

# SiCl<sub>4</sub>-catalyzed/PR<sub>3</sub>-mediated β-C(sp<sup>3</sup>)-H functionalization of nitrones to α,β-unsaturated imines and aromatic heterocycles

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## ABSTRACT

A novel method of SiCl<sub>4</sub>-catalyzed/PR<sub>3</sub>-mediated β-C(sp<sup>3</sup>)-H functionalization of nitrones with aldehydes/ketones to α,β-unsaturated imines was developed. The synthesis of α,β-unsaturated imines mainly involves deoxygenation and aldol condensation, each proceeding under a cooperation effect between Lewis acid and Lewis base. In addition, both the acidity and hydrolytic stability of the weak SiCl<sub>4</sub> were supposed to be enhanced by coordination with phosphine oxide (R = Et) or phosphoric triamide (R = NMe<sub>2</sub>) that originated from deoxygenation of nitrones by PR<sub>3</sub>. In the case of 6-membered nitron, a [1,3]-hydride shift within the resulted α,β-unsaturated imines renders the aromatization leading to 3,5-dialkylpyridines.

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## 1. Introduction

Alicyclic amines with varied functionalization play privileged role as structural motifs of many bioactive materials and synthetic origins.<sup>1</sup> Different strategies are available for the construction of such structural motifs, yet direct C–H bond functionalization of proper amines has drawn unwavering attentions. While the functionalization at α-C(sp<sup>3</sup>) of alicyclic amines has been extensively explored,<sup>2</sup> reports on those of more challenging functionalization at β-C(sp<sup>3</sup>) were sporadic. Two approaches were primarily employed to construct various C–C bonds at β-C(sp<sup>3</sup>) so far. The first one involves transition metal-catalyzed *in-situ* formation of electrophilic iminium ions from tertiary/protected amines upon dehydrogenation in the presence/absence of oxidants (Scheme 1A).<sup>3</sup> The subsequent isomerization of the iminium species leads to the formation of nucleophilic enamines, which will undergo cross-coupling reactions with the corresponding electrophiles at β-C(sp<sup>3</sup>). The second one, denoted as redox-neutral method, operates

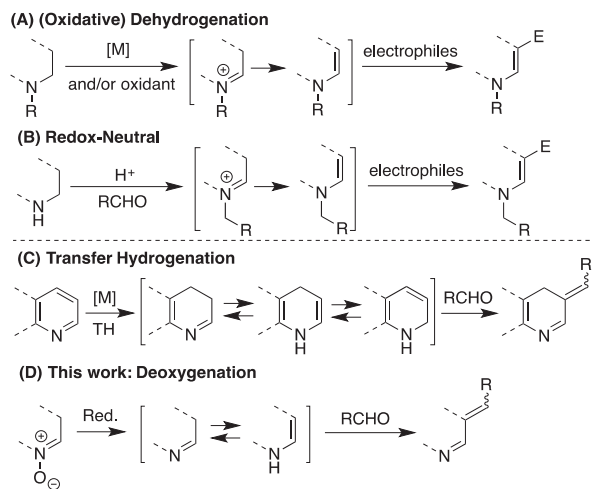
via intramolecular hydride transfer mechanism without the use of external oxidant (Scheme 1B).<sup>4</sup> Consequently, the generation of aromatic heterocyclics or unsaturated imines accompanied with β-functionalization from saturated cyclic amines and aldehydes was attained in an uncatalyzed fashion or was mediated by a carboxylic acid (>0.5 equiv.).<sup>4b</sup> It is to note that harsh conditions, such as high temperature and prolonged reaction time (without the aid of microwave), are usually required under this protocol.

