Self-Supported Ligands as a Platform for Catalysis: Use of a Polymeric Oxime in a Recyclable Palladacycle Precatalyst for Suzuki–Miyaura Reactions

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Abstract: A self-supported oxime palladacycle precatalyst for Suzuki–Miyaura reactions was synthesized based on the polyether ether ketone architecture. This precatalyst was found to be highly efficient in Suzuki–Miyaura reactions when aryl bromides were used as substrates, but was less efficient in cross-coupling reactions when aryl chlorides were used. The polymeric palladacycle could be recovered and reused up to four times in such reactions, affording excellent yield of the desired product. The approach represents a novel strategy for generating such self-supported complexes for catalysis.

Key words: self-supported catalysts, Suzuki–Miyaura reaction, oximes, palladacycles, polyether ether ketones

Along with the rapid development of new catalysts and reagents for organic synthesis in the past few decades, the recycling of these occasionally precious and/or toxic materials for economic and environmental reasons has also attracted attention. A general method with which to achieve this goal is to immobilize the catalysts and reagents on polymer supports.[1] Catalysts and reagents are often anchored either as pendant groups on the support, e.g., on cross-linked Merrifield-type polystyrene, or at the end of a linear polymer, for example, on poly(ethylene glycol) or polyisobutylene oligomers. In the past decade, the concept of incorporating organometallic catalysts in the main chain of a linear polymer or a three-dimensional polymeric network as 'self-supported' catalysts has also received attention.[2] As shown in Figure 1, such self-supported organometallic catalysts can be divided into two general categories. The first type of polymeric catalyst is formed by complexation of a metal and a dimeric ligand (Figure 1, a). For example, Chen and co-workers reported polymeric thiourea–Pd complex **1** and its use as a recyclable catalyst for Suzuki–Miyaura reactions (Figure 2).[3] More recently, Karimi and Akhavan reported recyclable self-supported *N*-heterocyclic carbene (NHC)–Pd complex **2**, also for Suzuki–Miyaura reactions.[4]

The second, and much less common, type of self-supported organometallic catalysts is based on the use of a polymeric ligand as the support for the metal (Figure 1, b).[5,6] For example, polymeric NHC–Ir complex **3** has recently been reported by Bielawski and co-workers.[7] However, its catalytic activity was not discussed.

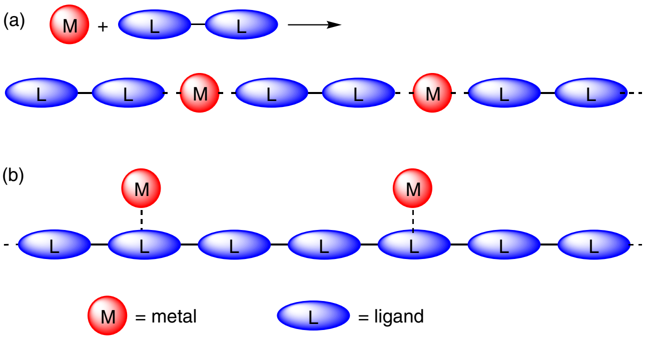
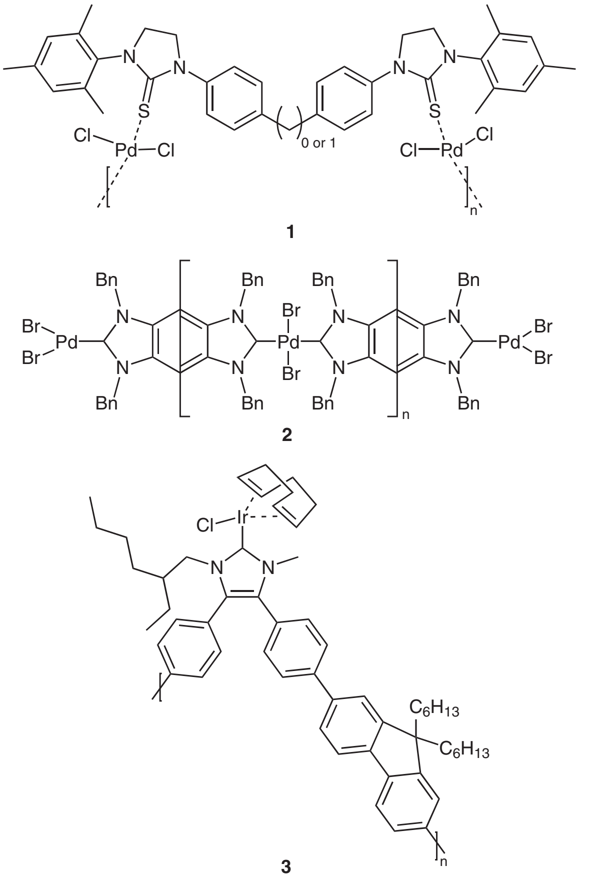


