Mild Conditions for Copper-Catalyzed Coupling Reaction of Phenols and Aryl Iodides and Bromides

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Abstract: Coupling of phenols and aryl bromides can be efficiently performed by means of catalytic amounts of copper iodide and the inexpensive ligand **1** (structure given in Table 1). The reaction is applicable to a wide range of substrates and proceeds at 60–80 °C, the lowest temperatures reported to date for an Ullmann-type synthesis of diaryl ethers. Moreover, the use of aryl bromides and inexpensive K_3PO_4 as base make this method attractive for applications on an industrial scale.

Keywords: aryl bromides; catalysis; copper; N ligands; phenol; tripotassium phosphate

Introduction

One of the most important routes to form diaryl ethers is the classic Ullmann method, which typically requires harsh reaction conditions (125–300 °C) and the need of stoichiometric or greater amounts of copper.[1,2] The large use of diaryl ethers as intermediates in organic synthesis[3f] and their importance as structural motifs in a great number of biologically active compounds[3] or polymers[4] provide a strong motivation for further methodological developments.[5] The ability of palladium-based catalysts to efficiently promote coupling reactions of phenol with aryl halides has thus been reported.[6] However, the sensitivity to moisture of palladium-mediated methods and the high costs of this metal limit the relevance of such strategies for industrial applications, which encouraged several groups to reinvestigate copper chemistry.[7] It was thus found that additives such as 1,10-phenanthroline,[7a, f] N,N-dimethylglycine·HCl,[7b] 2,2,6,6-tetramethylheptane-3,5-dione,[7c] triphenylphosphine,[7e] neocuproine,[7f] 8-hydroxyquinoline[7 g] and 1-naphthoic acid,[7i] enabled the Ullmann-type arylation of phenols to be performed under milder conditions (90–120 °C) and in the presence of catalytic amounts of the copper precursor. Our studies dealing with the arylation of N-, O- and C-nucleophiles[8,9] led us to discover that inexpensive chelating ligands combining nitrogen and/or oxygen donors considerably accelerated the copper-catalyzed arylation of phenols by aryl iodides:[9b] the reaction could indeed be performed under very mild temperature conditions in the presence of cesium carbonate, the base of choice in most protocols proposed for this type of reaction[5,7b, c,e, f,h, i].

We now report some recent studies concerning our copper-based catalytic systems and how we took advantage of these results to provide a method for the arylation of phenols that is as mild as the previous one, but even more economical. Indeed, two main improvements can be highlighted: first, diaryl ethers can be obtained from cheaper aryl bromides; secondly, the reaction can be carried out in the presence of tripotassium phosphate, an inexpensive base.
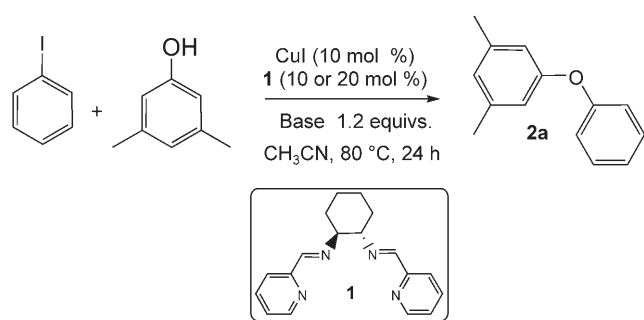
Results and Discussion

Coupling Reaction of Iodobenzene and 3,5-Dimethylphenol

In an endeavour to better understand the mechanism of the Ullmann diaryl ether synthesis, we studied the influence of a wide range of parameters on the arylation of 3,5-dimethylphenol by iodobenzene under the catalysis

