Redox Reactions

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Intramolecular Redox-Triggered C–H Functionalization**

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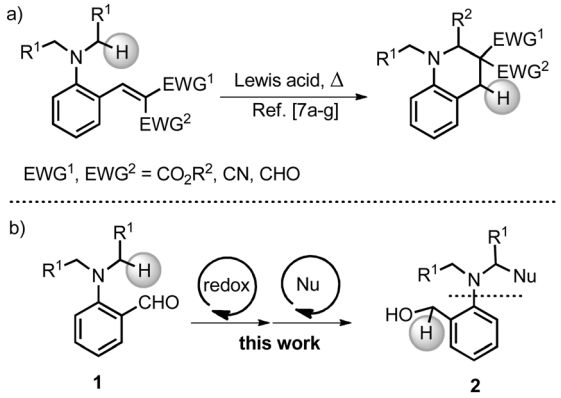
C–H functionalization strategies have made tremendous progress over the past decades. The fast-paced development of this vibrant area is likely due to the recognition by the chemical community of the potential that such methodologies possess to streamline synthetic routes. Indeed, the ability to selectively manipulate targeted C–H bonds precludes substrate prefunctionalization prior to the desired key steps and, therefore, represents a shift in the logical rationale of organic synthesis.[1] Particularly appealing for functionalization are C–H linkages located immediately adjacent to a heteroatom: the contemporary development of cross-dehydrogenative-coupling (CDC) reactions,[2] where the elegant functionalization of certain classes of amine substrates is achieved at the expense of an external oxidant, attests to this fact.[3]

In this context, the family of redox processes involving the intramolecular functionalization of one of the α,α′-positions of certain tertiary amines has witnessed a recent vigorous revival.[4–6] This transformation is based on the propensity of these amines to undergo a 1,5-hydride shift to an electrophilic moiety followed by cyclization of the zwitterionic intermediate formed (originally called the "*tert*-amino effect"). Interestingly, the majority of the research described is dominated by Michael acceptors as electropositive fragments (Scheme 1 a).[7] Only a limited number of reports have dealt with aldehydes or iminium ions.[5c,8,9]

We became interested in the design of a synthetic strategy for coupling such powerful intramolecular redox transformations with a subsequent, intermolecular functionalization step. The conversion of readily available, 2-substituted aminobenzaldehydes **1** to functionalized derivatives **2** was selected as a model platform to implement this plan (Scheme 1 b). This conversion would amount to a redox-triggered C–H functionalization through the sacrificial reduction of the neighboring carboxaldehyde group. We report herein our results on the development of this strategy, a number of relevant preliminary mechanistic studies, and an application of the method to a short total synthesis of a naturally occuring indolizidine alkaloid.



Scheme 1. a) Prior intramolecular redox methodologies based on the *tert*-amino effect. b) Proposed design for intermolecular redox-triggered C–H functionalization.

We screened different solvents and Brønsted/Lewis acids as catalysts for the envisaged redox process and found the use of 10 mol% of $Sc(OTf)_3$ in 1,2-DCE at 80 °C to be the optimal conditions.[10] We then combined this step with the key C–C bond-forming nucleophilic addition (Scheme 1 b).[11] To this end, a variety of commercially available Grignard reagents could be successfully employed (Scheme 2).[12] The corresponding α-functionalized amine products, bearing a wide range of appendages, could be obtained in generally good to excellent yields. It was possible to introduce alkyl, allyl, branched alkyl, vinyl, and aryl moieties with only marginal variations in yield (**5a–i**).[13] The procedure proved nonetheless to be sensitive to the nature of the secondary amine moiety. Upon the change from a pyrrolidine to a piperidine ring, the yield for the corresponding redox product dropped significantly (requiring increased catalyst loading, **5j**), whilst the nucleophilic capture step still proceeded smoothly.[14–16] Importantly, substitution at the aryl ring was also fully compatible with this sequence (**5k–s**).

