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Redox-Neutral Indole Annulation Cascades

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Supporting Information

ABSTRACT: Aminobenzaldehydes react with indoles in an unprecedented cascade reaction. This acid-catalyzed redox-neutral annulation proceeds via a condensation/1,5-hydride shift/ring-closure sequence. Polycyclic azepinoindoles and related compounds are obtained in a single step with good to excellent yields.

Direct functionalization of unactivated and relatively unreactive C−H bonds continues to be a major focus of inquiry.[1] Exciting progress in this intensely active research area has been achieved and many more advances can be anticipated. Much of the current research efforts are focused on the development of C−H bond functionalization processes by means of oxidative methods that require (super)stoichiometric amounts of oxidant. Fundamentally different from a mechanistic point of view and comparatively unexplored are reactions that lead to C−H bond functionalization through redox-neutral processes (e.g., Figure 1).[2,3] In these reactions, the C−H bond to be functionalized serves as a hydride source for a pendant acceptor moiety. After hydride transfer, the reduced and oxidized portions of the molecule recombine to form a new ring system.

Previously reported hydride shift-initiated C−H bond functionalizations often follow the general reaction sequence shown in Figure 1.[4,5] In the first step, aldehyde **1** is allowed to react with a nucleophile (H_2Nu) to form intermediate **2**. Thermal or catalyst promoted activation of **2** facilitates hydride shift/ring-closure to form **4** via the intermediacy of dipolar species **3**. In the majority of cases, this sequence is conducted in a stepwise manner that requires isolation and purification of intermediate **2**. Many of these reactions involve 1,5-hydride shifts and result in the formation of products that contain six-membered rings.[6]

As part of a program aimed at developing redox-neutral reaction cascades for the rapid buildup of molecular complexity,[7] we considered a new reaction cascade design in which an initial 1,5-hydride shift would ultimately result in the formation of larger rings. As outlined in Figure 2, the acid-catalyzed reaction of aldehyde **1** with a doubly nucleophilic compound is envisioned to initially result in the formation of the activated species **5**. Subsequent to intramolecular hydride transfer, the resulting intermediate **6** could react with the pendant nucleophile. Proton loss would then result in the formation of product **7**.

Due to its known nucleophilic properties, it occurred to us that indole should be able to serve as a double nucleophile in the proposed sequence.[8] Such a reaction would constitute a new one-step indole annulation. Whereas indole annulations to form carbazoles are numerous[9] and indole annulations that lead to dearomatization of the indole nucleus have been reported,[10] direct annulation of

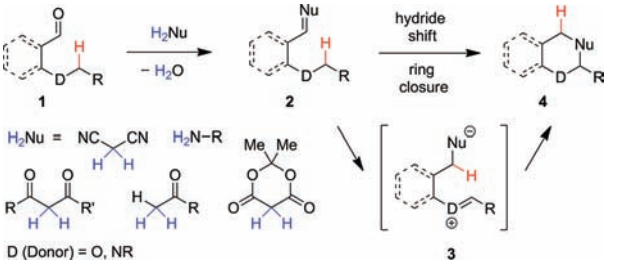


Figure 1. Redox-neutral C−H bond functionalization.

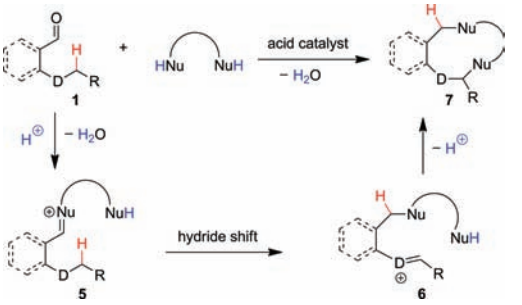
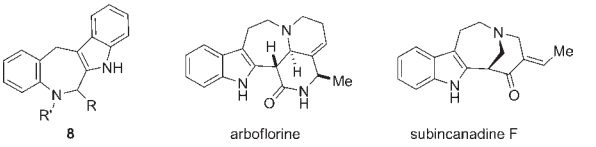


Figure 2. Design of a new redox-neutral reaction cascade.