Figure 1 General self-supported organometallic catalyst architectures



1

2

3

Figure 2 Examples of self-supported organometallic complexes

This concept of polymeric functional groups has also been applied to self-supported organocatalysts in which the re-

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peating units are the catalytic groups themselves (Figure 3). For example, polyNHC **4**, which was used to prepare **3**, was employed directly as a recyclable catalyst for benzoin condensation reactions.[8] Similarly, recyclable self-supported ionic polymers bearing chiral quaternary ammonium salts **5** were prepared by Itsuno and co-workers, and used to catalyze asymmetric benzylation of a glycine *tert*-butyl ester derivative (Figure 4).[9,10]

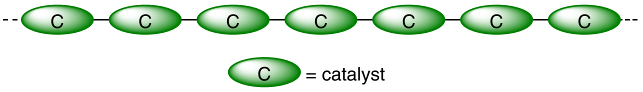
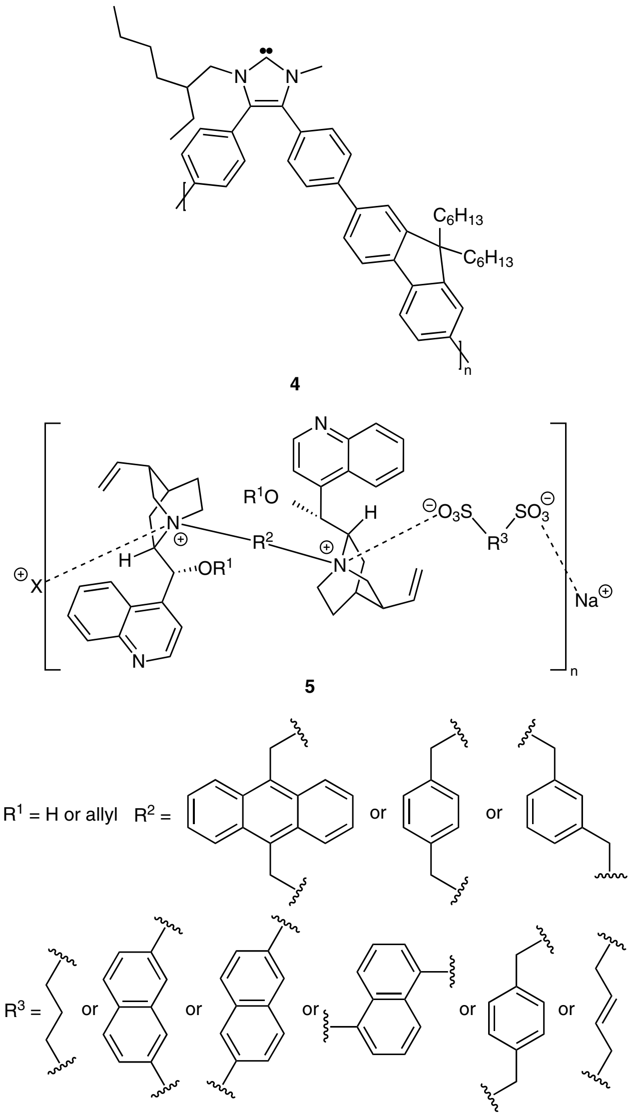


