ORGANIC
LETTERS

2010
Vol. 12, No. 6
1200−1203

Nickel, Manganese, Cobalt, and Iron-Catalyzed Deprotonative Arene Dimerization

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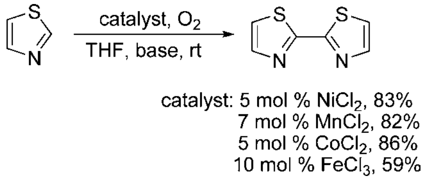
Received December 28, 2009

ABSTRACT



A number of first-row transition metal salts catalyze deprotonative dimerization of acidic arenes. Under the atmosphere of oxygen, nickel, manganese, cobalt, and iron chlorides have been shown to dimerize five- and six-membered ring heterocycles as well as electron-poor arenes. Both tetramethylpiperidide and dicyclohexylamide bases can be employed; however, the former afford slightly higher yields.

Carbon−hydrogen bond activation protocols allow the utilization of a C−H bond as a functional group, offering a direct and efficient route for the creation of carbon−carbon and carbon−heteroatom bonds. Unfortunately, most of the current methods for functionalization of carbon−hydrogen bonds employ second or third row transition metal catalysis.[1] First-row transition metals such as Fe, Co, Ni, Mn, or Cu are used relatively rarely.[2] These elements are substantially more abundant compared to their 4d and 5d analogues. For example, nickel is present at a concentration of 84 g/ton in the Earth's crust.[3] Its 4d homologue, palladium, is present at a concentration of 0.015 g/ton while platinum is found at the concentration of 0.005 g/ton.[3] Therefore, the past few years have witnessed an interest in developing methods that employ abundant first-row transition metal catalysts. We have reported a general method for copper-catalyzed arylation of C−H bonds.[4] Recently, we developed a method for copper-catalyzed, deprotonative arene dimerization by employing oxygen as the terminal oxidant.[5] By analogy with Glaser−Hay reaction,[6] in situ deprotonation is followed by the transmetalation, forming an organocopper species that affords biaryl under oxygen (Scheme 1). It is known that dimerization of organometallic species can be catalyzed or promoted by transition metals other than copper. For example, Mn, Fe, Co, and Ni salts have been shown to effect the dimerization of Grignard reagents.[7] In some cases, oxygen has been used

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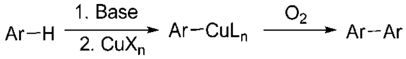
10.1021/ol902970z

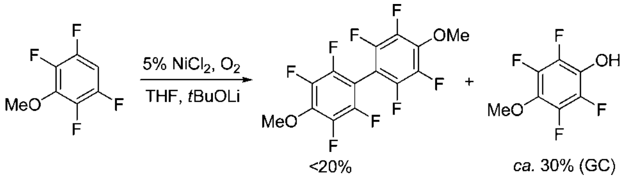
Scheme 1. Copper-Catalyzed Arene Dimerization



as the terminal oxidant.[8] As a consequence, one should be able to perform the deprotonation/oxidative dimerization sequences by employing first-row transition metals other than copper. Potential benefits of their use include relative nontoxicity of iron and manganese complexes. We report here a method for cobalt-, iron-, nickel-, and manganese-catalyzed arene deprotonative dimerization by using oxygen as the terminal oxidant.

Our initial attempts were directed toward developing optimized conditions for arene dimerization under nickel catalysis. In copper-catalyzed arene dimerization, the best product yields were obtained by employing magnesium or zinc amide bases.[5] Use of lithium or potassium alkoxide bases led to formation of major amounts of phenol byproduct. Similar results were obtained if $NiCl_2$ catalyst was employed (Scheme 2). By analogy with copper catalysis chemistry,[9] phenol byproduct can be formed either by the direct reaction of arylalkali metal intermediate with oxygen or by reaction of a high-valent arylnickel with hydroxide derived from water. Thus, a less polarized C−metal bond in the intermediate that should decrease the reactivity of arylmetal with oxygen and would bind hydroxide byproduct was needed. As observed for copper-catalyzed dimerization, zinc or magnesium bases of hindered amines were shown to be efficient. Synthesis of the bases is presented in Scheme 3. Both tetramethylpiperidides and dicyclohexylamides can be used; however, the more expensive tetramethylpiperidides afford somewhat higher yields as shown below. Magnesium tetramethylpiperidides were introducted by Eaton.[10] Numerous tetramethylpiperidide bases have been extensively investigated by Knochel for a variety of deprotonation/functionalization procedures.[11] It was found that optimal yields are obtained if a combination of zinc and magnesium bases is used.