Given the intrinsic versatility and synthetic usefulness of the alkyne functional group,[17] we became intrigued by the possibility of achieving $C(sp^3)$–C(sp) bond formation and eagerly probed lithium alkynyl trifluoroborates[18] as nucleophiles. In the event (Scheme 3), addition of excess lithium alkynyl borates following the redox transformation delivered the desired substituted amines **6** directly in good to very good yields for this one-pot operation. As indicates in Scheme 3, acetylides carrying alkyl, *tert*-butyl, silyl, and aryl moieties were generally well tolerated (**6a–d**). Functionalized alkyl moieties (**6e**) and densely substituted aryl residues (**6f–h**) were also tolerated by this process, as well as substitution at the aromatic ring of the substrate (**6i–o**). It is noteworthy that products **5** and **6** result from the overall addition of a strong

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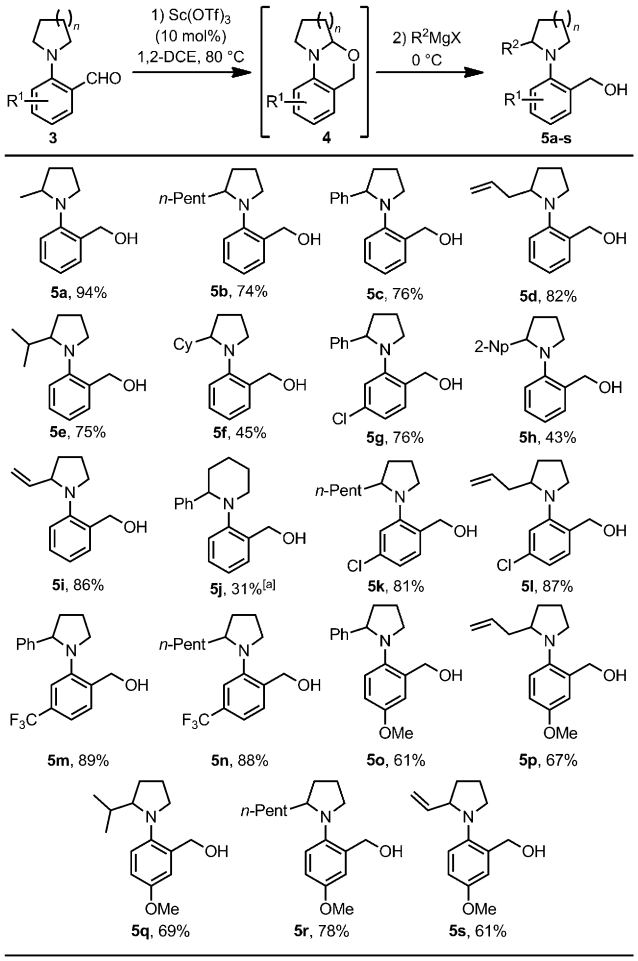
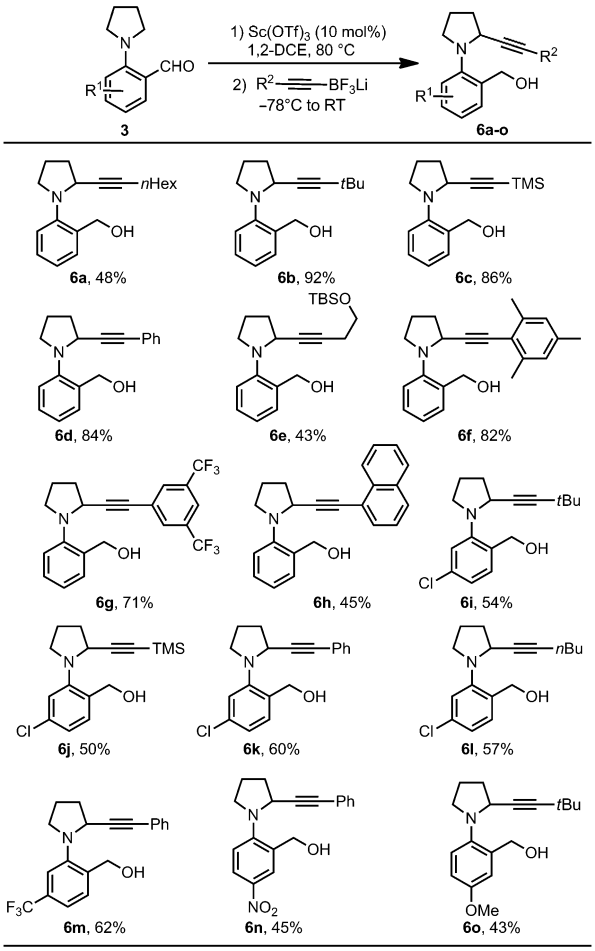


Scheme 2. Redox-mediated C–C bond formation employing Grignard nucleophiles. General conditions: amino aldehyde (0.3 mmol), $Sc(OTf)_3$ (0.03 mmol), 1,2-DCE (3 mL), and Grignard reagent (0.6 mmol). [a] Reaction performed with 40 mol% catalyst. DCE = dichloroethane, Cy = cyclohexyl, 2-Np = 2-naphthyl.