Figure 3 General self-supported organocatalyst architecture

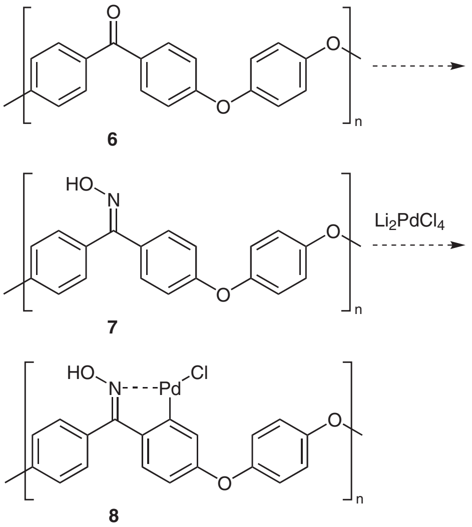


4

5

Figure 4 Examples of self-supported organocatalysts

Our group has had a long-term interest in investigating the design and use of new polymer-supported reagents and catalysts for synthesis.[11] We were inspired by the above reports of self-supported organocatalysts and were interested to see if a polymeric ligand based on the polyether ether ketone (PEEK) architecture[12] could be used as a catalyst platform. The most commonly used PEEK material, poly(oxy-1,4-phenyleneoxy-1,4-phenylenecarbonyl-1,4-phenylene) (**6**), is inexpensive and commercially available, and has been used as a thermoplastic in numerous applications, including in fuel cell ion exchange membranes (Scheme 1).[13] We envisioned that the benzophenone groups of **6** could be converted into oxime groups in **7**, and wondered whether this could be used to prepare oxime palladacycle **8**. In this way, self-supported oxime ligand **7** could serve as a platform for a precatalyst in Pd-catalyzed cross-coupling reactions.



6

7

8

Scheme 1 Proposed synthesis of **8** based on PEEK **6**

Among the known Pd catalysts and precatalysts, oxime palladacycles have been demonstrated to be air- and moisture-stable precatalysts that release active palladium species into reaction mixtures.[14,15] Given the nature of such palladacycles as reservoirs of catalytically active Pd(0) species, attaching them to a support or phase-tag facilitates the recovery and reuse of the catalysts. Indeed, palladacycles have been supported on silica (**9**), poly(ethylene glycol) (**10**), cross-linked polystyrene (**11**), and other materials.[16] Additionally, an oxime palladacycle with fluorous tails (**12**) has been reported,[17] as has the star-shaped, self-supported, and recyclable oxime palladacycle precatalyst **13**.[18] Selected examples of these palladacycles are shown in Figure 5. These supported oxime palladacycles were effective and recyclable precatalysts in Suzuki–Miyaura, Heck, Sonogashira, Stille, and Kumada reactions. However, due to the mass associated with the supports, the Pd loading of these palladacycles was quite low — usually less than 0.5 mmol/g. Due to the structurally simple and efficient PEEK architecture, our proposed self-supported oxime palladacycle should have the advantage of higher Pd loading, which, in turn, means that less catalyst is required for reactions.

Initially we attempted to convert **6** into **7** as outlined in Scheme 1. However, due the insolubility of **6** in common organic solvents, this transformation was unsuccessful.

