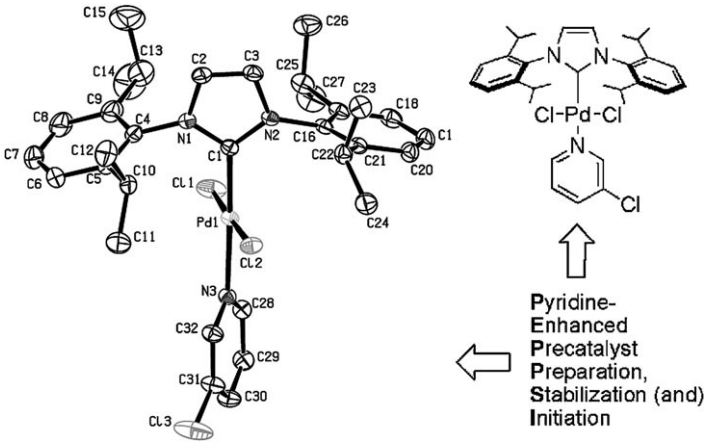
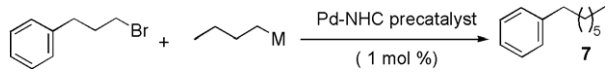


Figure 1. ORTEP representation of the crystal structure of **4**. The crucial role of the auxiliary pyridine ligand is highlighted.

was observed at room temperature (Table 1). Not only were the yields with the diethyl analogue **5** moderate (31–34%), the rate of the reaction was also much slower than with

Table 1. Catalytic activity of the Pd–NHC catalysts **4**–**6** in alkyl–alkyl cross-coupling reactions.



Entry	M	Yield of *n*-heptylbenzene (**7**) [%][a,b]		
		4	**5**	**6**
1	$ZnBr$[c]	100	34	8.0
2	BBu_2[d]	100	31	6.5

[a] GC yield (internal standard-undecane) after 24 h at RT; all reactions in duplicate. [b] Control experiments with no catalyst showed no conversion in all cases. [c] *n*-Butylzinc bromide (1.3 equiv), THF/NMP = 2:1. [d] Tri-*n*-butylborane (1.2 equiv), *t*BuOK (1.3 equiv), *i*PrOH.

complex **4** (Table 1, Figure 2). These results imply that bulky NHC ligands lead to fast reductive elimination, which suppresses undesired side reactions or catalyst decomposition in a manner analogous with bulkyphosphines.[14] It is unlikely that pyridine dissociation initiates catalyst activation considering the high stability of complex **4**.[13c] Rather, rapid reduction facilitated by the organometallic reagent takes place followed by pyridine dissociation from the generated Pd^0 species (Scheme 2). To support this rationale we treated complex **4** with two equivalents of *n*-heptylzinc bromide and

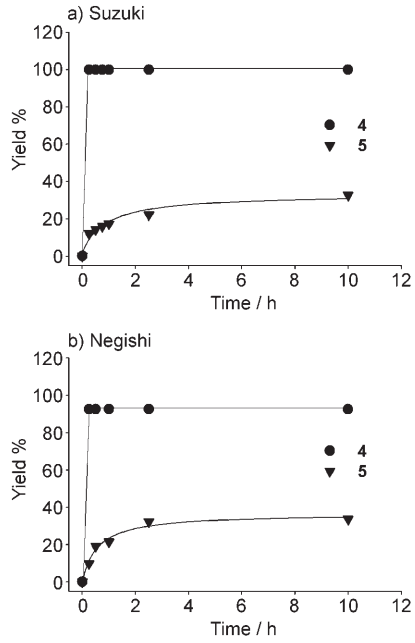
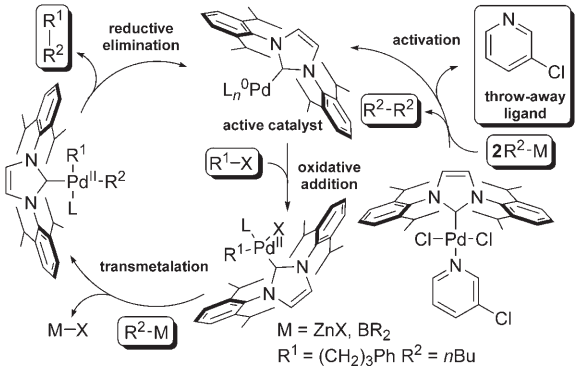


Figure 2. Rate studies with precatalysts **4** and **5** in the alkyl–alkyl cross-coupling reactions: a) Suzuki reaction; b) Negishi reaction. Yields determined by GC/MS against a calibrated internal standard (undecane).



