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C–C Cleavage

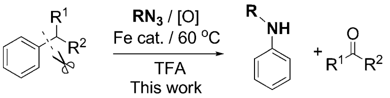
$FeCl_2$-Promoted Cleavage of the Unactivated C–C Bond of Alkylarenes and Polystyrene: Direct Synthesis of Arylamines[**]

Chong Qin, Tao Shen, Conghui Tang, and Ning Jiao[*]

Selective metal-promoted C–C bond cleavage under mild reaction conditions presents one of the most challenging and attractive processes[1] because: 1) it enables the straightforward utilization of hydrocarbons in organic synthesis; 2) polymers, which are not biodegradable and produce a large amount of environmental pollution, may be degraded and reused by chemical C–C bond cleavage; 3) the liquefaction of biomass and coal through selective C–C bond cleavage may alleviate the energy crisis we are facing. As a result of the inertness of C–C bonds and the competition of C–H activation,[2] examples of C–C bond activation are much less common, with the exception of strained C–C bonds,[3] functionalized substrates having functional fragments as the leaving group such as carbonyl,[4] cyano,[5] and carboxylic acids.[6] However, the metal-catalyzed cleavage of unactivated C–C bonds under mild reaction conditions is still undeveloped. Therefore, the discovery of a novel process for selective C–C bond cleavage is undoubtedly attractive and formidably challenging.

Arylamines are common and fundamental industrial feedstocks. For instance, N-alkylanilines are widely used in the synthesis of important dyes, polymers, herbicides, insecticides, pharmaceuticals, plant-growth agents, and antiknock agents for gasoline engines.[7] On behalf of green and sustainable chemistry, the direct intermolecular amination strategy of simple arenes through C–H or C–C bond cleavage has attracted considerable attention, but is very challenging[8–10] and has not yet been realized. In the case of direct C–H amination of non-preactivated arenes, the control of chemoselectivity, prior oxidation of the parent nucleophilic amines, and secondary amination when using primary amines as a coupling partner are the challenging issues. Alternatively, a selective C–C bond cleavage strategy with a suitable nitrogen source may provide a novel approach for diverse arylamine derivatives.

Herein, we describe the discovery of a $FeCl_2$-catalyzed cleavage of unactivated C–C bonds for the straightforward synthesis of various arylamines [Eq. (1)]. This transformation has a remarkably broad substrate scope. A variety of diarylmethanes and alkylarenes are compatible with this protocol. Significantly, the readily available and industrial feedstock cumene, which is usually used for industrial preparation of phenol (O_2, sulphuric acid, 180 °C),[11] could be converted into the corresponding economically important N-alkylanilines and propanone. Notably, even a mixture of alkylarenes could be employed as substrates, thus validating the potential application for industrial crude materials. Furthermore, the diversity of the aminating agent enables the wider application of the industrial chemical cumene. Significantly, polystyrene, which is an important commodity thermoplastic in our daily life does not biodegrade for hundreds of years and is resistant to photolysis, thus generating huge amounts of environmental pollution,[12] could be degraded by this strategy. This may provide a novel concept for polystyrene degradation and reuse. Furthermore, an inexpensive and environmentally benign iron salt is employed as the catalyst, thus making this strategy green and practical.



(1)

To test the possibility of the proposed direct arylamine synthesis through C–C bond cleavage, we chose as a model the reaction of diphenylmethane (**1a**) with 1-azidononane (**2a**; alkyl azides with long chain are stable; Table 1). The initial screening indicated that a Brønsted acid additive could assist the C–C bond cleavage,[13] thus generating the desired nitrogenation product *N*-nonylaniline (**3a**; 11–39 %) by employing $FeCl_2$ as catalyst in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant in 1,2-dichloroethane (DCE; Table 1, entries 2–4; for additional screening results see Table S1 in the supporting Information). When trifluoroacetic acid (TFA) was used as the solvent, **3a** was obtained in 75 % yield upon isolation, with the generation 72 % (GC) benzaldehyde (**4a**; entry 6). Nickel, cobalt, manganese, and copper salts also catalyze this transformation, but with low yields (entries 7–11). Although the reaction under metal-free conditions worked, with an average yield (40 %, entry 12), the iron catalyst is essential in for relatively unactivated alkylarene substrates. Other oxidants such as ceric ammonium nitrate (CAN) and $PhI(OAc)_2$ gave low yields (entries 13 and 14).