of CuI and the tetradentate ligand **1** (structure given in Table 1). Among other things, the effect of the ligand loading was investigated. The coupling reaction was thus performed in the presence of two ratios of ligand-to-copper (**1**/CuI): either 1:1 or 2:1, and it was noticed that this parameter had a crucial influence on the outcome of the reaction, especially when using K_3PO_4 as base (Table 1). When ligand **1** was added in excess towards the copper salt (**1**/CuI = 2), the coupling was considerably slower than in the presence of equimolar amounts of CuI and ligand **1** (Table 1). In the first case, 70 hours were necessary to obtain **2a** in 77–78% yield (Table 1, note[c]) whereas the same yield was reached within 24 hours for a ligand-to-copper ratio of 1:1. A possible explanation for this observation is that a large excess of ligand **1** drove the equilibria for complex formation towards coordinatively saturated copper species, which are unable to coordinate further reagents such as aryl iodide and phenate. Such an inhibition was not observed in the procedure employing Cs_2CO_3 as base (Table 1), **2a** being obtained in satisfactory yield (about 75%) whatever the quantity of added ligand. Cesium phenoxides, being more soluble and nucleophilic than their potassium counterparts,[7f,10] would perhaps effect substitution of the ligand onto the metal center more easily, thus protecting the catalyst from inhibition by an excess of **1**.

These preliminary results were all the more attractive since they highlighted that, for a ligand-to-copper ratio of 1:1, K_3PO_4 is a very economically interesting base from the industrial point of view could promote the cou-
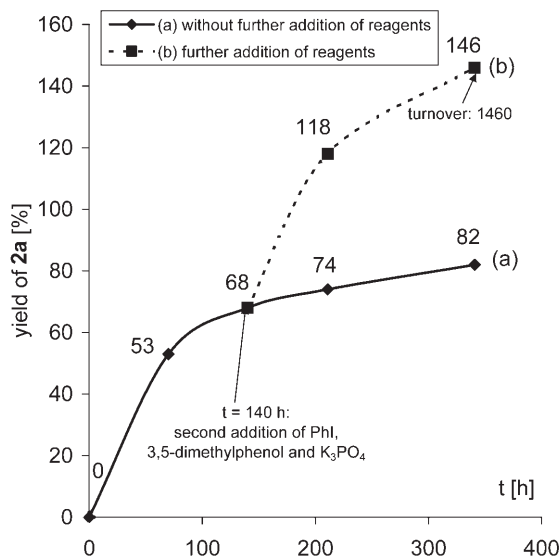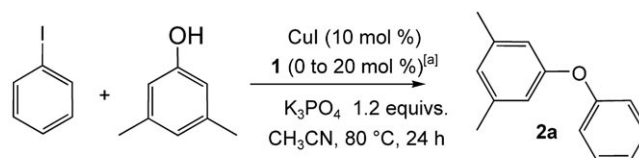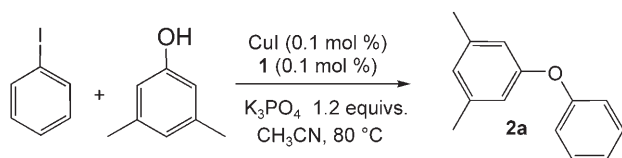
pling reaction as well as Cs_2CO_3 (Table 1); the latter is, however, generally used to carry out the arylation of phenols under copper catalysis.[5,7b, c,e, f,h, i] Moreover, we were pleased to find that, associated with K_3PO_4, the catalyst **1**/CuI (1:1) was particularly efficient since the arylation of 3,5-dimethylphenol by iodobenzene could even proceed under the action of only 0.1 mol % of the catalytic system (Figure 1). Several days were necessary to obtain diaryl ether **2a** in good yield, but what is worth noting is that neither inhibition nor deactivation of the catalyst **1**/CuI occurred in the course of the reaction. The coupling of additional iodobenzene and 3,5-dimethylphenol/K_3PO_4 (one equivalent more of each added after 140 hours) occurred with approximately the same rate as at the beginning of the reaction (Figure 1). A turnover number of 1460 could thus be obtained after about 340 hours at 80 °C and could likely be increased by performing a further addition of substrates. This result was rather interesting since it showed the robustness of the catalytic system involving CuI and tetradentate ligand **1** (**1**/CuI = 1). Moreover, to the best of our knowledge, such high turnover numbers have not been reported yet for copper-based catalysts.[11]

Furthermore, the strong effect of the ligand-to-copper ratio on the outcome of the coupling between iodobenzene and 3,5-dimethylphenol when using K_3PO_4 as a base prompted us to examine more in detail the influence of this parameter (Figure 2). Yields of **2a** were thus determined for **1**/CuI ratios varying from 0 to 2, 10 mol % of the copper salt being systematically used to promote the reactions (Figure 2). Selectivities are also mentioned for each ligand loading: the only by-product, if any, was benzene resulting from hydrodehalogenation of iodobenzene.

