

# Redox-Neutral $\alpha,\beta$ -Difunctionalization of Cyclic Amines\*\*

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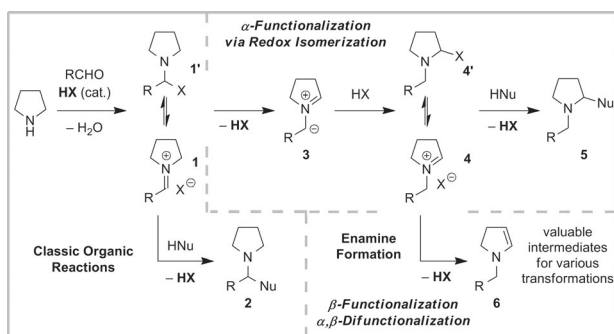
**Abstract:** In contrast to the continuously growing number of methods that allow for the efficient  $\alpha$ -functionalization of amines, few strategies exist that enable the direct functionalization of amines in the  $\beta$ -position. A general redox-neutral strategy is outlined for amine  $\beta$ -functionalization and  $\alpha,\beta$ -difunctionalization that utilizes enamines generated in situ. This concept is demonstrated in the context of preparing polycyclic *N,O*-acetals from simple 1-(aminomethyl)- $\beta$ -naphthols and 2-(aminomethyl)-phenols.

While oxidative approaches continue to dominate the vibrant field of amine  $\alpha$ -C–H bond functionalization,<sup>[1]</sup> redox-neutral methods continue to establish themselves as complementary strategies and viable alternatives.<sup>[2]</sup> Increasingly complex structures can be built efficiently from simple starting materials by replacing existing amine  $\alpha$ -C–H bonds without requiring pre-functionalization or the use of external oxidants or reductants. Whereas many redox-neutral amine  $\alpha$ -functionalizations involve hydride shifts or sigmatropic H-transfer steps,<sup>[3]</sup> we have developed an alternative approach that involves azomethine ylides as reactive intermediates (Scheme 1).<sup>[4–6]</sup> In stark contrast to amine  $\alpha$ -functionalization, methods that allow the direct  $\beta$ -functionalization of amines remain rare and typically require precious metal catalysts.<sup>[7–10]</sup> Herein we disclose a new strategy that enables the simulta-

neous  $\alpha,\beta$ -difunctionalization of amines via transient enamines.

Classic organic transformations, such as the Strecker and Mannich reactions, involve the addition of a nucleophile to an iminium ion **1** generated in situ to result in the formation of products of type **2** (Scheme 1). We have developed a strategy that averts the traditional reaction pathway by incorporation of an isomerization step, allowing for amine  $\alpha$ -functionalization and the generation of products with the general structure **5** (Scheme 1). These redox transformations are thought to involve the intermediacy of azomethine ylides **3** and endocyclic iminium ions **4**. Simple carboxylic acids have been found to catalyze a diverse set of amine  $\alpha$ -C–H bond functionalizations, including  $\alpha$ -cyanation,<sup>[4f]</sup>  $\alpha$ -phosphine oxide formation,<sup>[4j]</sup> and  $\alpha$ -arylation.<sup>[4k]</sup> Copper carboxylates have been found to catalyze the  $\alpha$ -alkynylation<sup>[4g]</sup> of amines. While considering new variants of these transformations, we recognized an opportunity to fundamentally alter the course of these reactions. Specifically, we reasoned that under appropriate conditions, intermediates **4/4'** may provide access to endocyclic enamines **6** by simple loss of HX. Enamines **6** are valuable precursors that could be utilized in a wide range of  $\beta$ -functionalization and  $\alpha,\beta$ -difunctionalization reactions.

In the course of attempting to expand the scope of our recently reported amine  $\alpha$ -arylation method,<sup>[4k]</sup> we discovered a unique opportunity to realize the first example of a redox-neutral amine  $\alpha,\beta$ -difunctionalization. Specifically, we were curious to learn whether it would be possible to isomerize compound **2a** to the regioisomeric product **5a**. An experiment in which a solution of compound **2a** was heated in toluene under microwave irradiation at 150 °C for 15 min in the presence of benzoic acid (20 mol %) did not result in any reaction, and starting material was recovered in essentially quantitative yield. However, upon increasing the temperature to 200 °C, the expected isomerization was indeed observed, giving **5a** and **2a** in an approximately 4:1 ratio, albeit in low yields [Eq. (1)]. Interestingly, the main product of this reaction was the unusual *N,O*-acetal **7a**, which was isolated

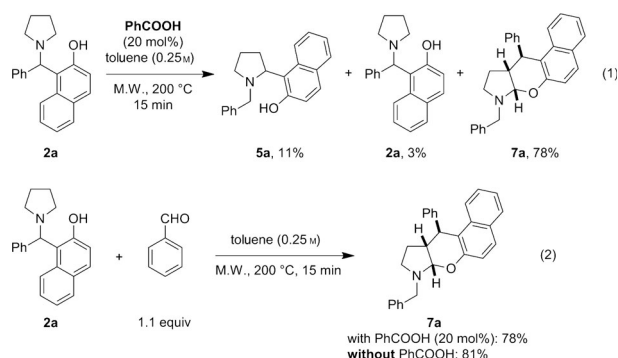


**Scheme 1.** Concepts for the redox-neutral amine  $\alpha$ -functionalization,  $\beta$ -functionalization, and  $\alpha,\beta$ -difunctionalization.

