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Organocatalysis in Cross-Coupling: DMEDA-Catalyzed Direct C−H Arylation of Unactivated Benzene

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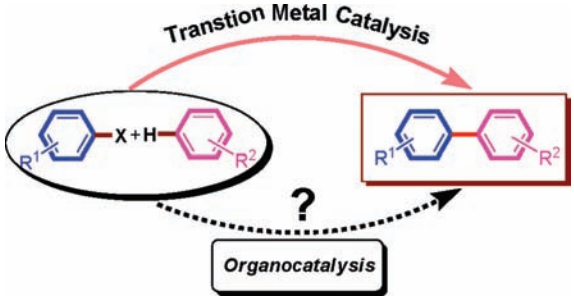
Abstract: A striking breakthrough to the frame of traditional cross-couplings/C−H functionalizations using an organocatalyst remains unprecedented. We uncovered a conceptually different approach toward the biaryl syntheses by using DMEDA as the catalyst to promote the direct C−H arylation of unactivated benzene in the presence of potassium *tert*-butoxide. The arylation of unactivated benzene with aryl iodides, or aryl bromides and even chlorides under the assistance of an iodo-group, could simply take place at 80 °C. The new methodology presumably involves an aryl radical anion as an intermediate. This finding offers an option toward establishing a new horizon for direct C−H/cross-coupling reactions.

Transition-metal-catalyzed direct arylation of aromatic C−H bonds is emerging as a valuable and efficient alternative to traditional cross-couplings in the construction of biaryl compounds.[1] Much effort has been focused on the direct arylation of heterocycles,[2] arenes with directing groups,[1c,d,3] and electron-deficient arenes.[4] As a completely unactivated arene, benzene has been directly arylated by a few efficient transition-metal-catalyzed methods[5] and other approaches.[6]

Scheme 1. Approaches for Direct Arylation



While chemists have been remarkably adept at coming up with coupling reactions and direct arylations, mainstream developments are still restricted to the transition-metal-assisted approach, such as brilliantly creative transition metal complexes and capricious ligands. Organocatalysis, however, emerged as a very rapidly growing area for chemical synthesis.[7] To the best of our knowledge, there is no example using organocatalysts in the direct arylation of arenes. Herein, we disclose an organomolecule catalyzed protocol for accessing biaryl molecules via the direct C−H arylation of unactivated benzene (Scheme 1).

Recently, we have launched the iron-catalyzed direct arylation of benzene with aryl halides (Ar−X, X = I, Br, Cl) employing DMEDA as a ligand and LiHMDS [lithium bis(trimethylsilyl)amide] as the base.[5e] Itami et al. observed that KOBu^t could promote direct arylation of nitrogen heterocycles with aryl iodides.[8] Serendipitously, we observed that the direct arylation of unactivated benzene with aryl iodides could be catalyzed by DMEDA (*N*,*N*′-dimethylethane-1,2-diamine) in the presence of potassium *tert*-butoxide (KOBu^t) even without adding any transition metals. To uncover this unprecedented, organomolecule-catalyzed biaryl synthesis, we embarked on studying the feasibility of this novel finding. The direct arylation of benzene with 4-iodotoluene **1a** was selected for our prototypical investigation (Table 1). No conversion of **1a** was observed in the absence of any organomolecule catalyst (Table 1, entry 1). Bipyridine, TMEDA, pyridine, and pyrazine did not furnish the desired coupling product as well (Table 1, entries 4, 5, 13, and 14). Surprisingly, organomolecules with free −NH or −OH moieties effectively catalyzed the reaction even at fairly ambient temperature (80 °C). *N*,*N*′-Dimethyl-ethylene diamine, ethylene diamine, 2-aminoethanol, and *cis*-cyclohexane-1,2-diol could serve as efficient catalysts to promote this direct arylation (Table 1, entries 3, 7, 8, and 11). It is noteworthy that the reaction using *trans*-cyclohexane-1,2-diol only provided 22% desired product **3a** (Table 1, entry 12), while the reaction in the presence of *cis*-cyclohexane-1,2-diol offered 81% direct arylation product (Table 1, entry 11). Having the sterically encumbered *tert*-butyl group attached to the −NH moiety rendered the organomolecule ineffective (Table 1, entry 9).