Without additional ligand (ratio **1**/Cu = 0), diaryl ether **2a** was selectively formed with a yield of 30% after 24 hours at refluxing acetonitrile. It is assumed that, in this case, 3,5-dimethylphenol itself acts as a ligand: the ability of phenols to have an accelerating effect in copper-catalyzed reactions has already been reported.[12]

For **1**/CuI ratios in the range of 0.25 to 1, a strong acceleration of the reaction was observed, and **2a** was obtained with a very good yield (85%) and an excellent selectivity (98%) for an optimal ratio of 0.5. An increase of ligand loading (**1**/CuI = 1.25 to 2) slowed the coupling reaction down, and lower yields as well as lower selectivities were obtained after 24 hours at 80 °C. In the presence of 20 mol % of the ligand **1** (**1**/CuI = 2), for example, the yield was as poor as in the absence of ligand (30%).

This survey thus emphasized that the composition of the precatalyst had a strong influence on the coupling of 3,5-dimethylphenol with iodobenzene and a ligand **1**-to-copper ratio of 0.5 was found to be optimal to promote this reaction. Moreover, we noticed that, using this ratio, quantitative arylation of 3,5-dimethylphenol by iodobenzene could be achieved by increasing the

Table 1. Influence of the ligand-to-copper ratio on the coupling of iodobenzene and 3,5-dimethylphenol using K_3PO_4 or Cs_2CO_3 as bases.[a]

1/CuI		2	1
Yield of 2a[b]	K_3PO_4	30[c]	78
	Cs_2CO_3	73	76

[a] *Reaction conditions:* iodobenzene (0.5 mmol), 3,5-dimethylphenol (0.6 mmol), base (0.6 mmol), CuI (0.05 mmol), ligand 1 (0.05 or 0.10 mmol), CH_3CN (300 µL), 80 °C, 24 h.
[b] GC yields determined with 1,3-dimethoxybenzene as internal standard.
[c] 77% after 70 h.

Figure 1. Coupling reaction of iodobenzene and 3,5-dimethylphenol under the catalysis of 0.1 mol % of CuI and ligand **1**. *Reaction conditions:* (a) without further addition of reagents: iodobenzene (5 mmol), 3,5-dimethylphenol (6 mmol), base (6 mmol), CuI (0.005 mmol), ligand **1** (0.005 mmol), CH$_3$CN (3 mL), 80 °C; (b) after 140 h at 80 °C, addition of iodobenzene (5 mmol), 3,5-dimethylphenol (5 mmol), base (5 mmol). GC yields determined with 1,3-dimethoxybenzene as internal standard. Solid line: without further addition of reagents; dashed line: with second addition of reagents.

amount of K$_3$PO$_4$ from 1.2 equivalents to 2 equivalents [comparison of Figure 2 (**1**/CuI ratio = 0.5) and Table 2, entry 1]. We thus tried to extend the scope of this powerful catalytic system to the coupling of the cheaper and more challenging aryl bromides.

Extension of the Scope to the More Challenging Aryl Bromides

We first observed that in the conditions allowing quantitative conversion of iodobenzene into **2a** (Table 2, entry 1), the reaction of 3,5-dimethylphenol with bromobenzene gave the corresponding diaryl ether **2a** in good yield at 80 °C (63%, entry 2). Increasing the excess of phenol from 1.2 to 1.5 equivalents towards bromobenzene enabled a significant acceleration at the same temperature (Table 2, entry 3), and when the reaction time was increased to 36 hours, the reaction went to completion (entry 4). It is worth noting that bromobenzene was
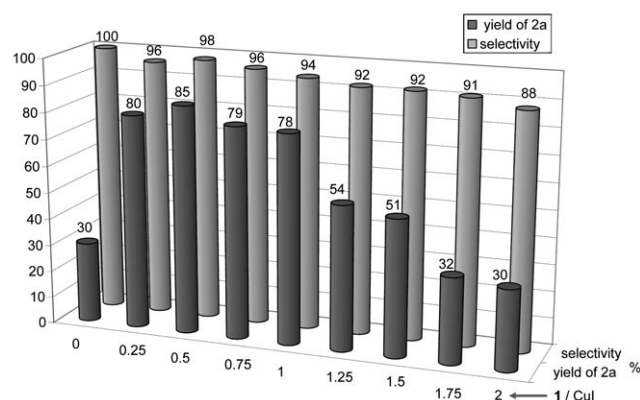
1/Cul	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2
Yield of **2a** [%][b]	30	80	85	79	78	54	51	32	30
Selectivities [%][c,d]	100	96	98	96	94	92	92	91	88

[a] *Reaction conditions:* iodobenzene (0.5 mmol), phenol (0.6 mmol), K$_3$PO$_4$ (0.6 mmol), CuI (0.05 mmol), ligand 1, CH$_3$CN (300 μL), 80 °C, 24 h.