Scheme 2. Phenol Byproducts in Dimerization



Scheme 3. Base Synthesis

Base 1	*i*PrMgCl*LiCl + tetramethylpiperidine (1:1.05)
Base 2	*i*PrMgCl*LiCl + dicyclohexylamine (1:1.05)
Base 3	Base 1 + $ZnCl_2$ (1:0.5)
Base 4	Base 2 + $ZnCl_2$ (1:0.5)

The rationale for the use of base mixtures is as follows. Combination of magnesium bases 1 and 2 with zinc bases 3 and 4 allows for a relatively rapid deprotonation (provided by Mg amides) and higher substrate stability (provided by Zn amides; enhanced functional group tolerance and phenol byproduct formation prevented). If Mg bases are used for sensitive substrates, lower yields are obtained.

The optimal results for nickel-catalyzed dimerization were obtained by employing 5 mol % of $NiCl_2$ catalyst at 0−60 °C in THF solvent under 1 atm of oxygen (Table 1). The scope of the reaction is similar to the scope of copper-catalyzed dimerization. Electron-rich heterocycles such as thiazole (entry 1) and benzofuran (entry 2) can be dimerized. 3-Chloropyridine is reactive, affording the dimer in 33% yield (entry 3). Electron-deficient 1,3-difluorobenzene and difluoronitrobenzene (entries 4 and 5) are reactive and the most acidic C−H bonds, those flanked by fluoro and nitro substituents, are functionalized. Entries 1 and 4 were run with both tetramethylpiperidide and dicyclohexylamide bases. The substantialy cheaper dicyclohexylamide is almost as efficient as the tetramethylpiperidide base.[12]

Manganese salts are known to promote Grignard dimerizations.[7c,8a] Selective cross-dimerization of organomagnesium species can be achieved by employing manganese catalysis.[8c] Manganese salts are less toxic than copper or nickel complexes.[13] As shown in Table 2, manganese(II) chloride catalyzes arene deprotonative dimerization under conditions that are similar to the ones described for nickel. Thiazole and 2-chlorothiophene are dimerized in good yields (entries 1 and 2). Electron-deficient methoxypyrazine is also reactive, affording the product in acceptable yield (entry 3). 1,2,4-Trifluorobenzene and ethyl 3,4-difluorobenzoate are converted into dimers in good yields (entries 4 and 5). Entries

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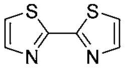
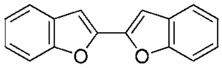
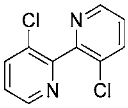
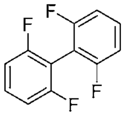
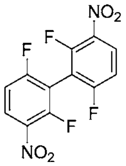
(12) 2,2,6,6-Tetramethylpiperidine is available at $524/mol, while dicyclohexylamine costs $4.7/mol (Aldrich).

(13) *NIOSH Pocket Guide to Chemical Hazards, DHHS (NIOSH)*; Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health: Cincinnati, OH, 2007; Publication No. 2005-149.

