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Synthetic Methods

Redox Chain Reaction—Indole and Pyrrole Alkylation with Unactivated Secondary Alcohols**

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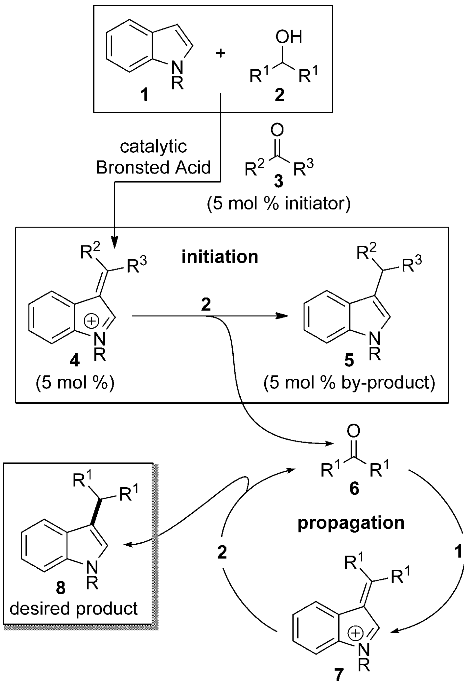
The direct alkylation of indoles with alcohols would be of considerable synthetic utility because of the wide availability of both starting materials. While this is readily accomplished with activated substrates such as allylic,[1] benzylic,[2] and propargylic alcohols,[3] the use of unactivated compounds such as secondary aliphatic alcohols is exceedingly rare and, to this day, represents a formidable challenge. Two examples were reported between 1940 and 1950.[4,5] Despite their limited scope, the unique mechanism by which they operate (i.e., disproportionative condensation), piqued our curiosity.[6] These transformations yielded C-alkylated products, but only under harsh reaction conditions (i.e., U.O.P. Ni catalyst, 30–600 mol% Na or K alkoxides, 174–220 °C, up to 64 h). Their synthetic utility, with respect to functional-group tolerance and product stability, would be considerably improved if milder reaction conditions could be identified.

We hypothesized that the fundamental mechanistic features of the base-promoted disproportionative condensation could be achieved under milder reaction conditions by employing an appropriate Brønsted acid catalyst (Scheme 1). As an illustrative example, indole **1** and alcohol **2** are treated with 5 mol% of the sacrificial ketone **3** and an appropriate acid catalyst. The reaction is initiated by condensation of **1** with **3** to furnish the indolyl cation **4** which is converted into the undesired by-product **5** and the new ketone **6** through a Meerwein–Ponndorf–Verley (MPV) reduction with **2** (Oppenauer oxidation of *i*PrOH).[7] Then **6** condenses with **1** to furnish a different indolyl cation **7** which is similarly reduced to the desired product **8**.[8] For every molecule of product that is formed, a molecule of **6** is regenerated, thereby propagating the reaction. We suggest *redox chain reaction* as an appropriate moniker for this process because of the similarities it shares with radical chain reactions,[9] and also to distinguish it from base-promoted disproportionative condensation.

In line with our ongoing interest in the reactivity of indolyl cations,[10] we report herein the successful application of the redox chain reaction to the alkylation of indole and pyrrole derivatives with unactivated secondary aliphatic alcohols. While catalytic variants are known,[11,12] Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reactions typically require stoichiometric amounts of Lewis acids. To the best of our knowledge, this work is also likely to be the first instance of an MPVO process catalyzed by a Brønsted acid.[13,14]



Scheme 1. Acid-catalyzed redox chain reaction.