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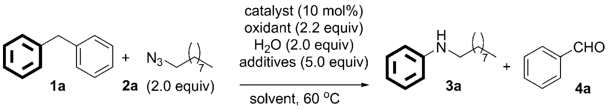
Table 1: Optimization for the reaction of **1a** with **2a**.[a]



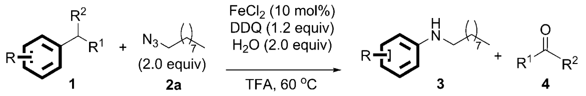
Entry	Solvent	Additives	Catalyst	Oxidant	**3a** Yield [%]
1	DCE	–	$FeCl_2$	DDQ	n.d.
2	DCE	TsOH	$FeCl_2$	DDQ	11
3	DCE	TfOH	$FeCl_2$	DDQ	24
4	DCE	benzoic acid	$FeCl_2$	DDQ	15
5	DCE	TFA	$FeCl_2$	DDQ	(39)
6[b]	**TFA**	**–**	**$FeCl_2$**	**DDQ**	**75 (72)**
7	TFA	–	$CoCl_2$	DDQ	65
8	TFA	–	$NiCl_2$	DDQ	57
9	TFA	–	$Mn(OAc)_3$	DDQ	47
10	TFA	–	CuI	DDQ	53
11	TFA	–	$FeCl_3$	DDQ	63
12	TFA	–	–	DDQ	40
13	TFA	–	$FeCl_2$	CAN	32
14	TFA	–	$FeCl_2$	$PhI(OAc)_2$	47

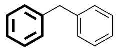
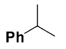
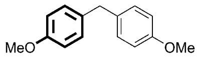
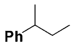
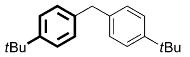
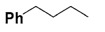
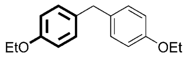
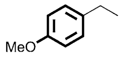
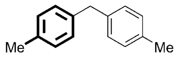
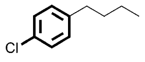
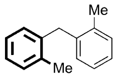
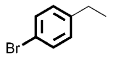
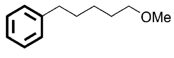
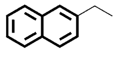
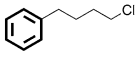
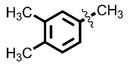
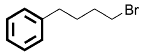
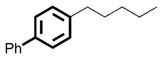
[a] Reaction conditions: **1a** (0.5 mmol) and **2a** (1.0 mmol), catalyst (0.05 mmol), oxidant (1.1 mmol), H_2O (1.0 mmol), solvent (2 mL), 60 °C. Yields determined by gas chromatography using *n*-octadecane as an internal standard. The yield of the isolated product is given within the parentheses. [b] 72% GC yield of benzaldehyde was detected. n.d. = not determined, Ts = 4-toluenesulfonyl, Tf = trifluoromethanesulfonyl.