Table 1. Nickel Catalysis[a]

$$\text{Ar–H} \xrightarrow[\text{THF, base, 0 - 60 °C}]{\text{5 mol \% NiCl}_2\text{, O}_2} \text{Ar–Ar}$$

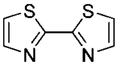
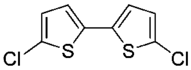
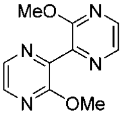
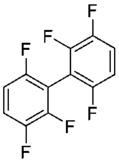
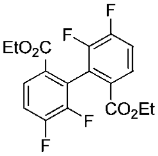
entry	Ar-H, base	product	yield, %
1	Thiazole, base 1 + base 3 (0.54/1)		83 71[b]
2	Benzofuran, base 1		45
3	3-Chloro-pyridine, base 1		33
4	1,3-Difluorobenzene, base 1 + base 3 (2/1)		75 70[b]
5	2,4-Difluoronitro-benzene, base 3		73

[a] Substrate (1 equiv), base (1.2−1.4 equiv). Yields are isolated yields. See the Supporting Information for details. [b] Dicyclohexylamide base.

1, 2, and 4 were run with both tetramethylpiperidide and dicyclohexylamide bases, with tetramethylpiperidides affording slightly higher yields.

Table 2. Manganese Catalysis[a]

$$\text{Ar–H} \xrightarrow[\text{THF, base, 0 °C - rt}]{\text{7 mol \% MnCl}_2\text{, O}_2} \text{Ar–Ar}$$

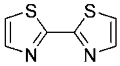
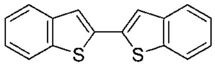
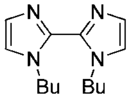
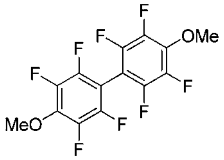
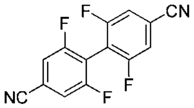
entry	Ar-H, base	product	yield, %
1	Thiazole, base 1 + base 3 (0.54/1)		82 74[b]
2	2-Chlorothiophene, base 1 + base 3 (5/1)		75 70[b]
3	Methoxypyrazine, base 1		42
4	1,2,4-Trifluorobenzene base 1 + base 3 (2/1)		81 71[b]
5	Ethyl 3,4-difluoro-benzoate, base 1		65

[a] Substrate (1 equiv), base (1.2−1.4 equiv). Yields are isolated yields. See the Supporting Information for details. [b] Dicyclohexylamide base.

Grignard dimerization under cobalt catalysis is known.[7b,8e] We were pleased to find out that cobalt-catalyzed deprotonative arene dimerization is also successful (Table 3). The thiazole dimerization efficiency is virtually the same as that for nickel and manganese catalysis, affording the dimer in 86% yield (entry 1). Benzothiophene (entry 2) and *N*-butylimidazole (entry 3) can be dimerized in excellent yields. Electron-poor tetrafluoroanisole (entry 4) and difluorobenzonitrile (entry 5) afford deprotonative dimerization products in 90% and 80% yields, respectively. As shown before for nickel and manganese catalysis, dicyclohexylamides afford results comparable to those of tetramethylpiperidide amides.

Table 3. Cobalt Catalysis[a]

$$\text{Ar–H} \xrightarrow[\text{THF, base, 0 °C - rt}]{\text{5 mol \% CoCl}_2\text{, O}_2} \text{Ar–Ar}$$

entry	Ar-H, base	product	yield, %
1	Thiazole, base 1 + base 3 (0.8/1)		86 70[b]
2	Benzothiophene, base 1		85 78[b]
3	*N*-Butylimidazole, base 1		80
4	Tetrafluoroanisole, base 1 + base 3 (7.3/1)		90 87[b]
5	3,5-Difluorobenzo-nitrile, base 1 + base 3 (1/2)		80

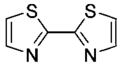
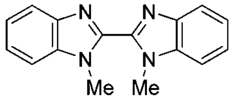
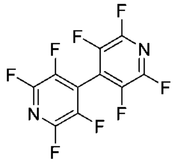
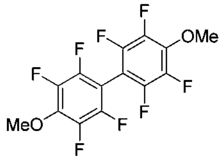
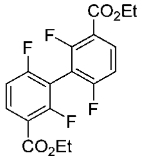
[a] Substrate (1 equiv), base (1.1−1.7 equiv). Yields are isolated yields. See the Supporting Information for details. [b] Dicyclohexylamide base.