[b] GC yields determined with 1,3-dimethoxybenzene as internal standard.

[c] Selectivity: 3,5-dimethylphenyl phenyl ether **2a** yield divided by iodobenzene conversion.
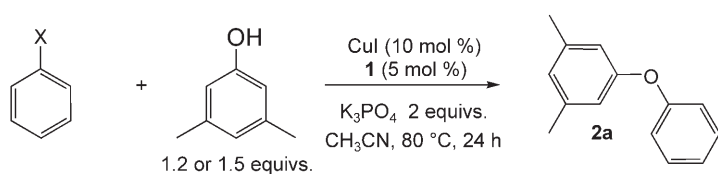
[d] Only by-product: benzene (0 to 5% yield).

Figure 2. Effect of the **1**-to-CuI ratio on the yield of diaryl ether after 24 hours at 80 °C in acetonitrile.

observed to react much slower than iodobenzene in our previously reported conditions involving the catalytic system **1**/Cu (2:1) combined with cesium carbonate as base: quantitative yield of diaryl ether **2a** required 75 h at 110 °C.[9b] Reducing the ratio of ligand-to-copper from 2:1 to 1:2 and replacing Cs$_2$CO$_3$ by K$_3$PO$_4$ enabled us to overcome this limitation and to provide an efficient method proceeding under the mildest temperature conditions to date. Indeed, to the best of our knowledge, the lowest temperature employed for copper-catalyzed coupling reactions of phenols and aryl bromides had been reported by Ma [in the presence of 10 mol % CuI, 30 mol % ligand (*N,N*-dimethylglycine hydrochloride) and less economical cesium carbonate, the coupling reactions efficiently proceed at 90 °C].[7b]

On the basis of the above results, the catalytic system **1**/CuI (1:2) was tested in coupling reactions involving several different phenols and aryl bromides (Table 3). The expected diaryl ethers were synthesized whatever the nature of the substituent on the aryl bromide, either electron-withdrawing trifluoromethyl, cyano or nitro groups, entries 2, 3, 4) or electron-donating (methoxy group, entry 5). The electron-poor *p*-bromobenzotri-

Table 2. Coupling reaction of iodobenzene and bromobenzene with 3,5-dimethylphenol under the catalysis of CuI and ligand 1 with a 1/CuI ratio of 0.5.[a]

Entry	X	Equivs. ArOH/PhX	Yield of 2a [%][b]
1	I	1.2	96
2	Br	1.2	63
3	Br	1.5	86
4	Br	1.5	97[c]

[a] *Reaction conditions:* aryl halide (0.5 mmol), phenol (0.6 or 0.75 mmol), K_3PO_4 (1 mmol), CuI (0.05 mmol), ligand 1 (0.025 mmol), CH_3CN (300 μL), 80 °C, 24 h.

[b] GC yields determined with 1,3-dimethoxybenzene as internal standard; selectivities: 96–97% (by-product: benzene).
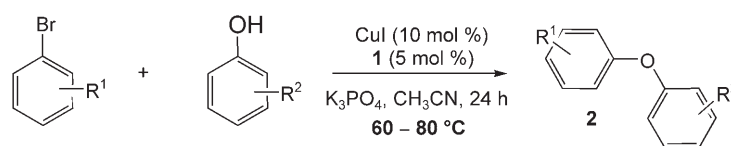
[c] 36 h instead of 24 h.