Under the optimized reaction conditions, the substrate scope of benzyl hydrocarbons was investigated (Table 2). A variety of diarylmethanes were found to be compatible with this protocol (entries 2–6). Substituted N-alkylanilines and benzaldehydes were simultaneously generated through the cleavage of benzyl C–C bonds of diarylmethanes. The nitrogenation process can also be extended to inert benzyl alkanes, thus producing the desired N-alkylaniline in moderate to good yields (entries 7–18). Aryl-derived N-alkylanilines were accessed through the iron-catalyzed unactivated C–C bond cleavage of the corresponding alkylbenzenes (entries 13–18). The tolerance for halogens on the aromatic ring in this transformation (**3g** and **3h**) offers an opportunity for subsequent cross-coupling, thereby facilitating expedient synthesis of complex aniline molecules. The alkyl naphthalene **1p** performed more efficiently, even in the mixed solvent DCE/TFA (5:1), and led to *N*-nonylnaphthalen-2-amine (**3i**) in 93% yield (entry 16). It is noteworthy that the regioselectivity is very high in the case of 1,2,4-trimethylbenzene (**1q**) because 3,4-dimethyl-*N*-nonylaniline (**3j**), as determined by ^1H-^1H nuclear overhauser enhancement (NOE) experiments, was the sole product, possibly because of a steric effect (entry 17). To investigate the effect of electronic factors in regioselectivity, the unsymmetrical diarylmethane substrate 1-benzyl-4-methoxybenzene (**1t**) was employed, and the two anilines, **3b** and **3a**, were obtained in 45% and 21% yields, respectively [Eq. (2)]. This result indicates that electron-rich arenes preferentially migrate to the nitrogen atom in the rearrangement process.

 (2)

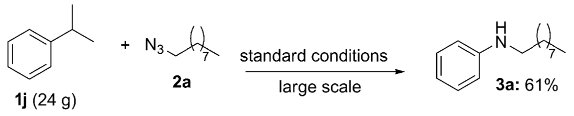
Table 2: The reaction of various benzyl hydrocarbons **1** to aniline **3**.[a]



Entry	Substrate		Product	Yield [%]	Entry	Substrate		Product	Yield [%]
1		**1a**	**3a** **4a**	75 (72)[b]	10		**1j**	**3a**	70
2		**1b**	**3b** **4b**	74 68	11		**1k**	**3a**	65
3		**1c**	**3c** **4c**	94 85	12		**1l**	**3a**	65
4		**1d**	**3d** **4d**	69 62	13		**1m**	**3b**	43
5		**1e**	**3e** **4e**	63 43	14		**1n**	**3g**	35
6		**1f**	**3f** **4f**	53 (51)[b]	15		**1o**	**3h**	41
7		**1g**	**3a**	62	16		**1p**	**3i**	93
8		**1h**	**3a**	66	17		**1q**	**3j**	35
9		**1i**	**3a**	76	18		**1r**	**3k**	71

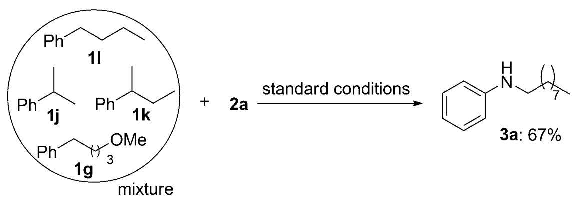
[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $FeCl_2$ (0.05 mmol), H_2O (1.0 mmol), DDQ (1.1 mmol) in TFA (2 mL) at 60 °C. Yields of isolated products. [b] Numbers in parentheses are yields as determined by GC. [c] Using DCE and TFA (10:1, 2 mL) as the solvent.

Importantly, by using common the industrial chemical cumene (**1j**) as the substrate *N*-nonylaniline (**3a**) could be obtained in 70% yield under these reaction conditions (Table 2, entry 10), and may provide an alternative approach to various N-alkylanilines just by changing the alkyl azide. To our delight, a large-scale reaction (24 g) proceeded well with similar efficiency (61%) by distillation and with the recovery of the TFA solvent (93%), which enhances the potential application in organic synthesis [Eq. (3)].