Iron is the fourth most abundant element in the Earths' crust.[3] Iron salts are relatively nontoxic.[13] Iron-promoted or catalyzed Grignard dimerizations have been reported.[7a,b,8a,e] We show that iron trichloride catalyzes deprotonative arene dimerization under an atmosphere of oxygen (Table 4). In general, the dimerization efficiency is lower compared to that of nickel, manganese, and cobalt catalysis. Somewhat higher catalyst loading (10 mol % as opposed to 5−7 mol %) is required for optimal results. Thiazole is dimerized in 59% yield (entry 1). Other five-membered-ring heterocycles such as 4,5-dimethylthiazole (entry 2) and *N*-methylbenzimidazole (entry 3) are also reactive. Tetrafluoropyridine, tetrafluoroanisole, and ethyl-2,4-difluorobenzoate (entries 4−6) afford dimerization products in good yields.

We ran several control experiments to determine if a trace of another transition metal might be catalyzing the dimerization (Scheme 4).[14] With reagent grade or ultrapure

Table 4. Iron Catalysis[a]

$$\text{Ar-H} \xrightarrow[\text{THF, base, 0 °C - rt}]{\text{10 mol \% FeCl}_3\text{, O}_2} \text{Ar-Ar}$$

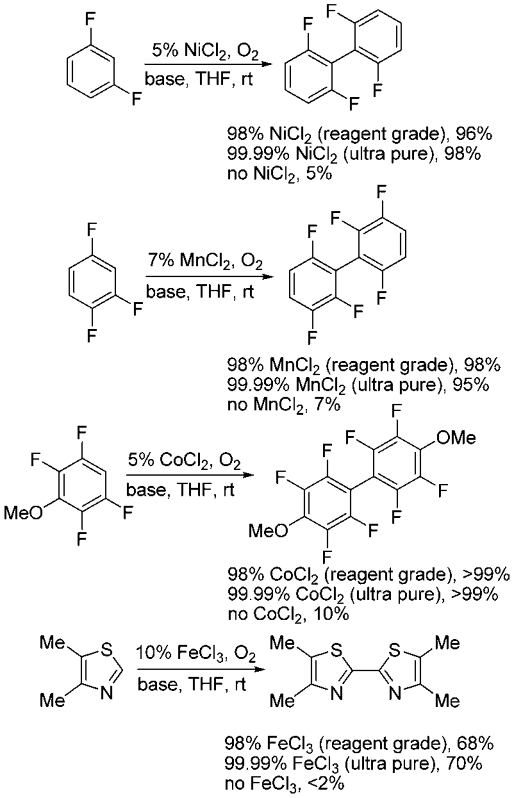
entry	Ar-H, base	product	yield, %
1	Thiazole, base 1 + base 3 (4.7/1)		59
2	4,5-Dimethylthiazole, base 1		68
3	*N*-Methylbenzimidazole, base 1		77
4	Tetrafluoropyridine, Base 3		54
5	Tetrafluoroanisole, base 1 + base 3 (0.9/1)		78
6	Ethyl 2,4-difluorobenzoate, base 1 + base 3 (4.6/1)		70

[a] Substrate (1 equiv), base (1.1−1.3 equiv). Yields are isolated yields. See the Supporting Information for details.

transition metal salts similar results were obtained, showing that catalysis by contaminants is unlikely. If the metal salt was omitted, only minor amounts of arene dimer were formed.

In conclusion, we have shown that transition metal-catalyzed deprotonative arene dimerization can be achieved by cobalt, iron, nickel, and manganese catalysis employing oxygen as the terminal oxidant. Electron-rich and electron-poor heterocycles as well as electron-poor arenes can be dimerized.

Scheme 4. Control Experiments (% conversion reported)



Acknowledgment. We thank the Welch Foundation (Grant No. E-1571), NIGMS (Grant No. R01GM077635), the A. P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, and the Norman Hackerman Advanced Research Program for supporting this research.

Supporting Information Available: Experimental details, data, and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902970Z

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