We further examine the efficacy of this transformation in the presence 20 mol % DMEDA as the catalyst by varying the bases (see Supporting Information). Only potassium *tert*-butoxide provided excellent conversion (>99%) and produced the corresponding arylation product in 84% yield, whereas LiHMDS only gave a 10% yield. All other tested bases, such as NaH, KOH, Na_2CO_3, KOAc, NaOBu^t, and LiOBu^t, were ineffective in promoting the direct arylation of benzene with 4-iodotoluene **1a**.

Since the major difference among LiOBu^t, NaOBu^t, and KOBu^t is the countercation, giving remarkably dissimilar results, we were attracted to investigating the role of the alkali metal ion. A stoichiometric amount of 18-crown-6 was added to trap the K^+ cation during the course of the reaction, and a significantly low conversion (22% conversion of **1a**, 15% product **3a**) was observed. This result suggested that the alkali metal cation possibly played a role in this transformation. In order to eliminate the possibility of

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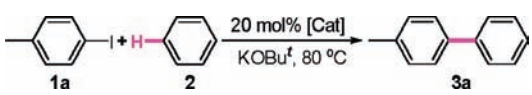
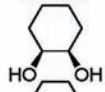
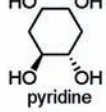
Table 1. Optimization of Direct Arylation of Benzene[a]

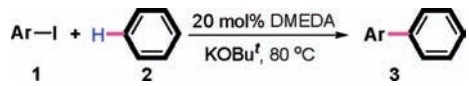


entry	[Cat]	yield (%)
1	/	*trace*
2	L-proline	34
3	***DMEDA***	***84***
4	Bipy	*trace*
5	TMEDA	0
6	Dppf	0
7	$NH_2CH_2CH_2NH_2$	81
8	$NH_2CH_2CH_2OH$	67
9	^{t}BuNHCH$_2$CH$_2$NH^{t}Bu	*trace*
10[b]	DMEDA	70
11[b]		81
12[b]		22
13	pyridine	*trace*
14	pyrazine	*trace*

[a] Reaction conditions: 0.5 mmol **1a**, 1.5 mmol of KOBu^t, in 4 mL of benzene. [b] 0.5 mmol of **1a** in 3 mL of benzene.

the presence of trace transition metal elements in the commercially available potassium *tert*-butoxide that would potentially affect our investigation, we indeed purified the KOBu^t by sublimation prior to our examination. Almost the same results were obtained between the nonpurified and purified base.

Table 2. DMEDA-Catalyzed Direct Arylation of Benzene with Ar−I[a]



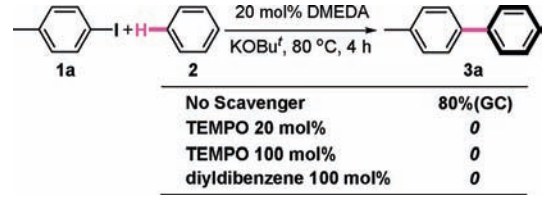
entry	Ar− group		product **3**	yield(%)
1	4-MeC_6H_4	**1a**	**3a**	84
2	C_6H_5	**1b**	**3b**	81
3	4-MeOC_6H_4	**1c**	**3c**	84
4	3-MeC_6H_4	**1d**	**3d**	76
5	2-MeC_6H_4	**1e**	**3e**	38
6	2-MeOC_6H_4	**1f**	**3f**	60
7	3-MeOC_6H_4	**1g**	**3g**	80
8	4-*i*PrC_6H_4	**1h**	**3h**	92
9	2-naphthalyl	**1i**	**3i**	88
10	4-PhC_6H_4	**1j**	**3j**	73
11[b]	4-FC_6H_4	**1k**	**3k**	68
12	4-CNC_6H_4	**1l**	**3l**	71(30[c])

[a] Reaction conditions: 0.5 mmol of **1**, 1.5 mmol of KOBu^t, in 4 mL of benzene. [b] 10% **3j** was also isolated. [c] 4-CNC_6H_4Br was the electrophile.

A wide range of aryl iodides could be employed as the electrophile in this novel DMEDA-catalyzed direct arylation reaction, and the results were compiled in Table 2. Notably, the electron-rich aryl iodides could be appropriate electrophiles in this transformation (Table 2, entries 1−8). For example, the reactions of 4-MeOC_6H_4I **1c** and 4-*i*PrC_6H_4I **1h** provided the desired arylation product in 84% and 92%, respectively (Table 2, entries 3 and 8). The sterically hindered 2-iodoanisole also furnished the product smoothly in 60% yield. Aryl bromides gave low conversions and low yields.