fluoride, *p*-bromobenzonitrile and *p*-nitrobromobenzene could even be successfully converted into the corresponding diaryl ethers at 60 °C (entries 2, 3, 4). Because of its steric hindrance, the *ortho*-substituted *o*-bromotoluene required longer reaction times to overcome its lack of reactivity (entry 6). The method was also extended to a heteroaryl bromide, 2-bromopyridine being for example quantitatively and selectively converted into **2 g** at 60 °C (entry 7).
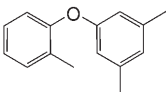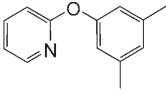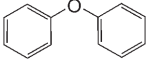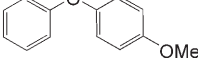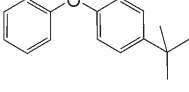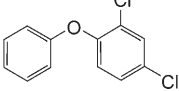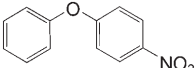
Phenol reactivity was compared using bromobenzene as an arylating agent (Table 3, entries 1, 8 to 12): electron-neutral and electron-rich substrates gave the corresponding diaryl ethers in good to very good yields (entries 1, 8 to 10). It is noteworthy that the hindered 2,4-dichlorophenol substituted by two electron-withdrawing chloro groups was selectively converted into the corresponding 2,4-dichlorophenyl phenyl ether **2e** in satisfactory yield (entry 11). On the contrary, substrates bearing strong electron-withdrawing groups such as *p*-nitrophenol proved to be unreactive under our conditions (entry 12) and bromobenzene was quantitatively recovered at the end of the reaction; this result is however quite general in the literature.[7b, c,13] In all these examples, the reaction was selective with respect to phenol derivatives and the only by-products detected by GC were arenes resulting from hydrodehalogenation of the corresponding aryl bromides. By-products derived from biaryl coupling were never observed.

Table 3. Couplings of aryl bromides with phenols in the presence of CuI/1 at 60–80 °C.[a]

Entry	R^1	R^2	Product		T [°C]	Yield [%][b]	Selectivity [%][c]
1	H	3,5-Me$_2$		**2a**	80	86 (80)[d]	96
2	4-CF$_3$	3,5-Me$_2$		**2b**	80	89 (83)	94
					60	73	93
3	4-CN	3,5-Me$_2$		**2c**	80	89 (82)	90
					60	74	92
4	4-NO$_2$	3,5-Me$_2$		**2d**	80	84 (73)	87
					60	76	90
5	4-OMe	3,5-Me$_2$		**2e**	80	72 (68)	91

Table 3 (cont.)

Entry	R^1	R^2	Product		T [°C]	Yield [%][b]	Selectivity [%][c]
6	2-Me	3,5-Me$_2$		**2f**	80	21 (55)[e]	100
7	2-Br-Py	3,5-Me$_2$		**2g**	60	100 (97)[f]	100
8	H	H		**2h**	80	95 (88)	98
9	H	4-OMe		**2i**	80	92 (88)	96
10	H	4-t-Bu		**2j**	80	75 (70)	98
11	H	2,4-Cl$_2$		**2k**	80	68 (62)	95
12	H	4-NO$_2$		**2 l**	80	0 [g]	–

[a] *Reaction conditions for isolated yields:* aryl bromide (2 mmol), phenol (3 mmol), K$_3$PO$_4$ (4 mmol), CuI (0.2 mmol), ligand 1 (0.1 mmol), CH$_3$CN (1.2 mL), 24 h. *Reaction conditions for GC yields:* aryl bromide (0.5 mmol), phenol (0.75 mmol), K$_3$PO$_4$ (1 mmol), CuI (0.05 mmol), ligand 1 (0.025 mmol), CH$_3$CN (300 μL), 24 h.

[b] Yields determined by GC (using 1,3-dimethoxybenzene as internal standard) and yields in brackets refer to isolated yields; yields are based on the default reagents (aryl bromides).

[c] Selectivities are expressed with respect to aryl bromides: the only by-product is the arene resulting from hydrodehalogenation of the corresponding aryl bromide.

[d] The same yield of 2a was obtained only after 36 h at 110 °C in the presence of our former system including ligand 1 (20 mol %) and Cs$_2$CO$_3$ as a base.[7b]

[e] After 85 h at 80 °C.

[f] The reaction time was not optimized.

[g] Bromobenzene quantitatively recovered.

Conclusion

In this paper, we have reported an efficient, cheap and practical copper-catalyzed method allowing coupling of phenols and aryl bromides under very mild conditions. Indeed, to the best of our knowledge, the coupling reaction proceeds at the lowest temperatures known to date (60 – 80 °C).