(3)

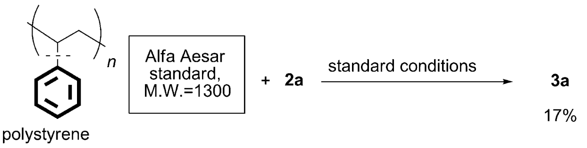
Furthermore, the mixture of alkyl benzenes **1l**,**j**,**k**,**g** under these reaction conditions produced **3a** in 67% yield [Eq. (4)], which demonstrates the potential for applying this oxidative cleavage of unactivated C–C bonds to the conversion of a crude mixture of benzyl hydrocarbons from the oil and coal industry into a single N-alkylaniline product. Moreover, the present strategy was also applicable to ring-opening reactions. The doubly functionalized product 2-(2-(propylamino)phenethyl)benzaldehyde (**3l**) can be easily obtained from dibenzosuberane (**1s**) in excellent yield (92%) by this direct oxidative C–C cleavage [Eq. (5)].



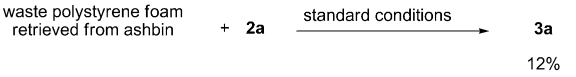
(4)

(5)

Polystyrene is an important commodity thermoplastic in our daily life and occupies about 20–22% of the total market based on worldwide consumption.[12] However, like other polymers, polystyrene degrades very slowly (more than 500 years for a single cup), and therefore generates large amounts of waste which accumulates in the environment. The waste polystyrene has been considered a serious environmental problem by the EPA (Environmental Protection Agency). When considering it an aromatic hydrocarbon, we envisioned that our selective C–C bond cleavage could be realized. Significantly, the desired *N*-nonylaniline (**3a**) was obtained in 17% yield when polystyrene (purchased from Alfa Aesar) was used as the substrate [Eq. (6)]. Moreover, the waste polystyrene foam performed well, giving **3a** in 12% yield [Eq. (7)]. This may provide a novel concept for polystyrene degradation and reuse.



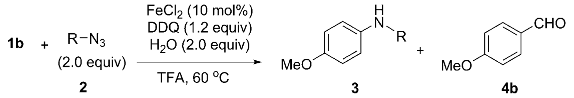
(6)

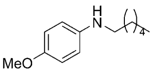
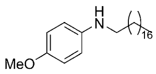
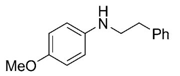
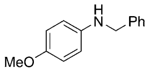
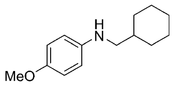
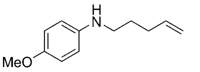
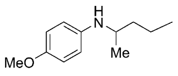
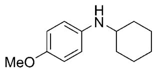
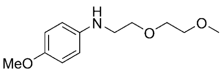


(7)

Moreover, the nature of the alkyl azides used in the reaction can be varied, therefore extending the utility of this transformation (Table 3). The length of the alkyl chain did not affect the efficiencies (**3m**,**n**). In addition, secondary azides remained intact in the reaction (**3s**,**t**). Alkyl azides having functional groups such as phenyl, alkenyl, and ethylene glycol units on the alkyl chain were also compatible (**3o**,**p**,**r**,**u**). Particularly noteworthy is that the alkyl azides, acting as aminating reagents in this transformation, can be rapidly obtained from the corresponding alkyl halides by reaction with NaN_3 without the traditionally redundant work-up involving distillation or chromatography (see the Supporting Information).

Table 3: Scope of organic azide **2** in this transformation.[a]



 **3m** 78% **4b** 74%	 **3n** 69% **4b** 66%	 **3o** 71% **4b** 69%
 **3p** 65% **4b** 51%	 **3q** 64% **4b** 53%	 **3r** 93% **4b** 87%
 **3s** 75% **4b** 67%	 **3t** 46% **4b** 44%	 **3u** 67% **4b** 62%

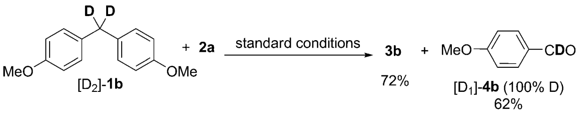
[a] Reaction conditions: **1b** (0.5 mmol) and **2** (1.0 mmol), $FeCl_2$ (0.05 mmol), H_2O (1.0 mmol), DDQ (1.1 mmol) in TFA (2 mL) at 60°C. Yields of the isolated products.