Meanwhile, other unactivated arenes were also investigated under the standard conditions. The direct arylation of naphthalene with **1a**, **1b**, and **1c** could take place smoothly and produced the desired arylation products (two regioisomers) in 75% (α:β = 81:19), 78% (α:β = 81:19), and 83% (α:β = 79:21) yields, respectively (see Supporting Information). No reactions occurred for the direct arylation of anisole or toluene under the same reaction conditions. In the presence of KOBu^t, Daugulis reported the intramolecular direct arylation of phenol and direct arylation of heterocycle arenes with aryl iodides, and they also proposed the benzyne-type pathway for such reactions.[2i,m,9] On the contrary, no regioisomers were identified from the direct arylation of benzene with substituted aryl iodides under our reaction conditions (Table 2), which unambiguously ruled out the benzyne-type mechanism for the DMEDA-catalyzed reactions.

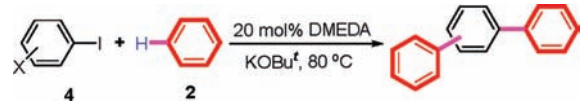
Scheme 2. Radical Trapping Experiments

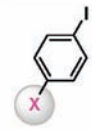
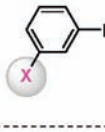
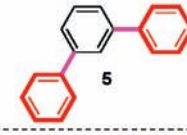
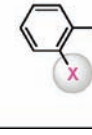


Itami et al. proposed a radical pathway for the sole KOBu^t promoted direct arylation of electron-deficient nitrogen heterocycles with aryl iodides.[8,10] To gather further insight into our novel DMEDA-catalyzed direct arylation of benzene, radical scavengers, such as TEMPO and 1,1-diphenylethylene (diyldibenzene), were employed in the reaction (Scheme 2). Authentically, the reactions were completely shut off, which could indicate that this transformation involved radical intermediates.

Moreover, experiments focused on the kinetic isotopic effect were also carried out. The K_H/K_D ratio was 1.29:1. This result suggested that C−H bond cleavage is not the rate-determining step (see Supporting Information).

Table 3. Direct Arylation of Benzene with Dihalobenzenes[a]



entry	4		product	yield(%)
1		X=I **4a**	**3j**	74
2		X=Br **4b**	**3j**	68
3		X=Cl **4c**	**3j**	71
4		X=I **4d**	 **5**	79
5		X=Br **4e**		60
6		X=Cl **4f**		32[b]
7		X=I **4g**	 **6**	21[c]
8		X=Br **4h**		30[d]
9		X=Cl **4i**		29[e]

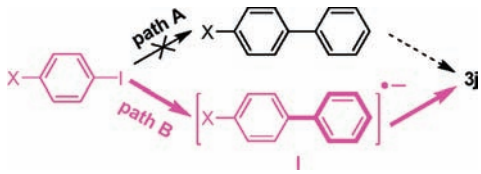
[a] Reaction conditions: 0.5 mmol of **4**, 3.0 mmol of KOBu^t, in 6 mL of benzene. [b] 35% 3-chlorobiphenyl was isolated. [c] 53% biphenyl was isolated. [d] 48% biphenyl was isolated. [e] 40% biphenyl was isolated.

When 1,4-diiodobenzene **4a** was employed as the substrate, the reaction generated 74% *bis*-arylated product **3j** and 8% monoary-

lated product **1j** (Table 3, entry 1). It is interesting that when 1-chloro-4-iodobenzene **4c** was subjected to the reaction conditions, it provided *bis*-arylation product **3j** in 71% isolated yield (Table 3, entry 3). 1-Bromo-4-iodobenzene **4b** could *bis*-arylate smoothly and generated the desired **3j** in 68% yield (Table 3, entry 2). The reactions of the *meta*-substituted chloro, bromo, and iodo-iodobenzene as the electrophiles (**4f**, **4e**, and **4d** in Table 3) were also investigated. The corresponding *bis*-arylated products were isolated under the standard conditions in 32%, 60%, and 79% yields, respectively (Table 3, entries 4−6). The reactions of the *ortho*-substituted **4g**, **4h**, and **4i** generated *bis*-arylated **6** in 21%, 30%, and 29% yields, as well as a significant reduction product biphenyl (53%, 48%, and 40% respectively) due to the possible sterical influence. It is worthy of note that no reactions were observed where aryl chlorides (without the iodo-group) were employed as the electrophiles, and less than 5% direct arylation with phenyl bromide was identified.

