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An Unusual Peroxide-Mediated Amination of Cycloalkanes with Nitroarenes

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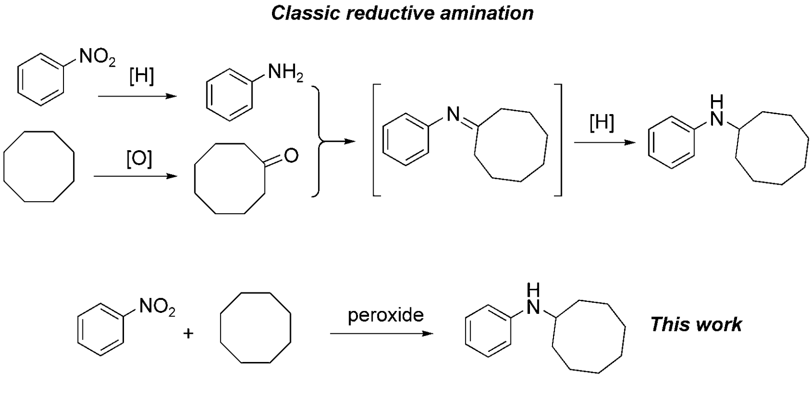
Abstract: A direct amination of simple cycloalkanes with nitroarenes mediated by peroxides has been discovered. Various secondary arylamines were obtained efficiently from cycloalkanes. The reaction tolerates a wide range of functionalities as well as aqueous conditions. No metal was required for this novel amination reaction.

Keywords: amination; cycloalkanes; nitroarenes; peroxides

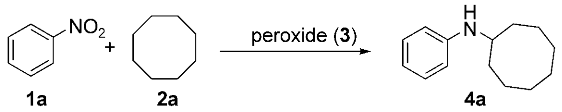
Functionalization of inert alkanes to more valuable products (e.g., carboxylic acids, alcohols, ketones) has attracted much attention.[1] Although the selective and practical functionalization of alkanes is still challenging, great progress has been achieved in the selective cleavage and functionalization of C–H bonds of alkanes.[2,3] Secondary amines (especially aromatic secondary amines) are important motifs of dyes, pharmaceuticals and agrochemicals.[4] The reductive amination of aldehydes and ketones is one of the most useful methods for synthesizing secondary amines, and pre-functionalization of alkanes and reduction of nitro compounds are necessary (Scheme 1).[5] Direct amination of simple alkanes is still rare.[6] In 1960, Jackson and Waters observed that the nitro group in nitrobenzene could be reduced to a hydroxylamine in the presence of *tert*-butyl peroxide.[7] This interesting reduction of nitrobenzene by peroxide did not attract much attention due to the substrate limitation and extremely low yield (6.4%). Recently, we developed a series of methods to couple cycloalkanes with other C–H bonds to generate new C–C bonds mediated by peroxides.[8] We also found that cyclooctyl radicals could add to imines, similar to a Grignard reagent.[9] On the other hand, a Grignard reagent has been shown to add to the nitro group.[10] We thus postulated that it might be possible to form secondary amines in one step by reacting the nitro group with cycloalkanes in the presence of peroxide (Scheme 1). Herein, we report *an efficient and unprecedented selective arylamination* of simple cycloalkanes with nitroarenes mediated by peroxide in the absence of a metal catalyst to give synthetically useful secondary aromatic amines.

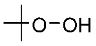
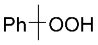
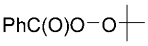
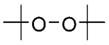
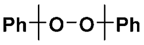
To begin our study, the commercially available and inexpensive nitrobenzene (**1a**) was used as a model



Scheme 1. Preparation of *N*-cyclooctylbenzenamine.

Table 1. Optimization of the reaction conditions.[a]



Entry	Peroxide (equiv.)			T [°C]	Yield [%][b]
1	--			137	0
2		(**3a**)	(2.0)	137	12
3		(**3b**)	(2.0)	137	22
4		(**3c**)	(2.0)	137	59
5		(**3d**)	(2.0)	137	65
6		(**3e**)	(2.0)	**137**	**84**
7	(**3e**)		(2.0)	120	42
8	(**3e**)		(1.0)	137	44
9[c]	(**3e**)		(2.0)	137	80
10[d]	(**3e**)		(2.0)	137	62
11[e]	(**3e**)		(2.0)	137	57
12[f]	(**3e**)		(2.0)	137	82

[a] Compound **1a** (24.6 mg, 0.2 mmol), cyclooctane (0.5 mL, 3.7 mmol), 16 h in air unless otherwise noted.