The mechanism and possible key intermediates have been investigated. One possible pathway starts with the nitrene, generated from the azide, inserting into the benzyl C–H bond. However, no benzylamine was detected in the reaction of **1b** under similar reaction conditions in the absence of DDQ (see the Supporting Information). Although a trace amount of benzophenone can be observed as a by-product in some cases, 4,4′-dimethoxybenzophenone (**5**) cannot be converted into **3b** and **4b** under standard reaction conditions [Eq. (8)], thus

5

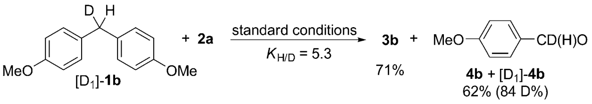
(8)

suggesting that the reaction does not undergo oxidation of diphenylmethane to benzophenone. Furthermore, the deuterated substrate [D_2]-**1b** was subjected to the reaction and produced the deuterated product 4-methoxybenzaldehyde ([D_1]-**4b**) in 62% yield [Eq. (9)], thus possibly excluding the pathway involving the initial oxidation to a ketone or the

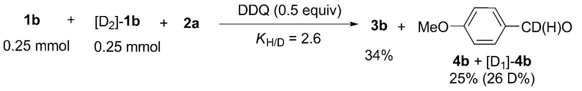


(9)

formation of an imine intermediate through the nitrene before the aryl shift. Furthermore, the intra- and intermolecular kinetic isotopic effects (k_H/k_D) were 5.3 and 2.6, respectively [Eq. (10) and (11)].[14]

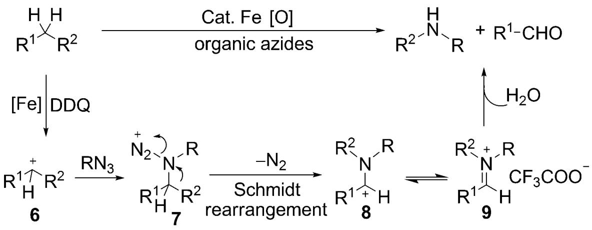


(10)



(11)

Although we cannot be certain of the exact mechanism of this C–C bond cleavage/ammination process, we propose an iron-assisted oxidation[15] of the substrate to cation **6** (Scheme 1), which undergoes attack by nucleophilic organic azides[16] to generate the intermediate **7**. The subsequent Schmidt-type rearrangement[17] process involves release of nitrogen and migration of the *trans* aryl group R^2 from the carbon to nitrogen atom, thus generating the intermediate **8**. Subsequent isomerization of the cation **8** leads to an iminium cation, which may exist as the iminium trifluoroacetic acid salt **9** in the reaction mixture. Finally, N-alkylanilines and benzaldehydes are generated by hydrolysis of **9**.



Scheme 1. Proposed mechanism of the iron-catalyzed nitrogenation of unactivated alkylarenes.

The application of the selective C–C bond cleavage strategy in organic synthesis presents an attractive and challenging goal. From the results of the present nitrogenation reaction and the proposed mechanism, it should be possible to develop some novel chemical transformations through C–C bond cleavage. Versatile substrates including industrially common cumene and aminating partners for this method may enable the potential applications for the synthesis of N-alkylarylamines. With the selective cleavage of unactivated C_{sp^2}–C_{sp^3} bonds, the method may provide a strategy for degradation of polystyrene under mild reaction conditions, and therefore prove important for laboratory and industrial purposes. Additional studies to better understand the reaction mechanism and discover synthetic applications are ongoing in our group.

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