Bunnett et al. had investigated the "nucleophilic" replacement of two halogens in dihalobenzenes without the intermediacy of monosubstitution products under irradiation.[11] They proposed that the radical anion intermediacy is the type utilizing an intermediate **I** with higher reactivity.[11] Radical trapping experiments and the abnormal reactivities of dihalobenzenes in Table 3 induced us to propose that the DMEDA-catalyzed direct arylation of benzene also involved an aryl radical anion intermediate (Scheme 3). In fact, a radical anion could be generated from vicinal diamines (such as ethylenediamine, DMEDA, etc.) in the presence of KO^{t}Bu.[12] It could activate ArI to form the aryl radical anion intermediates.

Scheme 3. Speculated Intermediate of Reaction of Dihalobenzene with Benzene



The reaction profile of the direct arylation of benzene with **1a** indicated the existence of an inductive period (Figure 1A). Further monitoring of the product distribution within time intervals revealed that the yield of *bis*-arylated product **3j** increased with time, while the monoarylated product **1j** remained around 10% during the reaction period (Figure 1B). The reaction profile in Figure 1C clearly illustrated that the reactivity of **1j** is less than that of **4a**. A further competitive experiment with equal molar amounts of **4a** and **1j** in the presence of benzene was also carried out (Figure 1D). The consumption of **4a** is much faster than that of **1j**. The formation of **3j** was related to the consumption of **4a**.

The above reaction profiles in Figure 1 unambiguously ruled out path A but supported path B in Scheme 3. It also indicates that intermediate **I** has a higher reactivity than **1j** and **4a** (X = I).

According to the DFT calculations (see Supporting Information), the C−I bond distance of intermediate **I** is 0.300 nm, which is 0.085 nm longer than that of **1j** (0.215 nm) and 0.086 nm longer than that of **4a** (0.214 nm). These are consistent with the hypothesis in Scheme 3. The C−Cl bond of the 4-chlorobiphenyl radical anion was 0.266 nm, which is 0.090 nm longer than that of 4-chlorobiphenyl (0.176 nm). These calculation data could rationalize the "abnormal" reactivities of dihalobenzenes in Table 3.

In summary, we uncovered a conceptually different approach toward biaryl syntheses by using an organomolecule (DMEDA) as a catalyst to promote the direct C−H arylation of unactivated

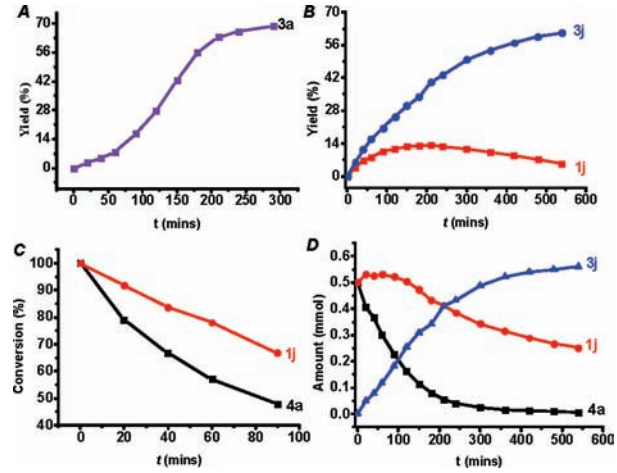


Figure 1. (A) Reaction profile of the direct arylation of benzene with **1a**. (B) Distribution of *bis*-arylated **3j** and monoarylated **1j** with reaction time during the reaction of **4a** with benzene. (C) The reaction profiles (amount of **1j** or **4a** and reaction time) of the direct arylations of benzene with **4a** and **1j**, respectively. (D) The reaction profiles of the competitive reaction of equal molar **1j** and **4a** with benzene (for more details, see Supporting Information).

benzene in the presence of potassium *tert*-butoxide. The arylation of unactivated benzene with aryl iodides, or aryl bromides and even chlorides under the assistance of an iodo-group, could simply take place at 80 °C. The new methodology presumably involves an aryl radical anion as an intermediate. This finding offers an excellent option toward establishing a new horizon for direct C−H/cross-coupling reactions. The detailed kinetic and mechanistic studies are currently undergoing in our laboratory, and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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