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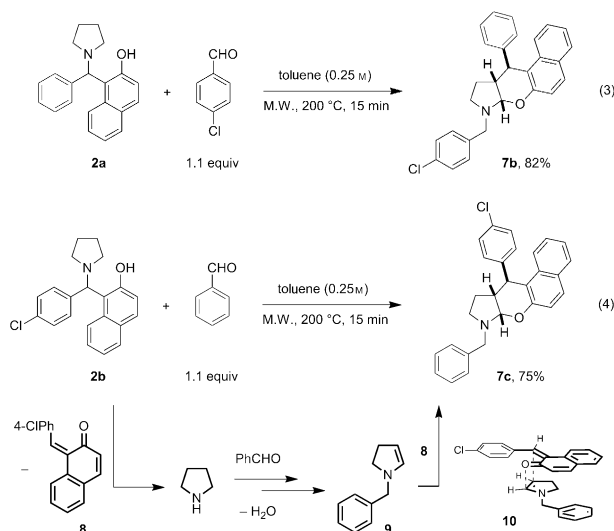
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as a single diastereomer in 78% yield<sup>[11]</sup> (relative configuration established by X-ray crystallography).<sup>[12–15]</sup>

The formation of product **7a** is consistent with the intermediacy of an endocyclic enamine, corresponding to proposed compound **6** (Scheme 1). Considering that the formation of **7a** from **2a** requires the incorporation of one unit of benzaldehyde (or a benzaldehyde equivalent), we performed the reactions outlined in Equation (2). Exposure of **2a** to a small excess of benzaldehyde (1.1 equiv) yielded **7a** in 78% yield for a reaction conducted in the presence of benzoic acid (20 mol %). Interestingly, the use of benzoic acid as a catalyst was not required. In fact, in the absence of any additive, **7a** was obtained in an improved yield of 81%.

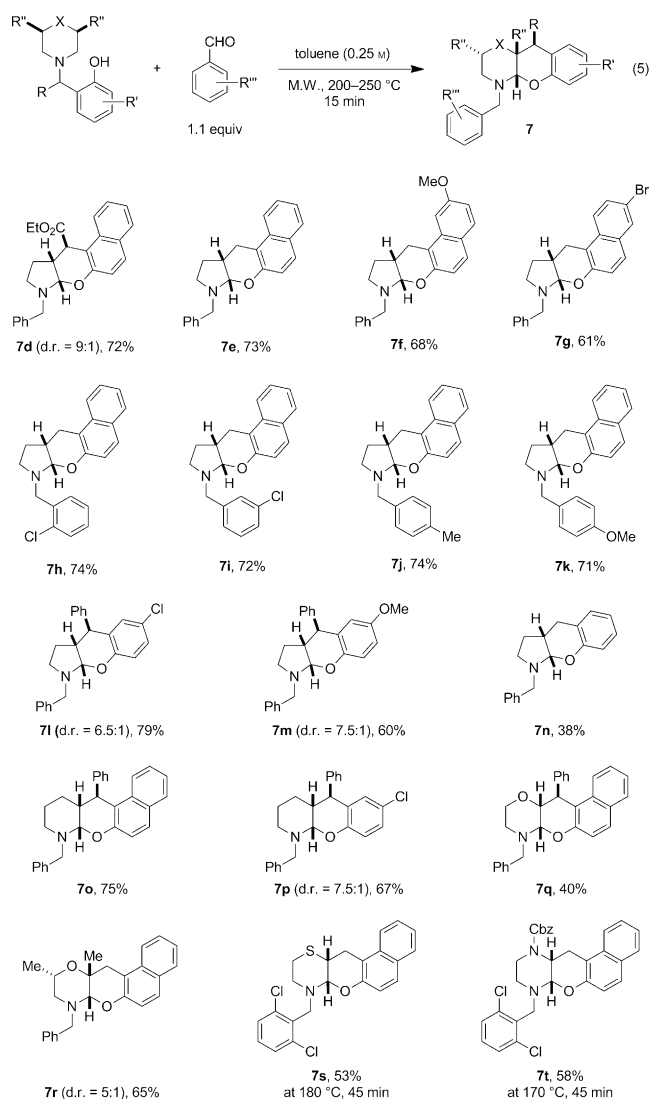
With the goal of establishing the course of this intriguing transformation, we performed the experiments shown in Scheme 2. When **2a** was allowed to react with 4-chlorobenzaldehyde, N,O-acetal **7b** was isolated as the only product in 82% yield [Eq. (3)]. The complementary reaction of **2b** and benzaldehyde afforded regioisomeric N,O-acetal **7c** in 75% yield [Eq. (4)].