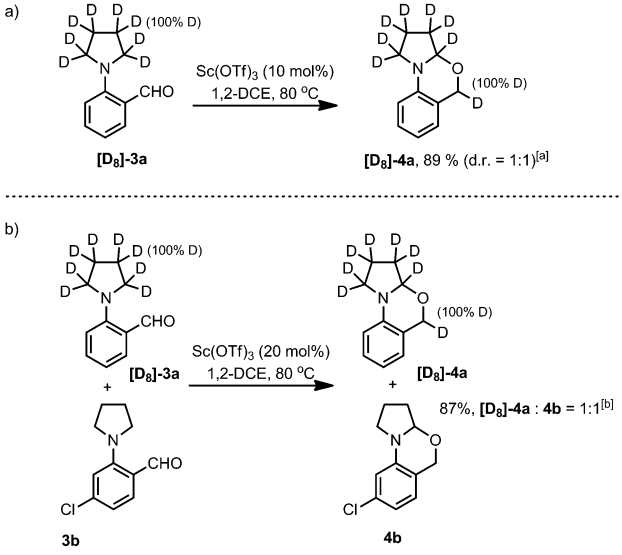


Scheme 3. Redox-mediated C–C coupling employing alkynylborate nucleophiles. General conditions: amino aldehyde (0.2 mmol), $Sc(OTf)_3$ (0.02 mmol), 1,2-DCE (2 mL), and lithium alkynylborate (1.0 mmol). TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

nucleophile to the amine functionality of the starting amino-aldehydes **3**, in clear contrast to what would be expected from the well-established, classical reactivity of aldehydes towards such nucleophiles.

At this stage, preliminary mechanistic experiments aimed at elucidating details of the redox event were performed (Scheme 4). As expected, the perdeuterated aminoaldehyde **[D_8]-3a** afforded the corresponding benzoxazine **[D_8]-4a** in 89% yield, with complete transfer of the deuterium label to the benzylic position (Scheme 4a). In addition, a crossover experiment (Scheme 4b) involving equimolar amounts of aminoaldehydes **[D_8]-3a** and **3b** revealed no deuterium incorporation at the benzylic position of **4b** (i.e., no crossover products). This observation is in full agreement with a postulated strictly intramolecular process.

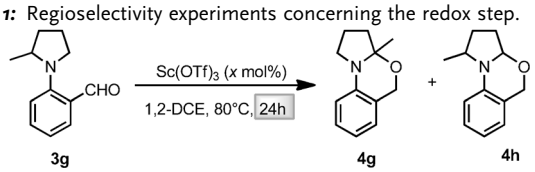
We then examined the regioselectivity of the redox step in more detail. It is generally accepted that in nonsymmetrically substituted donors, the hydride-transfer pathway leading to the most stabilized carbocation should dominate.[6,7h] In the case of the simple substrate **3g**, the regioselectivity appeared to be particularly sensitive to the reaction conditions. The



Scheme 4. a) Labeling experiment. b) Crossover experiment.

reaction of aminoaldehyde **3g** with increasing amounts of $Sc(OTf)_3$ afforded increasing amounts of the "expected" (more highly substituted) regioisomer **4g** relative to regioisomer **4h** (Table 1). At lower conversions of **3g** (5–10 mol% of catalyst, entries 1 and 2), a nearly 1:1 mixture of isomers

Table 1: Regioselectivity experiments concerning the redox step.



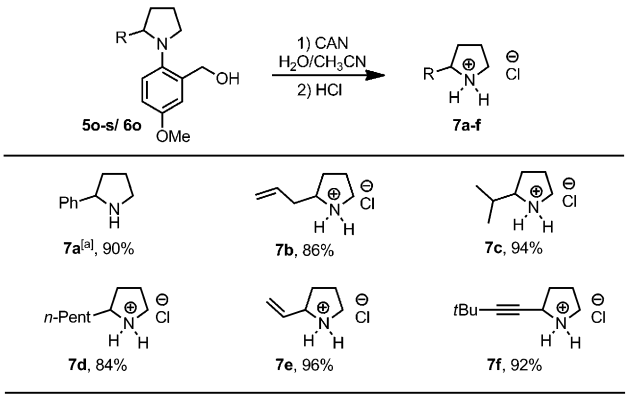
Entry	*x*	**3g**/**4g**/**4h**[a]
1	5	7:1.8:1
2	10	1:13.9:10
3	20	0:2.1:1
4	50	0:24:1[b]

[a] Ratio determined by GC analysis. The peaks of the diastereoisomers of **4h** overlap in the GC traces (ratio not determined). [b] The yield of isolated compound **4g** was 90%.