The forementioned reactions on β-C(sp<sup>3</sup>)-H functionalization of alicyclic amines necessitate the transiency imine or its enamine tautomer function as nucleophile in the subsequent cross-coupling. Specifically, the direct aldol condensation of cyclic imines (in a trimer form) with aldehydes at the β-C(sp<sup>3</sup>) position was once reported by Tomoda,<sup>5</sup> which provided unsaturated imines with moderate yields (10–77%) with a prolonged reaction time (>43 h). These unstable nucleophilic species could also be obtained via reduction of inert chemical bonds. For instance, reduction of quinoline substrate gives rise to active intermediate which can

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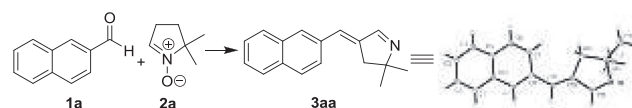
**Scheme 1.** Summary of  $\beta$ -C(sp<sup>3</sup>)-H Functionalization of Alicyclic Amines.

undergo intramolecular hydrogen transfer, thereby facilitating the direct reductive quinolyl  $\beta$ -C(sp<sup>3</sup>)-H alkylation with aldehydes (Scheme 1C).<sup>6</sup> By following the reduction strategy, alicyclic imines can also be provided from nitrones *via* deoxygenation, wherein halides,<sup>7</sup> hydrides,<sup>8</sup> heteroatom-based nucleophiles,<sup>9</sup> Lewis acids,<sup>10</sup> low-valent transition metals<sup>11</sup> were frequently utilized as the oxo-acceptor. Some of these examples were promoted by reactive transition metal complexes, but still lacking of efficiency.<sup>9d,e</sup> The deoxygenated nitrones promise a subsequent coupling with electrophiles, thereby affording alicyclic amines with  $\beta$ -C(sp<sup>3</sup>) functionalized (Scheme 1D). However, development of novel methodologies that operates under mild conditions still remains challenging, wherein the high reactivity of nitrones towards the upcoming electrophiles should be suppressed.<sup>12</sup> Herein, we report an example of SiCl<sub>4</sub>-catalyzed/PR<sub>3</sub>-mediated  $\beta$ -C(sp<sup>3</sup>)-H functionalization of cyclic nitrones. Upon reacting 5-membered cyclic nitrones with SiCl<sub>4</sub>/PR<sub>3</sub> followed by cross-coupling with aldehydes/ketones, alicyclic  $\alpha,\beta$ -unsaturated imines were obtained with mild to excellent yields. It was found both deoxygenation and aldol condensation performed under a cooperation effect between SiCl<sub>4</sub> and PR<sub>3</sub>. The process is also applicable for 6-membered nitronium which can be transformed into dialkyl-substituted aromatic heterocycles.

## 2. Results and discussion

Inspired by Yoo's<sup>11a</sup> and previous studies<sup>13</sup> on cobalt catalysis, we envisioned the introduction of a combination of Co(II) phosphine complex and metal powder might both promote the deoxygenation of nitrones *via* the *in-situ* generated low-valent cobalt and provide Lewis acidic environment for the subsequent aldol condensation with aldehyde substrates. The model reaction of 2-naphthaldehyde (**1a**) with 5,5-dimethyl-1-pyrroline-N-oxide (DMPO, **2a**) was thus carried out in the presence of CoCl<sub>2</sub> (10 mol%), 1,2-bis(diphenylphosphanyl)ethane (dppe) (15 mol%) and stoichiometric In (1.2 equiv.) at 120 °C for 24 h under argon (Table 1, entry 1). The expected  $\alpha,\beta$ -unsaturated imine **3aa** was obtained, but in a poor yield (12%). The isolated product was found to have the C=C double bond exclusively with *E*-configuration. The structural recognition of **3aa** was unambiguously confirmed by single crystal X-ray diffraction analysis besides NMR and ESI-MS experiments. Surprisingly, quantitative 1,2-bis(diphenylphosphino)ethane dioxides, which features a typical <sup>31</sup>P NMR signal at  $\delta$  33.2 ppm,<sup>14</sup> was