Scheme 2. Activation and use of complex **4**.

analyzed the reaction mixture by GC/MS. From this analysis we observed the formation of *n*-tetradecane and liberation of 3-chloropyridine.[15] Additionally, preliminary computational studies further collaborate our proposed activation mechanism.[15b] Thus, after palladium reduction the pyridine dissociates, analogous to the loss of a phosphine group. A significant increase in rate was observed when catalysis with precatalyst **4** at 1 mol% was compared to the $[Pd_2(dba)_3]$/**1** (dba = dibenzylideneacetone) in situ protocol at 4 mol% (Figure 3a). Extremely fast rates at 1 mol% of **4** made it difficult to reliably measure the reaction rate, therefore a loading of 0.1 mol% was used (Figure 3b). Interestingly, after one hour there was a considerable difference in turnover frequency (TOF, Figure 3b) when the isolated complex and in situ processes were compared. If we assume that the same active catalyst is generated in solution when either protocol is employed and that turnover number (TON) and

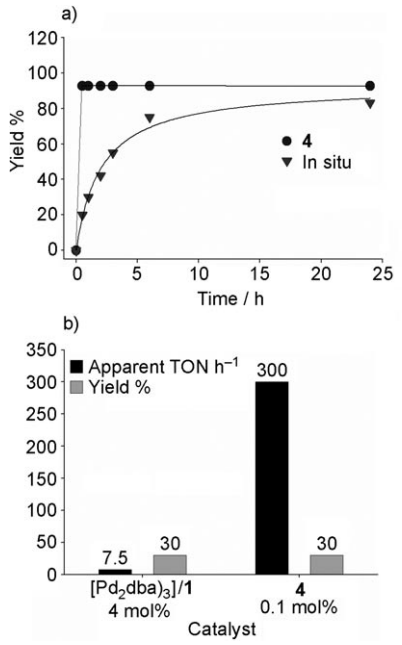
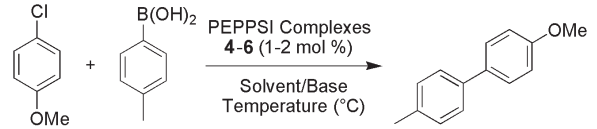


Figure 3. In situ catalyst versus NHC-$PdCl_2$-3-chloropyridine complexes in the alkyl–alkyl Negishi reaction: a) rate comparison with $[Pd_2(dba)_3]$/**1** and **4**; b) TON comparison between $[Pd_2(dba)_3]$/**1** and **4** after 1 h.

TOF are inherent properties of a compound it appears that only ~0.1 mol% of active catalyst is actually formed when utilizing the in situ protocol, even though 4 mol% of the precursors are used. The fact that most published protocols make use of in situ catalyst formation, with the inherent problems detailed above, may account for the limited use and capricious nature of Pd–NHC-based methodology.

To further demonstrate the utility of compounds **4–6**, we decided to evaluate the complexes in a highly industrial applicable process, the Suzuki–Miyaura reaction. The palladium-catalyzed Suzuki–Miyaura reaction is the most readily utilized C–C cross-coupling protocol due to boronic acid availability and stability, substrate compatibility, ease-of-use, and waste disposal. In recent years there have been significant advances in palladium–phosphine-based Suzuki–Miyaura methodology.[16] Fu and co-workers detailed the employment of alkyl halides and toylates with alkylboranes, a variety of boronic acids, and in one instance an alkyl boronic acid.[17] The coupling of hindered aromatic halides with aryl and vinyl boronic acids was disclosed by Buchwald and co-workers.[18] Additionally, Capretta et al.[19] successfully coupled secondary bromides with aryl boronic acids. In contrast to phosphine-ligated processes, the development of NHC-based protocols has been less successful. Indeed, palladium–NHC catalysts lack the substrate scope and ease-of-use of their phosphine cousins.[1] Progress has been made, but either the cross-coupling reaction or catalyst synthesis must be carried out in a rigorously dry and inert environment, typically employing a glove box.[3,20] Furthermore, most NHC methodology relies on in situ formation of the active catalyst, which leads to irreproducibility and wide yield variations.[5] We therefore submitted complexes **4–6** into a variety of Suzuki–Miyaura reaction conditions with no anhydrous precautions taken (Table 2). We were delighted to find that all complexes functioned as excellent catalysts at 80°C (Table 2, entries 1, 2 and 4).