**Scheme 2.** Experiments designed to determine the course of the annulation reaction and proposed mechanism.<sup>[18]</sup>

Based on the outcome of these experiments, we propose the reaction mechanism shown in Scheme 2. Upon heating, **2b** reversibly fragments into pyrrolidine and *ortho*-quinone methide **8**. Hydrogen-bonding between the nitrogen atom and the naphthol hydroxy group, as previously observed in X-ray crystal structures of related compounds,<sup>[16]</sup> is expected to facilitate this step. The released pyrrolidine is intercepted by benzaldehyde to eventually form enamine **9** via the sequence of events detailed in Scheme 1. The formation of N,O-acetal **7c** from **8** and **9** is consistent with a diastereoselective hetero-Diels–Alder reaction (for example, via **10**), although a stepwise pathway cannot be ruled out.

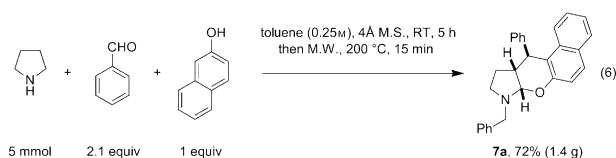
The scope of the N,O-acetal formation was then examined (Scheme 3). Gratifyingly, a number of 1-(aminomethyl)- $\beta$ -naphthols and 2-(aminomethyl)-phenols readily underwent the reaction with benzaldehyde and other aromatic alde-



**Scheme 3.** Substrate scope for the  $\alpha,\beta$ -difunctionalization/N,O-acetal formation. Reactions were performed on a 0.5 mmol scale; substrates containing pyrrolidine and piperidine/morpholine moieties were heated at 200 and 250 °C, respectively. Yields are combined yields of both diastereomers (if any); the major diastereomer is shown.

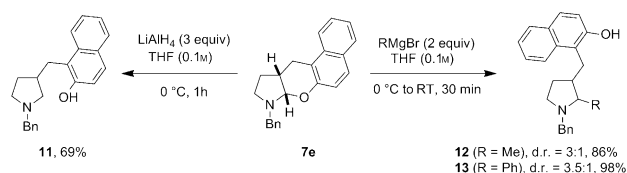
hydes. The expected products were obtained in moderate to good yields following a reaction time of just 15 min. Good to excellent diastereoselectivities were observed in most instances. Notably, substrates incorporating piperidine, morpholine, thiomorpholine, and piperazine moieties readily participated in the  $\alpha,\beta$ -difunctionalization. This is despite the fact that these heterocycles are typically challenging substrates for redox-neutral amine  $\alpha$ -C–H bond functionalization.

Given that 1-(aminomethyl)- $\beta$ -naphthols such as **2a** can be easily formed from the corresponding amine,  $\beta$ -naphthol, and aldehyde,<sup>[17]</sup> we were curious to learn whether the amine *N*-alkylation/ $\alpha,\beta$ -difunctionalization could be performed as a one-pot process simply by employing two equivalents of the aldehyde. To also evaluate the potential scalability of such a process, a test reaction was conducted on a 5 mmol scale [Eq. (6)]. Gratifyingly, treatment of a 1:2.1:1 mixture of



pyrrolidine, benzaldehyde, and  $\beta$ -naphthol with molecular sieves in toluene at room temperature for five hours, followed by exposure to microwave heating at 200 °C for 15 min, led to the isolation of **7a** in 72 % yield. Notably, the efficiency of this two-stage/one-pot approach is similar to that of the two-step procedure.

The product N,O-acetals can be transformed in a number of different ways (Scheme 4). For instance, treatment of compound **7e** with lithium aluminum hydride in tetrahydrofuran resulted in C–O bond cleavage and the formation of  $\beta$ -



**Scheme 4.** Product modification.

substituted *N*-benzyl pyrrolidine **11** in 69 % yield. In line with a previous report by Maulide et al. that nicely demonstrated the utility of *N*-aryl N,O-acetals in reactions with various nucleophiles,<sup>[3r]</sup> **7e** also readily engaged Grignard reagents to form the  $\alpha,\beta$ -disubstituted products **12** and **13** in excellent yields.

In conclusion, we have developed an unprecedented redox-neutral  $\alpha,\beta$ -difunctionalization cascade reaction of simple cyclic amines. Polycyclic N,O-acetals are now available in just two steps from cheap commercial materials via an annulation of transient enamines. We anticipate widespread application of the method described herein and the emergence of related processes.

## Experimental Section

General procedure for the redox-neutral  $\alpha,\beta$ -difunctionalization of amines: A 10 mL microwave reaction tube was charged with a 10  $\times$  8 mm SiC passive heating element, the 1-(aminomethyl)- $\beta$ -naphthol or 2-(aminomethyl)-phenol (0.5 mmol, 1 equiv), toluene (2 mL), and the aldehyde (0.55 mmol, 1.1 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi, for substrates containing a pyrrolidine moiety) or 250 °C (200 W, 150–200 psi, for substrates containing piperidine/morpholine moieties) for 15 min. After cooling with compressed air flow, the solution was transferred to a 50 mL round-bottom flask. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

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- [18] CCDC 963306 (**7a**), CCDC 963308 (**7c**), and CCDC 963307 (**7o**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).