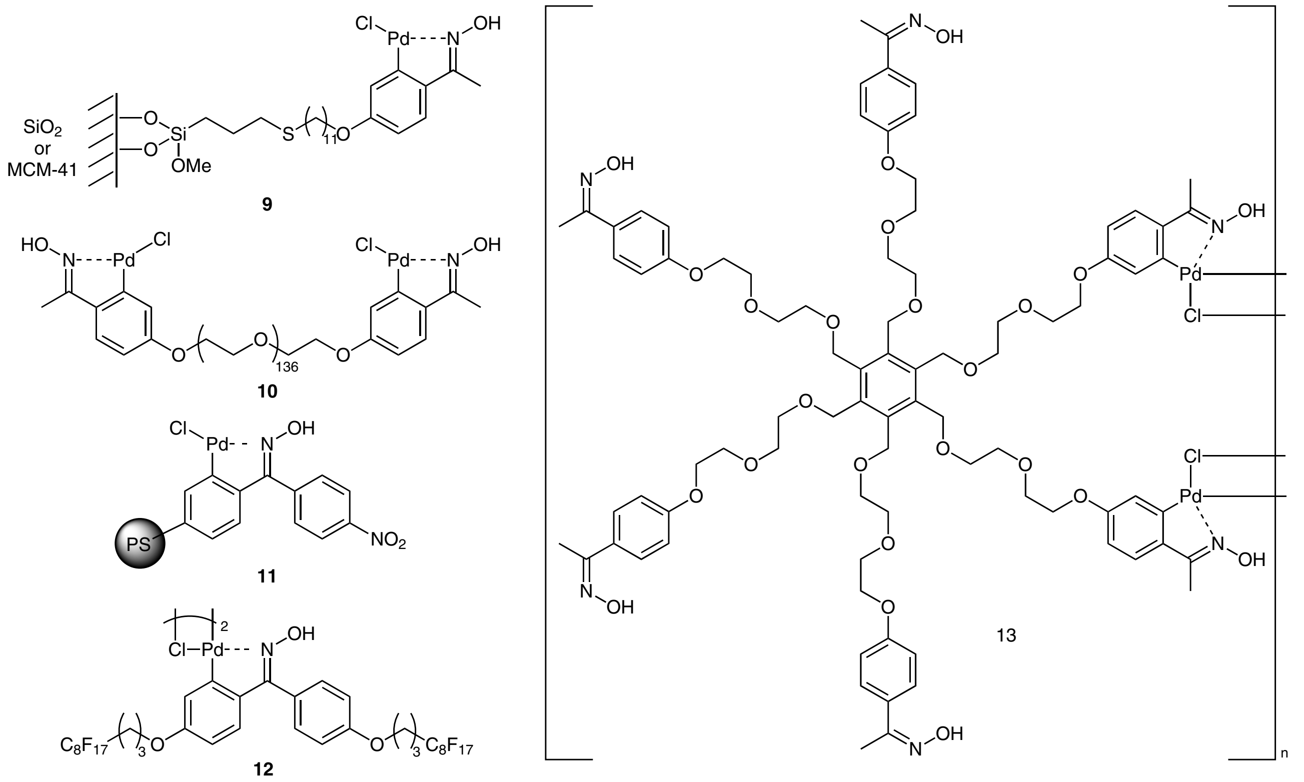
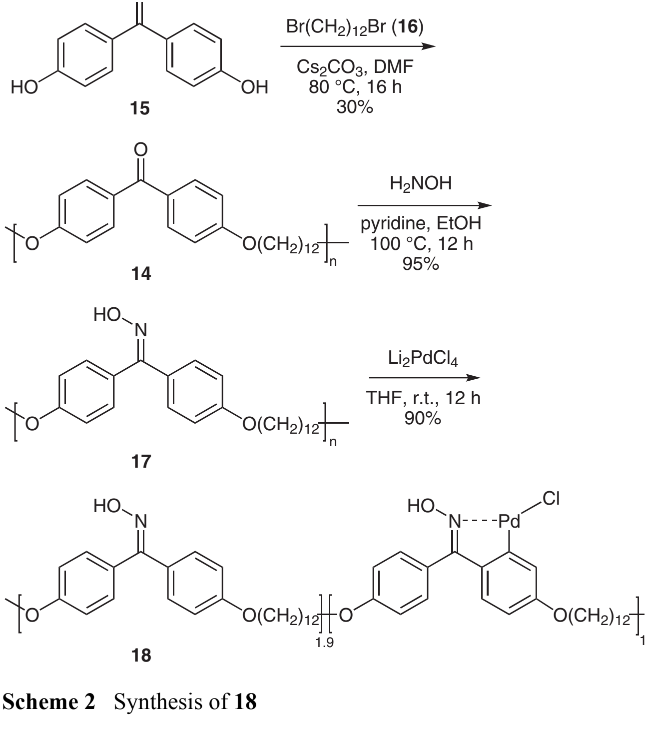


Figure 5 Examples of supported and phase-tagged oxime-palladacycle precatalysts

Therefore, we envisioned that a flexible alkane linker between the benzophenone moieties may make the resulting polymer soluble, and allow for oxime formation and solution-state spectroscopic characterization of the resulting polymer. The synthesis of our designed self-supported oxime palladacycle therefore started with the preparation of **14** from 4,4′-dihydroxybenzophenone (**15**) and 1,12-dibromododecane (**16**; Scheme 2).[19] The ketone groups of **14** were then transformed into oximes in **17**, which was then converted into the desired palladacycle **18**. It should be noted that **18** is only slightly soluble in DMF, THF, dichloromethane, and chloroform, and is insoluble in water, ether, and hexanes. Molecular weight determination of **14** by GPC and MALDI-TOF MS was inconclusive due to its low solubility and lack of suitable standards and matrix. Importantly, the Pd loading level of **18** was determined by ICP-MS to be 0.77 mmol/g.