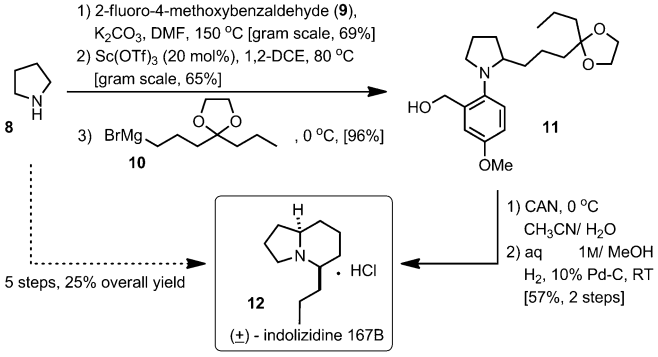
4g/**4h** was produced, whereas at close to full conversion, **4g** was the dominant product (20–50 mol% of catalyst, entries 3 and 4). Interestingly enough, when the isolated product mixture obtained with 20 mol% catalyst (**4g**/**4h** = 2.1:1, entry 3 of Table 1) was resubmitted to the reaction conditions with 50 mol% of the scandium salt, a new mixture significantly enriched in **4g** (new ratio of **4g**/**4h** = 32:1) was formed. These observations suggest two intriguing and unusual points: 1) the formation of **4g**/**4h** from **3g** is subject to thermodynamic control, with **4g** being the thermodynamic product; and 2) the formation of **4h** (and possibly even **4g**) is reversible under the reaction conditions, implying the existence of a mechanism for interconversion between **4g** and **4h**. To the best of our knowledge, this is the first observation of such a phenomenon in redox processes of this kind.[19] We also could measure a significant primary kinetic isotope effect of 2.9, which strongly supports hydride transfer as the rate-determining step.[20,21]

Importantly, if the aromatic substituent bears a *para*-methoxy substituent (such as in substrates **5o–s** and **6o**), smooth cleavage of the aromatic residue can be achieved under mild conditions,[22] thus providing suitably functionalized, synthetically useful amines **7a–f** in high yields (Scheme 5).[23]

Finally, the synthetic utility of the method outlined herein is showcased in the context of the total synthesis of the natural product (±)-indolizidine 167B.[24] As depicted in Scheme 6, alkylation of pyrrolidine **8** with 2-fluoro-4-methoxybenzaldehyde **9**, followed by sequential treatment with 20 mol% of $Sc(OTf)_3$ and the Grignard reagent **10** afforded the anisidine intermediate **11**,[25] with an overall yield of 43% for the three steps. Subsequent cleavage of the aryl protecting group with CAN was accompanied by partial deprotection of the dioxolane moiety.[26] Therefore, the crude reaction mixture was directly subjected to hydrogenolysis at ambient pressure in aqueous HCl (1M) to achieve the total synthesis of (±)-indolizidine 167B (**12**) in a combined 57% yield for these two



Scheme 5. CAN-mediated C–N bond cleavage of a "PMP-like" protecting group. General conditions: arylamine (0.2 mmol), $(NH_4)_2Ce(NO_3)_6$ (1 mmol) in H_2O/CH_3CN (3 mL/2 mL). [a] Isolated as the free amine owing to its higher boiling point. CAN = cerium(IV) ammonium nitrate.



Scheme 6. Total synthesis of (±)-indolizidine 167B (**12**).

last steps (Scheme 6). This final transformation is a domino reaction consisting of acetal cleavage and a diastereoselective intramolecular reductive amination. The target indolizidine was synthesized from pyrrolidine in only five steps and 25% overall yield. Importantly, the initial operations of this short synthetic sequence can be readily conducted on a gram scale, highlighting the robustness of the procedure.

In summary, we have developed a one-pot C–H functionalization process for cyclic tertiary amines, in which the sacrificial reduction of a neighboring carboxaldehyde group directs the addition of Grignard reagents and lithium alkynyl trifluoroborates to the α-position of the amine moiety. Important mechanistic results pertaining to this class of internal redox reactions relying on the *tert*-amino effect were obtained, showcasing the potential for kinetic versus thermodynamic control and pointing towards an unprecedented isomerization of the reactive intermediates involved. The removal of the sacrificial substituent under mild conditions at the end of the sequence provides α-functionalized amine products of clear synthetic value, which was laid out in a concise and direct total synthesis of (±)-indolizidine 167B. The concepts and insights disclosed herein have obvious potential for further applications and progress in this area shall be reported in due course.

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