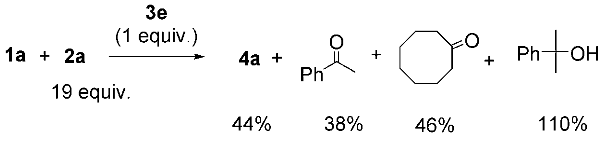
[b] Yields determined by using NMR methods in which 1,2-dichloroethane was the internal standard.

[c] Under nitrogen.

[d] Under oxygen.

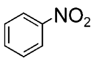
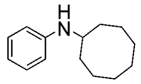
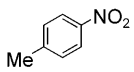
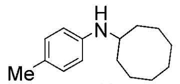
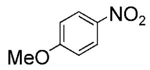
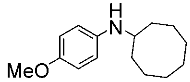
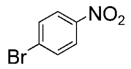
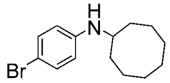
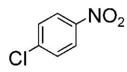
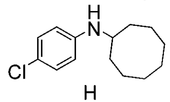
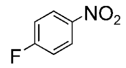
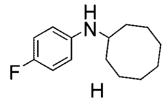
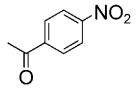
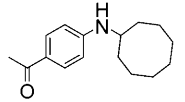
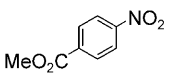
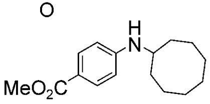
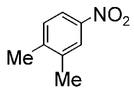
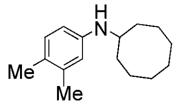
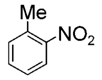
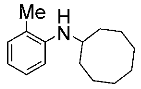
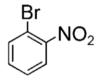
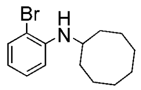
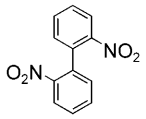
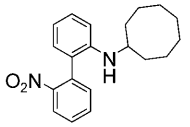
[e] Cyclooctane was reduced to 5 equiv. (1.0 mmol).

[f] Water (100 μL, 5.5 mmol) was added.



Scheme 2. ^{1}H NMR study of the reaction.

Table 2. Reactions of nitroarenes with cyclooctane.[a]

Entry	Nitroarene		Product		Yield [%][b]
1		**1a**		**4a**	63 (60)[c]
2		**1b**		**4b**	80
3		**1c**		**4c**	62
4		**1d**		**4d**	80
5		**1e**		**4e**	79
6		**1f**		**4f**	75
7		**1g**		**4g**	47
8		**1h**		**4h**	51
9		**1i**		**4i**	73
10		**1j**		**4j**	81
11		**1k**		**4k**	35
12		**1l**		**4l**	43

[a] *Conditions:* **1** (0.2 mmol), **2a** (3.7 mmol, 0.5 mL), **3e** (0.4 mmol), 135–139 °C, 16 h, under air.

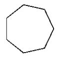
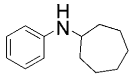
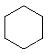
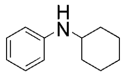
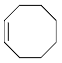
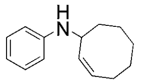
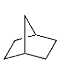
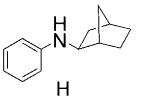
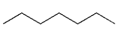
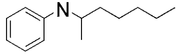
[b] Isolated yield.

[c] Yield in parentheses was carried out at a 2 mmol scale.

substrate. When nitrobenzene was reacted with cyclooctane (**2a**) in the absence of peroxide, no desired product was formed as determined by GC-MS and ^{1}H NMR methods (Table 1, entry 1). Subsequently, various peroxides were investigated for this reaction under an atmosphere of air (entries 2–6). When *tert*-butyl hydroperoxide (**3a**) was used, the desired product *N*-phenylcyclooctanamine (**4a**) was formed in 12% yield. Other peroxides showed higher efficiency in mediating this reaction. The best yield was obtained by using dicumyl peroxide (**3e**) as a mediator (entry 6). No alkylation was observed at the position *ortho* to the nitro group. Decreasing the reaction temperature or the amount of the peroxide decreased the product yield (entries 7 and 8). A lower yield was obtained when the reaction was carried out in oxygen (entry 10). A moderate yield was obtained by reducing the amount of cyclooctane to 5 equiv. (entry 11). Furthermore, an excellent yield was also achieved in the presence of water (entry 12).