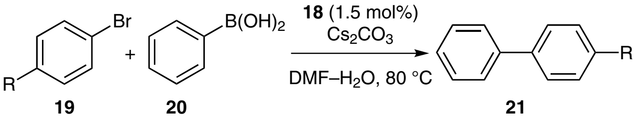
We then set out to examine the performance of **18** as a self-supported precatalyst for the Suzuki–Miyaura reactions of aryl bromides **19** and phenylboronic acid (**20**). For these reactions, a catalytic quantity of **18** was suspended in the reaction mixture to allow release of the catalytically active Pd species (Table 1). When the reaction was complete, the reaction mixture was cooled to room temperature, and ether and water were added to facilitate precipitation of **18**. In this manner **18** could be easily recovered by filtration.[20] The reactions proceeded smoothly with activated electron-poor aryl bromides and bromobenzene (entries 1–6), and were complete within two hours. For reactions using deactivated electron-rich aryl bromides (entries 7 and 8), excellent yields were obtainable within 12 hours. It should be noted that these yields are similar to those reported using other supported oxime-palladacycle precatalysts shown in Figure 5. The biphenyl products **21** isolated after aqueous workup were essentially pure according to ^{1}H and ^{13}C NMR spectroscopic anal-

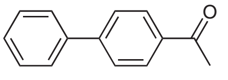
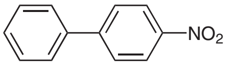
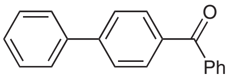
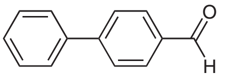
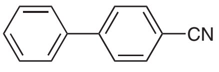
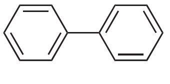
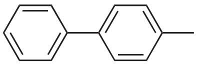
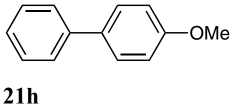


Scheme 2 Synthesis of **18**

ysis. These results indicate that **18** is an efficient precatalyst that can be separated from the desired reaction product by simple filtration.

Table 1 Suzuki–Miyaura Reactions of **19** with **20**[a]



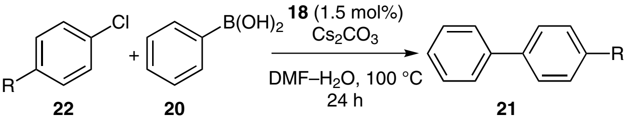
Entry	R	Time (h)	Product	Yield (%)[b]
1	COMe	2	 **21a**	99
2	NO_2	2	 **21b**	99
3	COPh	2	 **21c**	97
4	CHO	2	 **21d**	95
5	CN	2	 **21e**	99
6	H	2	 **21f**	99
7	Me	12	 **21g**	95
8	OMe	12	 **21h**	96

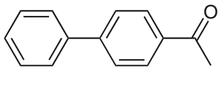
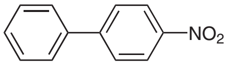
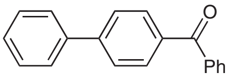
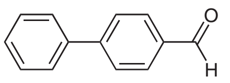
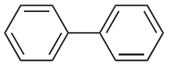
[a] Reaction conditions: **19** (1.0 mmol), **20** (1.2 mmol), **18** (0.015 mmol), Cs_2CO_3 (1.5 mmol), DMF (2.5 mL), H_2O (2.5 mL), 80 °C for the indicated reaction time.

[b] Isolated yield.

When aryl chlorides **22** were used as the substrate, the reactions proceeded much more sluggishly (Table 2). Therefore, higher temperatures and longer times were required to push the reactions towards completion. However, even after 24 hours, only activated aryl chlorides afforded the desired biphenyl products in moderate yields (entries 1–4). The reaction with chlorobenzene did not proceed under such conditions (entry 5).