At the onset, we set out to identify the most efficient initiator and Brønsted acid catalyst, as well as their optimal loadings. After extensive experimentation (see the Supporting Information), we determined that 5 mol% of 2-methoxyacetophenone (**3a**) as an initiator and 10 mol% of TfOH in toluene at 100 °C provided the highest yield of **8ad** (88%) for the reaction between *N*-benzylindole (**1a**) and *i*PrOH (**2d**; Scheme 2). Cyclohexanone and acetophenone (both 5 mol%) were also effective initiators, but because their by-products (corresponding to **5**) sometimes coeluted with the desired products on silica gel, we decided to adopt **3a** as the standard initiator. Importantly, control reactions in which either **3a** or TfOH was omitted resulted in no detectable product.

With the optimized reaction conditions in hand, we proceeded to explore the scope of the methodology. As is evident in Scheme 2, the reaction is tolerant to a variety of functional groups including esters, amides, nitro, nitriles, and ethers. The aminoalcohol **2g** can also be used, but in this case

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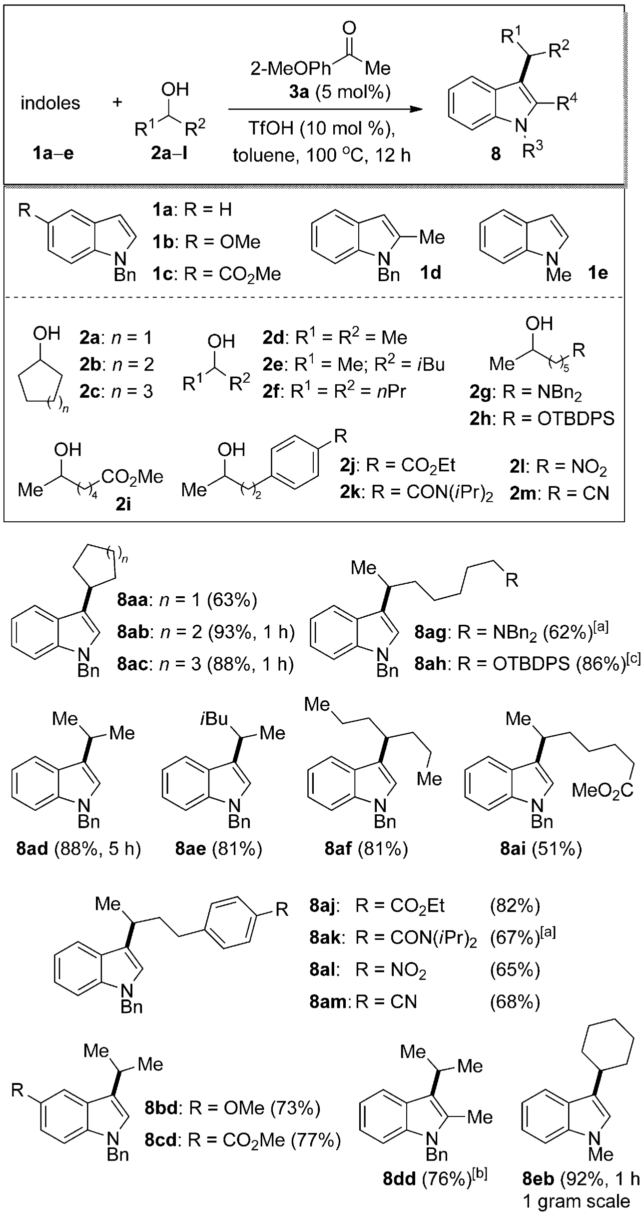
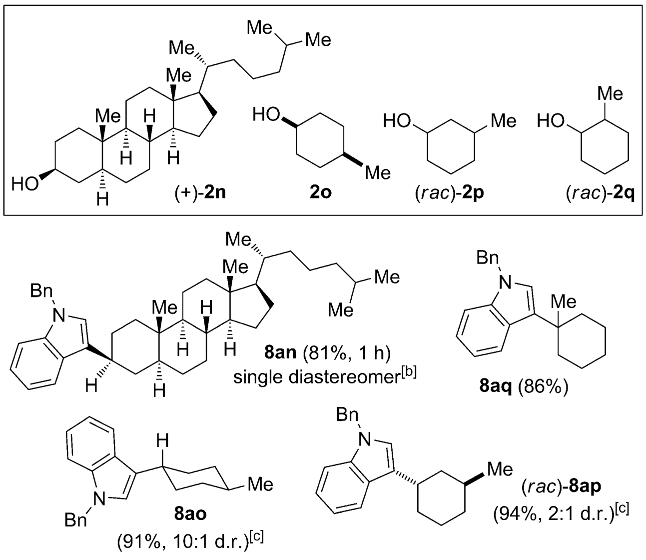