With the optimized conditions in hand, the scope of the reaction with respect to nitrobenzene derivatives and alkanes was investigated (Table 2 and Table 3). In general, the dicumyl peroxide-mediated reduction and amination occurs smoothly to provide the desired product in good to excellent yields. The substituent at different positions of the nitroarenes affects the reaction yield significantly. The reaction showed good functional group tolerance: nitroarenes bearing an ester group or acetyl group at the *para*-position react-

Table 3. Reaction of nitrobenzene (**1a**) with alkanes (**2**).[a]

Entry	Alkanes		Product		Yield [%][b]
1		**2b**		**4m**	61
2		**2c**		**4n**	30
3		**2d**		**4o**	71
4		**2e**		**4p**	58
5[c]		**2f**		**4q**	26

[a] *Conditions:* **1a** (0.2 mmol), **2** (3.7 mmol), **3e** (0.4 mmol), 135–139 °C, 24 h, under air.

[b] Isolated yield.

[c] Other isomers also formed; total yield (^{1}H NMR) is about 50%.

ed with cyclooctane to give the corresponding products in moderate yields (Table 2, entries 7 and 8). The reaction also tolerates the presence of halogens (Table 2, entries 4–6 and 11). Other cycloalkanes such as cycloheptane, norbornane also reacted smoothly with nitrobenzene to give the desired products in good yields (Table 3, entries 1 and 4). Cyclohexane reacted with nitrobenzene and gave the desired product in only 30% yield (50% NMR yield) due to its low boiling point (*note:* to ensure a higher temperature, the tube was wrapped with aluminum foil) (entry 2). Besides cycloalkanes, the amination reaction also proceeded smoothly with cyclooctene to give the allylic amination product in good yield and selectivity (Table 3, entry 3). The reaction of linear heptane and nitrobenzene gave **4q** as the major product (Table 3, entry 5) together with other regioisomers.[11]

The reaction mechanism is not clear at this moment. To get more information, nitrobenzene was reacted with cyclooctane in the presence of 1 equiv. of dicumyl peroxide and monitored by ^{1}H NMR directly, which showed that the desired product was formed in 44% yield together with acetophenone, cyclooctonone and 2-phenylpropan-2-ol in 38%, 46% and 110% yields, respectively (Scheme 2). The results suggest mechanistic similarity to the Grignard addition to nitrobenzene.[10] It was also found that more than 95% of nitrobenzene remained unchanged when the reaction was carried out in the absence of cyclooctane, which demonstrated the critical role of cycloalkane in this reaction.

In summary, we have developed an unprecedented direct arylamination of cycloalkanes with nitroarenes mediated by peroxide. Secondary aromatic amines were formed selectively in the absence of a transition metal catalyst. Although commonly used as radical initiator and oxidants, *peroxides act as nitro group reducing reagents* in this novel amination reaction. The study opens a new avenue for functionalization of simple cycloalkanes. Further investigations including the scope and mechanism of this reaction are in progress in our laboratory.

Experimental Section

Typical Experimental Procedure (4a)

In a 10-mL microwave tube, nitrobenzene (**1a**; 24.7 mg, 0.2 mmol), dicumyl peroxide (**3e**; 108 mg, 0.4 mmol) and cyclooctane (**2a**; 0.5 mL, 3.7 mmol) were added under atmospheric air. Then the tube was sealed with a Teflon-lined cap and the resulting solution was heated in a 135–139 °C oil bath with vigorous stirring for 16 h. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by flash column chromatography on silica gel (hexane to hexane: ethyl acetate = 99: 1) to provide **4a** (CAS: 13310–25–3) as a yellow oil; yield: 25.7 mg (63%). A more pure product for analysis could be obtained by column chromatography (dichloromethane/hexane = 10:90). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.22–7.14$ (dd, $J = 8.7, 7.4$ Hz, 2H), 6.72–6.65 (tt, $J = 7.2, 1.1$ Hz, 1H), 6.59–6.55 (dd, $J = 8.7, 1.0$ Hz, 2H), 3.58–3.51 (m, 2H), 1.97–1.89 (m, 2H), 1.80–1.56 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 147.2, 129.2, 116.6, 113.2, 52.2, 32.6, 27.0, 25.9, 24.0; MS (EI): *m/z* (%) = 203, 160, 132 (100), 119, 106, 93, 77. These values are consistent with those reported in the literature.[5a]

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