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Peroxide-mediated efficient addition of cycloalkanes to imines

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A novel direct addition of cycloalkanes to imines mediated by peroxide was developed. The reaction tolerates a wide range of functionalities as well as aqueous conditions.

The Grignard reaction[1] is an important reaction in organic chemistry and has made the synthesis of numerous important organic compounds possible.[2] In their most general form, an organometallic reagent such as an organomagnesium reagent reacts with C=O, C=N, and C≡N bonds to form nucleophilic addition products (route A, Fig. 1).[3–5] A fundamental drawback of Grignard-type reactions is the requirement for generating an organometallic reagent from organic halides and a stoichiometric amount of metal. On the other hand, we envisioned an alternative transformation to generate Grignard-type reaction products via the catalytic reaction of simple alkanes with C=O, C=N, and C≡N bonds without using an organometallic reagent, with the potential of high atom-economy[6] (route B, Fig. 1). Toward such a goal, herein we wish to report a highly efficient direct addition of cycloalkanes with imines mediated by peroxide to give Grignard-type addition products (Scheme 1).

The 1,2-addition of alkyl group to C=N bonds is a key method for the preparation of various amines.[7,8] To begin our study, we discovered that the reaction of (*E*)-*N*-benzylidenebenzenamine (**1a**) with cyclooctane (**2a**) at 135 °C under an atmosphere of air generated 13% of *N*-(cyclooctyl(phenyl)methyl)benzenamine (**4a**) (Table 1, entry 1). The yield was increased to 36% by using 2 equiv of *tert*-butyl hydroperoxide (**3a**) (Table 1, entry 2). Other peroxides such as **3b** and **3c** are also effective. When dicumyl peroxide (**3d**) was used, the desired product was obtained in 89% yield (Table 1, entry 5). The best yield was observed by using *tert*-butyl peroxide (**3e**) as a mediator (Table 1, entry 6). Decreasing the reaction temperature (Table 1, entry 7) or the amount of the peroxide (Table 1, entries 8 and 9) decreased the product yield. Most importantly, it is also possible to perform the reaction with only a catalytic amount of peroxide, albeit with a decreased yield (Table 1, entry 9). Furthermore, an excellent yield was also achieved in the presence of water (Table 1, entry 10).[9]

With the optimized conditions in hand, we examined the scope of the addition of various cycloalkanes to imines (Table 2). In

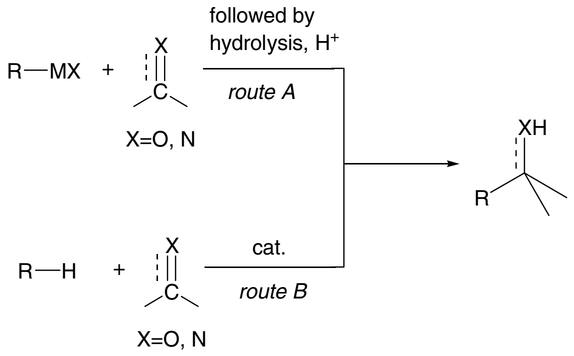
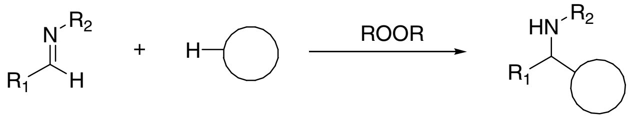


Figure 1. Classical Grignard-type reaction and Grignard-type reaction with alkane.



Scheme 1. Addition of cycloalkanes to imines.

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E-mail address: cj.li@mcgill.ca (C.-J. Li).

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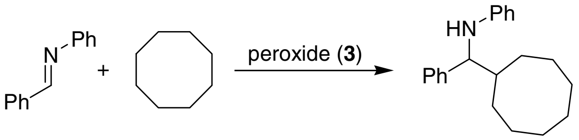
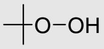
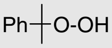
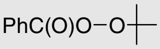
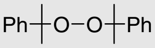
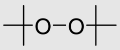
Table 1
Optimization of reaction conditions[a]



1a **2a** **4a**

Entry	Peroxide (equiv)	T (°C)	Yield[b] (%)
1	–	135	13
2	 (**3a**) (2.0)	135	36
3	 (**3b**) (2.0)	135	33
4	 (**3c**) (2.0)	135	42
5	 (**3d**) (2.0)	135	89
6	 (**3e**) (2.0)	135	96
7	(**3e**) (2.0)	120	50
8[c]	(**3e**) (1.0)	135	88
9[c]	(**3e**) (0.2)	135	47
10[d]	(**3e**) (2.0)	135	81

[a] Conditions: all reactions were carried out with **1a** (0.2 mmol) and **2a** (0.6 mL, 4.5 mmol) in 15 h under an atmosphere of air, unless otherwise noted.

[b] H NMR yields were determined by using 1,2-dichloroethane as an internal standard.

[c] Reaction time: 30 h.

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

general, the *tert*-butyl peroxide-mediated addition occurs smoothly to provide the desired Grignard-type reaction products in good to excellent yields. Various electron-withdrawing and electron-donating substituents at different positions of the *N*-aryl-arylimines did not affect the reaction significantly (Table 2, entries 2–15). The reaction showed a good regio-selectivity when a long chain substituted imine was used: only the imine–cycloalkane addition product was observed (Table 2, entry 4) and no reaction was observed due to the alkyl chain. The reaction also showed good functional group tolerance: an arylimine bearing an ester group (unlikely to survive under the classical Grignard-type reactions) at the *para*-position reacted with cyclooctane to give the corresponding product in 82% yield (Table 2, entry 8). It is noteworthy mentioning that the reaction also tolerates the presence of halogens (Table 2, entries 5–7, 9, and 12). Other cycloalkanes such as cycloheptane and cyclohexane also reacted smoothly with (*E*)-*N*-benzylidenebenzenamine to give the desired addition products in good yields (Table 2, entries 16–18). A decreased yield was observed when cyclopentane was used as a reagent due to its low boiling point. It should be noted that imines pre-synthesized or generated in situ from the corresponding aldehyde and aniline provided similar results.