Scheme 2. Scope of C3 alkylation of indoles. [a] 1.0 equiv alcohol, 1.1 equiv TfOH. [b] 2.0 equiv alcohol, 1.0 equiv TfOH, 10 mol% **3a**. [c] 2.0 equiv alcohol, 5 mol% TfOH, 10 mol% **3a**. Bn = benzyl, Tf = trifluoromethanesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

stoichiometric TfOH was required since up to 1 equivalent of acid could be consumed by the basic nitrogen center. *N*-methylindole (**1e**) as well as 2-methyl-*N*-benzylindole (**1d**) are both compatible, thus producing **8dd** and **8eb** in good yields. The use of NH indole as the nucleophile resulted in no reaction.

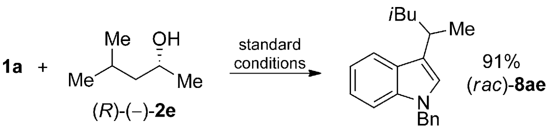
As a testament to the improved efficiency of the redox chain reaction as compared to disproportionative condensation, we highlight the reaction between **1a** and cyclohexanol (**2b**) which occurs within only 1 hour at 100 °C to provide **8ab** in 93% yield upon isolation. The formation of three other products **8ac**, **8eb,** and **8an** (see Scheme 3) was also complete within 1 hour. In contrast, the alkylation of indole with cyclohexanol utilizing base-promoted disproportionative condensation requires 64 hours at 174–185 °C and furnishes the desired product in only 54% yield.[4a] The use of primary alcohols resulted in the formation of only **5** (< 5%). It is likely that the attenuated reactivity of primary alcohols as hydride donors, relative to secondary alcohols, precludes efficient propagation of the redox chain reaction.

Excellent levels of diastereoselectivity can be realized using alcohols with pre-existing stereocenters. As illustrated in Scheme 3, when we attempted the late-stage indolylation of (+)-dihydrocholesterol (**2n**) with **1a**, the expected product **8an** was isolated in 81% yield as a single diastereomer (stereochemical configuration was confirmed with single-crystal X-ray analysis). With *cis*-4-methylcyclohexanol (**2o**), high diastereoselectivity (**8ao**, 10:1 d.r.) was also achieved. Axial delivery[15] of hydride to the respective indolyl carbocationic intermediates correctly predicts the observed selectivities for **8an** and **8ao**. Alkylation using **2p** (mixture *cis/trans*) furnished a 2:1 mixture of **8ap**. Curiously, alkylation with the 2-substituted cyclohexanol **2q** (mixture *cis/trans*) generated mainly the rearranged product **8aq**. By-products derived from 1,2-hydride shifts were not detected.



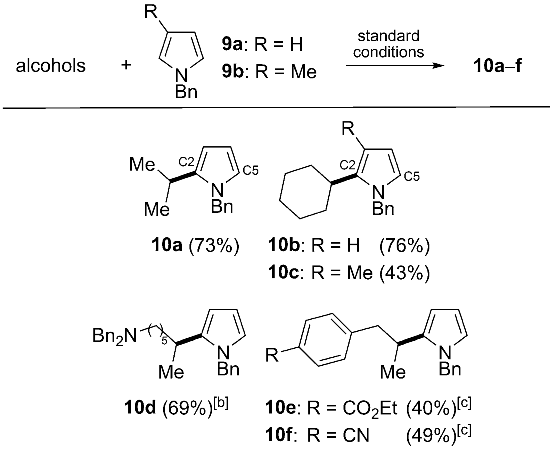
Scheme 3. Diastereoselective alkylation reactions. [a] Standard reaction conditions as described in Scheme 2. [b] Relative stereochemistry was confirmed by single-crystal X-ray analysis.[17] [c] Confirmed by comparison of J_{HH} values to **8an**.