**Table 1**  
Condition Optimization for Generation of **3aa** from Reaction of **1a** with **2a**.<sup>a</sup>



Entry	LA	Base	Solvent	Conv. (%) <sup>b</sup>	Yield (%) <sup>b</sup>
1 <sup>c,d</sup>	CoCl <sub>2</sub>	dppe	toluene	59	12
2 <sup>d</sup>	CoCl <sub>2</sub>	dppe	toluene	39	13
3 <sup>d</sup>	—	dppe	toluene	36	5
4 <sup>e</sup>	CoCl <sub>2</sub>	dppe	toluene	45	25
5	InCl <sub>3</sub>	PEt <sub>3</sub>	toluene	28	15
6	InBr <sub>3</sub>	PEt <sub>3</sub>	toluene	32	32
7	In(OTf) <sub>3</sub>	PEt <sub>3</sub>	toluene	98	69
8	In(OTf) <sub>3</sub>	PPh <sub>3</sub>	toluene	54	9
9	In(OTf) <sub>3</sub>	PCy <sub>3</sub>	toluene	60	9
10	In(OTf) <sub>3</sub>	P( <i>t</i> -Bu) <sub>3</sub>	toluene	49	12
11	In(OTf) <sub>3</sub>	P(NMe <sub>2</sub> ) <sub>3</sub>	toluene	100	70
12 <sup>f</sup>	In(OTf) <sub>3</sub>	P(NMe <sub>2</sub> ) <sub>3</sub>	1,4-dioxane	100	85
13 <sup>g</sup>	SiCl <sub>4</sub>	P(NMe <sub>2</sub> ) <sub>3</sub>	DCE	98	92
14 <sup>g</sup>	SiCl <sub>4</sub>	PEt <sub>3</sub>	DCE	98	88

<sup>a</sup> Reaction conditions: **1a** (0.20 mmol), **2a** (2.0 equiv.), LA (10 mol%), base (1.2 equiv.), solvent (1 mL), 120 °C, 24 h, under Ar.

<sup>b</sup> Determined by <sup>1</sup>H NMR with CH<sub>2</sub>Br<sub>2</sub> as internal standard.

<sup>c</sup> In (1.2 equiv.).

<sup>d</sup> Base (15 mol%).

<sup>e</sup> Base (0.5 equiv.).

<sup>f</sup> **2a** (3.0 equiv.).

<sup>g</sup> 60 °C; LA: Lewis acid; DCE: dichloroethane.

simultaneously formed as a white solid precipitated in the reaction solution. Moreover, the yield of **3aa** is not affected without In (entry 2), but remarkably reduced in the absence of CoCl<sub>2</sub> reacting as a catalyst (entry 3). We can thus postulate that the basic dppe reacts as an oxo-acceptor rather than ligand for the low-valent cobalt complex generated *in-situ*. However, the reactivity was not significantly improved by increasing the amount of dppe to 0.5 molar equivalent, a theoretically stoichiometric amount (entry 4).

In an effort to address the problem of poor efficiency and to understand the reaction mechanism in more details, a variety of Lewis acids and PR<sub>3</sub> (trisubstituted phosphine or phosphorous triamide) reagents were investigated (Table 1). Reaction conditions varying the solvents and temperatures were examined (Tables 1 and S1). The best yield of **3aa** (92%) was obtained from the reaction of **1a** and **2a** (2.0 equiv.) at 60 °C for 24 h in the presence of weak acid SiCl<sub>4</sub> (10 mol%) and P(NMe<sub>2</sub>)<sub>3</sub> (1.2 equiv.) in dichloroethane (DCE, 1 mL) under argon (entry 13). The combination of active In(OTf)<sub>3</sub> and P(NMe<sub>2</sub>)<sub>3</sub> provides an alternative choice to give **3aa** in a satisfactory yield up to 85%, but only being effective when the loading of **2a** (3.0 equiv.) was increased and the reaction was conducted in polar 1,4-dioxane (1 mL) at 120 °C (entry 12). This may be attributed to the intrinsic instability of both **2a** as a nitronium and the corresponding imine intermediate upon deoxygenation as substantial decomposition occurred when the temperature was raised up to 120 °C. During the condition optimization, the variety of Lewis acids and the structure of PR<sub>3</sub> were found to strongly influence the reactivity (entries 7–11). As compared to triethylphosphine (PEt<sub>3</sub>), either less nucleophilic triphenyl (PPh<sub>3</sub>) or more steric hindered tricyclohexyl (PCy<sub>3</sub>) and tri-*tert*-butyl (P(*t*-Bu)<sub>3</sub>) phosphine led to reduced selectivity, whereas the more basic phosphorous triamide (P(NMe<sub>2</sub>)<sub>3</sub>) exhibited equally effective (entry 7 vs. 11 and entry 13 vs. 14).

We next examined the limit and scope of carbonyl substrates (**1**) under SiCl<sub>4</sub> catalysis (Scheme 2), wherein the yield of each product was determined after isolation. It was observed that electronic

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