A tentative mechanism to rationalize this reaction of cycloalkane with imine is illustrated in Scheme 2. When heated, the peroxide **3** decomposes to generate an alkoxide radical. The alkoxyl radical then abstracts a hydrogen from cycloalkane **2** to give a cycloalkyl radical together with an alcohol.[10] Addition of the cycloalkyl radical to imine **1** generates an addition product bearing a nitrogen radical,[11] which gives the desired product **4** by abstracting a hydrogen from another cycloalkane and regenerates the cycloalkane radical at the same time.

In summary, we have developed a novel direct addition of cycloalkanes to imines mediated by peroxide.[12] The study provides

Table 2
Addition of cycloalkanes to imines[a]

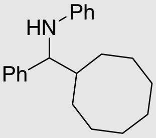
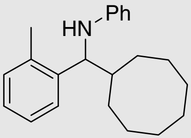
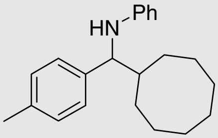
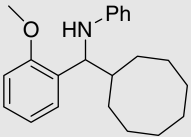
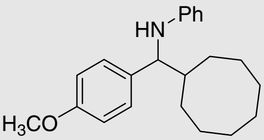
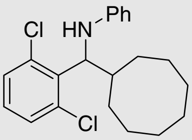
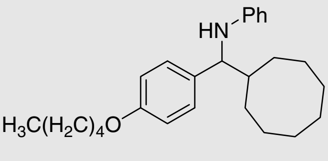
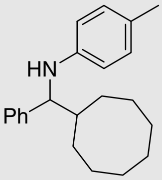
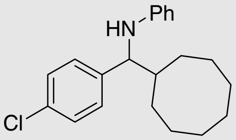
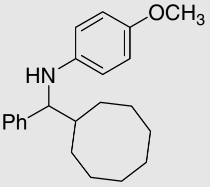
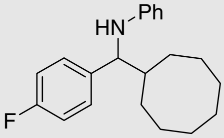
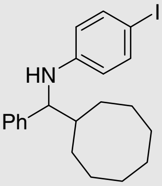
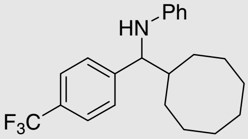
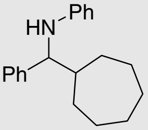
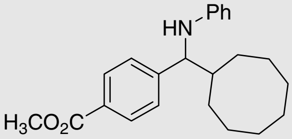
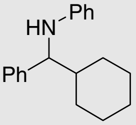
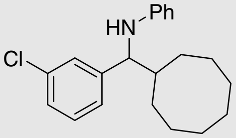
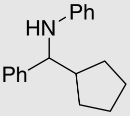
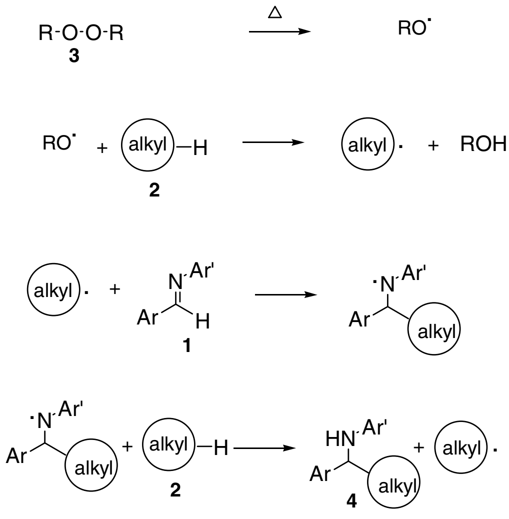
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **4a**	81	10	 **4j**	75
2	 **4b**	65	11	 **4k**	84
3	 **4c**	62	12	 **4l**	83
4	 **4d**	83	13	 **4m**	72

Table 2 (*continued*)

Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
5	 **4e**	68	14	 **4n**	53
6	 **4f**	80	15	 **4o**	58
7	 **4g**	71	16	 **4p**	71
8	 **4h**	82	17	 **4q**	60
9	 **4i**	70	18	 **4r**	37

[a] Conditions: al reactions were carried out with imine (0.2 mmol), *tert*-butyl peroxide (0.4 mmol), cycloalkane (4.5 mmol), 15 h in air at 135 °C.

[b] Isolated yields.



Scheme 2. Tentative mechanism for the addition of cycloalkanes to imines mediated by peroxides.

a new avenue for synthesizing Grignard-type imine addition products by using cycloalkanes rather than organometallic reagents. Further investigations including the scope, mechanism, a catalytic reaction, and asymmetric addition of this reaction are in progress in our laboratory.

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12. *Typical experimental procedures*: A reaction vessel was charged with **1** (0.2 mmol), peroxide **2** (0.4 mmol), and cycloalkane **3** (4.5 mmol). Then the reaction vessel was sealed and the resulting solution was stirred at 135 °C for 15 h. After cooling to room temperature, the volatiles were removed in vacuo and the residue was purified by column chromatography (silica gel, hexane/dichloromethane = 9:1) to give product **4**. All new compounds were characterized by means of ^{1}H NMR, ^{13}C NMR, MS (EI), and HRMS.