Table 2. Optimization of Suzuki–Miyaura conditions for boronic acids.



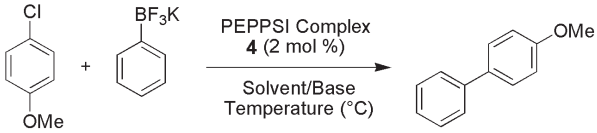
Entry	Catalyst (mol%)	Solvent	Base (equiv)	T [°C]	Yield [%][a,b]
1	**6** (2)	dioxane	Cs_2CO_3 (2)	80	74
2	**5** (2)	dioxane	Cs_2CO_3 (2)	80	95
3	**5** (2)	DME	Cs_2CO_3 (2)	80	54
4	**4** (2)	dioxane	K_3PO_4 (2)	80	48
5	**4** (2)	dioxane	Cs_2CO_3 (2)	80	92
6	**4** (2)	DME	Cs_2CO_3 (2)	80	77
7	**4** (2)	dioxane	K_2CO_3 (2)	80	80
8	**4** (2)	dioxane	K_2CO_3 (3)	80	95
9	**4** (2)	dioxane	K_2CO_3 (3)	60	97
10	**4** (2)	dioxane	K_2CO_3 (3)	RT	86
11	**4** (1)	dioxane	K_2CO_3 (3)	80	74
12	**4** (1)	*i*PrOH	*t*BuOK	RT	97

[a] GC yield (internal standard, undecane) after 2 h at RT; all reactions in duplicate. [b] Control experiments with no catalyst showed no conversion.

However, under closer scrutiny we found that complex **4** was superior as it was possible to conduct reactions in both dioxane and *i*PrOH at room temperature with a judicious choice of base (Table 2, entries, 10 and 12).

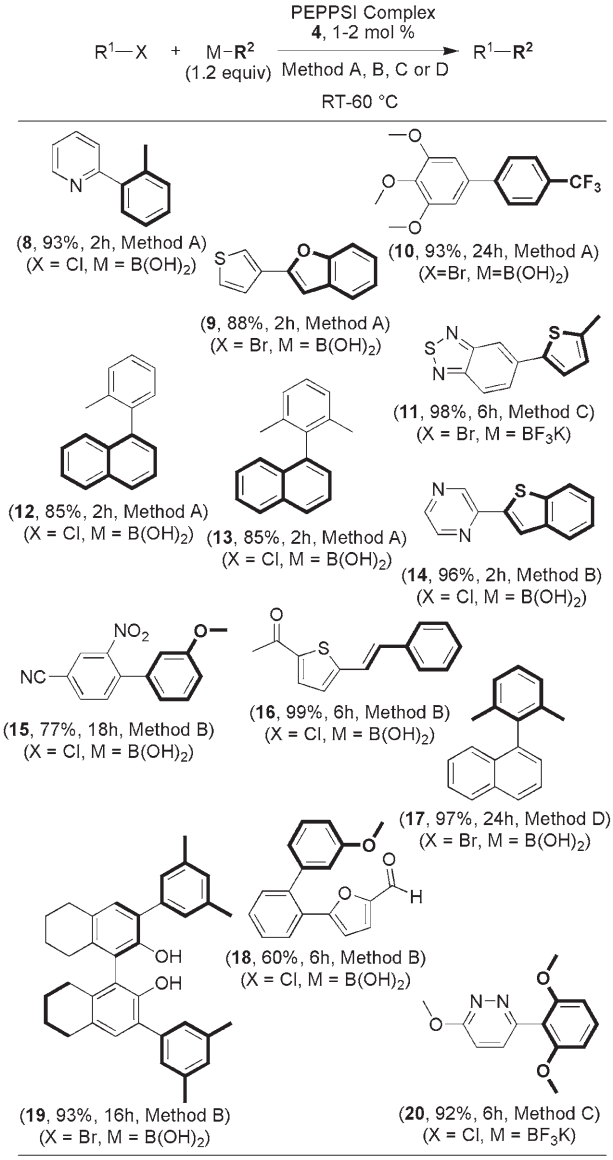
Expansion of the protocol to potassium trifluoroboroates was accomplished by simply changing the solvent to methanol (Table 3, entries 2 and 5–8). The employment of a variety of reaction conditions allowed a large array of hindered biaryls and drug-like heteroaromatics to be easily synthesized (Scheme 3). A notable result is the synthesis of **19**