This new advance can largely be ascribed to the use of K$_3$PO$_4$ as a base and to an appropriate tetradentate ligand **1** loading, this parameter having been shown to strongly influence the efficiency of the CuI/**1** catalytic system. The best catalytic activities were obtained for ligand-to-copper ratios in the range of 0.25 to 1, with an optimum being found for a **1**/CuI ratio of 0.5. Moreover, the robustness of the catalyst involving stoichiometric amounts of CuI and **1** (**1**/CuI ratio of 1) has been highlighted since it allowed us to achieve the coupling reaction of 3,5-dime-thylphenol and iodobenzene at very low catalyst levels (lower than 0.1% in copper salt and ligand **1**).

Finally, the general procedure allowing the synthesis of diaryl ethers from less expensive aryl bromides can easily be adapted at an industrial scale and is all the more attractive since it works with K$_3$PO$_4$, a cheaper base than the Cs$_2$CO$_3$ generally required in this type of reaction. Efforts to expand our methodology to other arylating agents such as even more challenging aryl chlorides are in progress in our laboratory.

Experimental Section

General Remarks

All reactions were carried out in 35-mL Schlenk tubes or in Carousel "reaction stations RR98030" Radley tubes, under a

pure and dry nitrogen atmosphere. Acetonitrile was distilled from P_4O_{10} and was stored on 4 Å activated molecular sieves under a nitrogen atmosphere. Cesium carbonate (Aldrich) and tripotassium phosphate (Riedel-de Haën) were ground to a fine powder and stored under vacuum in the presence of P_4O_{10}. All other solid materials were stored in the presence of P_4O_{10} in a bench-top desiccator under vacuum at room temperature and weighed in the air. Copper(I) iodide was purified according to literature procedures[14] and stored protected from light. The synthesis of ligand **1** was reported in our previous papers.[9a, c] Iodobenzene, aryl bromides and phenols were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). If solids, they were recrystallized in an appropriate solvent.[15] If liquids, they were distilled under vacuum and stored under an atmosphere of nitrogen. Special care was taken with iodobenzene which was regularly distilled and stored protected from light. All phenols were also stored protected from light.

Materials and Instrumentation

Column chromatography was performed with SDS 60 A C.C silica gel (35–70 μm). Thin layer chromatography was carried out using Merck silica gel 60 F_{254} plates.

All products were characterized by their ^1H NMR, ^{13}C NMR and GC/mass spectra. NMR spectra were recorded at 20°C on a Bruker AC 200 MHz or on a DRX-250 spectrometer working respectively at 200.13 and 250.13 MHz for ^1H, at 50.32 and 62.90 MHz for ^{13}C and at 188.31 and 236.36 for ^{19}F. Gas chromatography-mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and a HP5-MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm). GC/MS method: initial temperature: 45°C; initial time: 2 min; ramp: 2°C/min until 50°C then 10°C/min; final temperature: 250°C; final time: 10 min. Melting points were determined using a Büchi B-540 apparatus and are uncorrected.

General Procedure for Copper-Catalyzed Coupling Reaction of Phenols and Aryl Bromides (2-mmol Scale)

After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar was charged with CuI (38.1 mg, 0.2 mmol), ligand **1** (29.2 mg, 0.1 mmol), the phenol (3.0 mmol), K_3PO_4 (848 mg, 4.0 mmol) and the aryl bromide (2.0 mmol), if a solid. The tube was evacuated, back-filled with nitrogen. If a liquid, aryl bromide was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed acetonitrile (1.2 mL). The tube was sealed under a positive pressure of nitrogen, stirred and heated to 60 or 80°C for the required time period. After cooling to room temperature, the mixture was diluted with diethyl ether (~20 mL) and filtered through a plug of celite®, the filter cake being further washed with diethyl ether (~5 mL). The filtrate was washed twice with water (~10 mL × 2). Gathered aqueous phases were twice extracted with dichloromethane (~10 mL). Organic layers were gathered, dried on $MgSO_4$, filtered and concentrated under vacuum to yield the crude product which was purified by silica gel chromatography with an eluent of hexanes and dichloromethane. The products were characterized by ^1H NMR, ^{13}C NMR and mass spectra comparisons with those of authentic samples.

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