We wondered whether or not enantioenriched secondary alcohols would deliver hydride to the prochiral indolyl cation intermediates in a stereospecific fashion. Unfortunately, the reaction between **1a** and (*R*)-(−)-**2e** generated **8ae** as a racemate [Eq. (1)].[16]



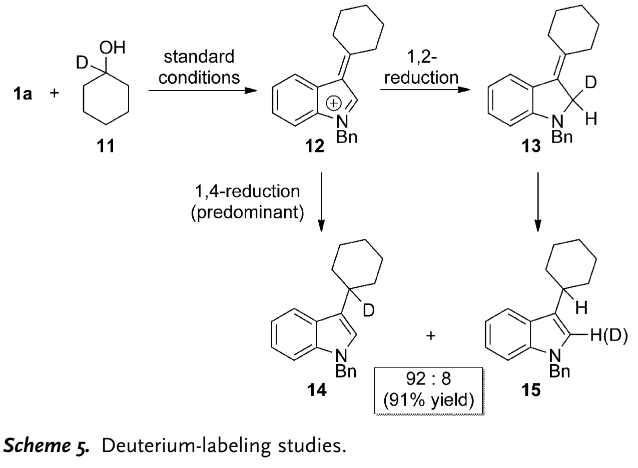
(1)

This methodology is also compatible with pyrrole nucleophiles (**9a–b**). Under the optimized reaction conditions, we obtained good yields of the anticipated C2-substituted pyrroles **10a–f** (Scheme 4). Importantly, we did not detect any di- or polysubstituted products. We hypothesize that for steric reasons, after the first alkylation, the benzyl group is directed away from the newly installed C2 substituent and towards C5. Substantial nonbonding interactions experienced by electrophiles approaching C5 of **10** would disfavor a second alkylation event. For **9b**, we believe that alkylation takes place proximal to the C3 methyl group because C2 is more electron rich than C5. Furan and thiophene were not suitable nucleophiles as they resulted in either decomposition or no reaction, respectively.



Scheme 4. Scope of C2 alkylation of pyrroles. [a] Standard reaction conditions as described in Scheme 2. [b] 1.0 equiv alcohol, 1.1 equiv TfOH. [c] 2.0 equiv alcohol, 20 mol% TfOH, 10 mol% **3a**.

Preliminary mechanistic studies are depicted in Scheme 5. The alkylation of **1a** with deuterated cyclohexanol **11** generated a 92:8 ratio of the isotopic isomers **14** and **15**. 1,4-Reduction would lead exclusively to **14**. Alternatively, 1,2-reduction and subsequent TfOH-promoted tautomerization/rearomatization would furnish **15**. Based on the 92:8 preference for the formation of **14**, we conclude that 1,4-reduction is the predominant pathway. These results also provide evidence in support of the intermediacy of indolyl carbocation **12**.



Scheme 5. Deuterium-labeling studies.

In conclusion, we have developed the Brønsted acid catalyzed redox chain reaction as it pertains to the alkylation of indole and pyrrole derivatives with unactivated secondary alcohols. Broad functional-group tolerance has been demonstrated. Deuterium-labeling studies support the intermediacy of an indolyl carbocation which undergoes MPVO conjugate reduction as a likely reaction mechanism.

We anticipate that it might be possible to apply the concept of the redox chain reaction to the alkylation of other nucleophiles such as nonbasic nitrogen atoms, enamines, and electron-rich benzene derivatives. We are also exploring the possibility of using chiral Lewis and Brønsted acids to induce asymmetry.

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