Table 3. Optimization of Suzuki–Miyaura conditions for potassium trifluoroborates.



Entry	Solvent	Base (equiv)	T [°C]	Yield [%][a,b]
1	dioxane	K_2CO_3 (3)	60	0
2	MeOH	K_2CO_3 (3)	60	90
3	EtOH	K_2CO_3 (3)	60	30
4	*i*PrOH	K_2CO_3 (3)	60	27
5	MeOH	K_2CO_3 (3)	RT	86
6	MeOH	CsF	60	0
7	MeOH	KOH	60	91
8	MeOH	K_3PO_4	60	84

[a] GC yield (internal standard, undecane) after 24 h at RT; all reactions in duplicate. [b] Control experiments with no catalyst showed no conversion.



Scheme 3. Sp^2–sp^2 substrate scope. All reactions were performed by using standard laboratory techniques. Method A: **4** (1 mol %), K*t*OBu (1.3 equiv), reagent grade isopropanol, RT. Method B: **4** (2 mol %), dioxane, 60 °C . Method C: **4** (2 mol %), K_2CO_3 (3.0 equiv), methanol, 60 °C. Method D: **4** (2 mol %), KOH_s (3.0 equiv), dioxane, RT. Compound **11** was isolated in 70% yield after 12 h at RT. Compound **19** was prepared from **4** (4 mol %) K_2CO_3 (6.0 equiv), and $RB(OH_2)$ (2.4 equiv); this product has been made on a 10 g scale with a yield of 80%.

(Scheme 3), which when used in combination with triethylphosphine has been demonstrated to form a highly effective asymmetric Morita–Baylis–Hillman (MBA) catalyst.[21]

Use of isopropanol/*t*BuOK (Method A) allowed for rapid cross-coupling at room temperature, whereas more sensitive coupling partners were effectively coupled utilizing K_2CO_3 in dioxane (Method B) or methanol in the case of potassium trifluoroborates (Method C).

In conclusion we have developed a series of NHC-$PdCl_2$-3-chloropyridine complexes that are: 1) readily prepared in air on a large-scale from cheap starting materials, 2) handled and stored in air—no glove box necessary, and 3) in the case of **4**, easily reduced to a highly active Pd^0–NHC species. We believe the pyridine ligand plays a pivotal role in the facile preparation and stabilization of the Pd^{II} complex, while readily dissociating upon catalyst activation. We have coined the term PEPPSI (pyridine-enhanced precatalyst, preparation, stabilization, and initiation) to describe this effect. Additionally the method of preparation of complex **4** is a substantial improvement over previously reported Pd–NHC complexes and allows easy synthesis on a kilogram scale.[13b,22] The high activity of complex **4** (PEPPSI-IPr; IPr = diisopropylphenylimidazolium derivative) in alkyl–alkyl couplings with Zn and B derivatives (arguably the most challenging case) holds great promise that **4** will be generally applicable to a wide variety of cross-coupling protocols. To this end we demonstrated the utility of **4** in the Suzuki–Miyaura reaction. The employment of various reaction conditions allowed a large array of hindered biaryl and drug-like heteroaromatic compounds to be synthesized without difficulty. In one case a highly active MBA catalyst was readily produced in one step. We believe that complex **4** with all of the advantages stated above will be widely adopted in industrial and academic research laboratories world wide.[22,23]

Experimental Section

Below are representative procedures for the formation of the PEPPSI complexes and the Suzuki–Miyaura cross-coupling reactions. A detailed account of reaction conditions and characterization of products can be found in the Supporting Information.