Table 2 Suzuki–Miyaura Reactions of **22** with **20**[a]



Entry	R	Product	Yield (%)[b]
1	COMe	 **21a**	65
2	NO_2	 **21b**	40
3	COPh	 **21c**	63
4	CHO	 **21d**	42
5	H	 **21f**	0

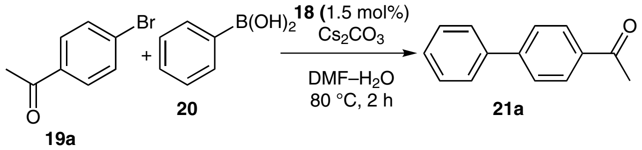
[a] Reaction conditions: **22** (1.0 mmol), **20** (1.2 mmol), **18** (0.015 mmol), Cs_2CO_3 (1.5 mmol), DMF (2.5 mL), H_2O (2.5 mL), 100 °C, 24 h.

[b] Isolated yield.

After examining the reactivity of **18** in a range of Suzuki–Miyaura reactions, we then examined its recyclability. We chose 4-bromoacetophenone (**19a**) as the substrate for this, using the reaction conditions detailed in Table l. The self-supported oxime palladacycle **18** collected by filtration after reaction was directly used for the following run (Table 3). In this way, **18** was recovered and reused six times, producing excellent yields of the desired product in the first five runs. To further investigate the recyclability of **18**, samples of freshly prepared **18** and recovered **18** after the first run were analyzed by ICP-MS. The results indicated no significant decrease of Pd loading, with used **18** maintaining a loading level of 0.75 mmol/g. The average Pd content of the products of the first five runs was 0.28 ppm, suggesting that **18** was efficiently removed from the products during workup. The diminished yields from run 6 seemed to arise from accumulated physical loss of **18** during workup of previous runs, for example, loss of **18** on the filter paper. In addition, gradually formed inactive palladium black, which was observed during the course of recycling experiments, may also be partially responsible for the lower yields after run 5.

In conclusion, we have prepared a self-supported oxime palladacycle **18** based on the PEEK architecture as a precatalyst for Suzuki–Miyaura reactions, using readily avail-

Table 3 Recycling Experiments[a]



Run	Isolated Yield (%)
1	97
2	99
3	99
4	99
5	90
6	65
7	11

[a] Reaction conditions: **19a** (1.0 mmol), **20** (1.2 mmol), **18** (0.015 mmol), Cs_2CO_3 (1.5 mmol), DMF (2.5 mL), H_2O (2.5 mL), 80 °C, 2 h.

able and inexpensive starting materials. Self-supported **18** proved to be an efficient precatalyst when aryl bromides were used as substrates. When aryl chlorides were used as substrates, only reactions involving activated aryl chlorides afforded moderate yields of the desired products. In addition, **18** could be recovered and reused up to four times to give excellent product yield with low levels of Pd leaching. We are investigating the reactivity and recyclability of **18** in other Pd-catalyzed cross-coupling reactions, and are exploring the use of other self-supported polymeric ligands as platforms for organometallic catalysts. As shown in Figure 1, it is anticipated that the general strategy for catalyst immobilization described in this manuscript will expand the range of organometallic catalysts that can be self-supported to include complexes with only a single ligand group, eliminating the requirement that the metal center complex two identical ligand groups

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) See the Supporting Information for details.

(20) **Suzuki–Miyaura Reaction; General Procedure:** Aryl halide **19** or **22** (1.0 mmol), phenylboronic acid (**20**; 1.2 mmol, 0.146 g), **18** (0.015 mmol, 0.002 g), Cs_2CO_3 (1.5 mmol, 0.489 g), DMF (2.5 mL), and H_2O (2.5 mL) were placed in a 25 mL round-bottomed flask equipped with a magnetic stirrer. The flask was immersed in an oil bath regulated at 80 or 100 °C for the reaction time indicated in Table 1 or Table 2. After the reaction mixture was cooled to r.t., Et_2O (8 mL) and H_2O (8 mL) were added to the flask. The resulting mixture was vigorously stirred for 5 min, and then filtered. The solid **18** collected on the filter was washed with H_2O (10 mL) and Et_2O (10 mL) and then dried. The filtrate was transferred to a separation funnel and the organic phase was separated and washed with H_2O (5 × 25 mL) and brine (10 mL), and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was analyzed by ^1H and ^{13}C NMR spectroscopy. When aryl chlorides were used as substrates, the crude products were purified by silica gel column chromatography.