Synthesis of the NHC-$PdCl_2$-3-chloropyridine complexes: In air, a vial was charged with $PdCl_2$ (177 mg, 1.0 mmol), NHC·HCl (1.1 mmol), K_2CO_3 (691 mg, 5.0 mmol) and a stirrer bar. 3-Chloropyridine (4.0 mL) was added, the vial was capped with a Teflon®-lined screw cap and heated with vigorous stirring for 16 h at 80 °C. After cooling to RT, the reaction mixture was diluted with CH_2Cl_2 and passed through a short pad of silica gel covered with a pad of Celite eluting with CH_2Cl_2 until the product was completely recovered. Most of the CH_2Cl_2 was removed (rotary evaporator) at RT, and the 3-chloropyridine was then vacuum-distilled (water aspirator vacuum) and saved for reuse. The pure complexes **4**–**6** were isolated after triturating with pentane, decanting of the supernatant and drying in high vacuum.

Data for complex 4: Using the above method NHC·HCl (468 mg, 1.1 mmol) gave complex **4** (677 mg, 97%) as a yellow solid. M.p. 240 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 7.7 Hz, 4H), 7.16 (s, 2H), 7.09 (dd, J = 8.0 Hz, 5.7 Hz, 1H), 3.18 (m, 4H), 1.50 (d, J = 6.7 Hz, 12H), 1.14 ppm (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 150.5, 149.4, 146.7, 137.4, 135.0, 132.0, 130.3, 125.1, 124.3, 124.1, 28.7, 26.3, 23.2 ppm; elemental analysis calcd (%) for $C_{32}H_{40}Cl_3N_3Pd$: C 56.57, H 5.93, N 6.18; found: C 56.90, H 5.99, N 6.52.

Procedure for method A: In air, a vial was charged with potassium *tert*-butoxide (154 mg, 1.30 mmol) and complex **4** (6.8 mg, 0.01 mmol), and the vial was sealed and purged with argon (3×). Technical grade isopropanol (1.0 mL) was added and the contents were stirred at room temperature until a color change from yellow to red/brown was observed (~10 min). Under a cone of argon, the boronic acid (1.20 mmol) was added, the vial was resealed with a septum, and the organohalide (1.00 mmol) was injected with a microliter syringe. Alternatively, if the boronic acid was soluble in isopropanol, it can be added as a solution (1.0 mL). The

solution was stirred at room temperature for the indicated period of time. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round-bottomed flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. Each reaction was performed in duplicate and the contents were combined, concentrated onto silica gel, and purified by flash chromatography.

Procedure for method B: In air, a vial was charged with complex **4** (6.8 mg, 0.01 mmol), potassium carbonate (207 mg, 1.50 mmol), the boronic acid (0.6 mmol), and the organohalide (0.5 mmol). The vial was sealed with a septum and purged with argon (3×). Dioxane (2.0 mL) was added and the contents were stirred at 60 °C for the specified period of time. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round-bottomed flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. Each reaction was performed in duplicate and the contents were combined, concentrated onto silica gel, and purified by flash chromatography.

Procedure for method C: In air, a vial was charged with complex **4** (6.8 mg, 0.01 mmol), potassium carbonate (207 mg, 1.50 mmol), the potassium trifluoroborate (0.55 mmol), and the organohalide (0.5 mmol). The vial was sealed with a septum and purged with argon (3×). Technical grade methanol (2.0 mL) was added and the contents stirred at 60 °C for the specified period of time. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round-bottomed flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. Each reaction was performed in duplicate and the contents were combined, concentrated onto silica gel, and purified by flash chromatography.

Procedure for method D: Method B was followed; however, in the place of solid potassium carbonate, solid KOH (84 mg, 1.50 mmol) was utilized. Additionally, the reaction was carried out at room temperature instead of 60 °C.

Acknowledgement

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