(partially) saturated rings onto simple indoles is relatively rare in cases where indole retains its aromaticity. This is particularly true for annulations with larger than six-membered rings.[11]

Given the importance of indole in medicinal chemistry,[12] the prospect of rapidly generating new indole-containing molecular frameworks appeared particularly appealing. Reaction of an appropriate aminobenzaldehyde with indole should result in one-step formation of azepinoindoles such as **8**. The azepinoindole substructure is found in a number of natural products (e.g., arboflorine and subincanadine F) and biologically active drug candidates.[13]



We initiated our studies by investigating the reaction of indole with aminobenzaldehyde **9a** under a variety of conditions. Not surprisingly, a reaction conducted in ethanol at room temperature led to the formation of the bis(indolyl)methane **10a** in 62% yield (eq 1).[14] As outlined in eq 2, using very similar conditions but higher reaction temperatures (reflux in *n*-butanol) resulted in the unexpected formation of the reduced product **11a** (vide infra). Gratifyingly, the

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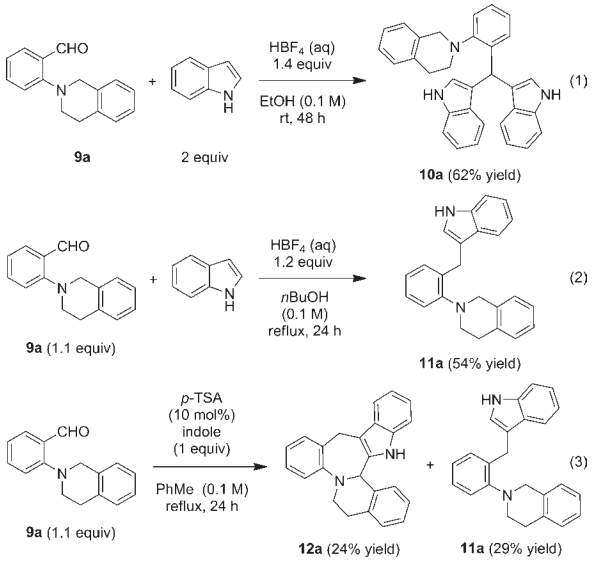
desired product **12a** could be obtained in a reaction conducted in toluene under reflux and in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA). However, the azepinoindole **12a** was obtained in only 24% yield, and its formation was accompanied by the generation of product **11a** in 29% yield (eq 3). In addition, small amounts (7%) of the bis(indolyl)methane **10a** were isolated as well (not shown).



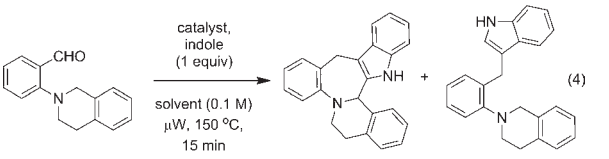
Various other reaction conditions were evaluated in order to improve the overall efficiency of this reaction and to maximize the yield of the desired product **12a**. As part of this study, we found that reactions conducted under microwave irradiation produced particularly promising results and allowed for conveniently short reaction times.

Different acid additives are summarized in Table 1. Optimal results were obtained with 20 mol % of diphenyl phosphate (DPP) in toluene (entry 14).[15] Under these conditions, the indole annulation product **12a** was obtained in 83% yield, and formation of the undesired product **11a** was almost completely suppressed. A reaction conducted at reflux in toluene but in otherwise identical conditions went to completion within 3 h. In this instance, **12a** was obtained in 57% yield in addition to **10a** (25%) and **11a** (10%). The corresponding reaction in refluxing xylenes gave **12a** (60%), **10a** (13%) and **11a** (11%) after 2 h.

With the optimized reaction conditions at hand, a number of other readily available indoles were allowed to react with aminobenzaldehyde **9a**, including relatively electron-rich and electron-poor indoles. As summarized in Chart 1, the corresponding annulation products **12** were obtained in good yields. The structure of the *N*-methylindole-derived product **12f** was confirmed further by X-ray crystallography.

The scope of the indole annulation with regard to the aminobenzaldehyde is shown in Chart 2. A number of aminobenzaldehydes underwent reaction with indole to yield the expected products **14** in good to excellent yields. Minor amounts of the corresponding reduced products were isolated in some instances. In case of the 2-methylpyrrolidine-derived aminobenzaldehyde **13e** (not shown), the resulting product **14e** was obtained as a single regioisomer. The fact that the more substituted of the two possible regioisomers was isolated is consistent with earlier observations[7b,c] and with the notion that a tertiary C−H bond is a better hydride donor than a secondary C−H bond. Interestingly, the corresponding 2-methylpiperidine-derived product **14f** was obtained as a 4:1 mixture of regioisomers. However, the preference for the formation of the more substituted product was maintained (minor regioisomer not shown, dr = 3:2). The structure of **14h** was confirmed by X-ray crystallography.

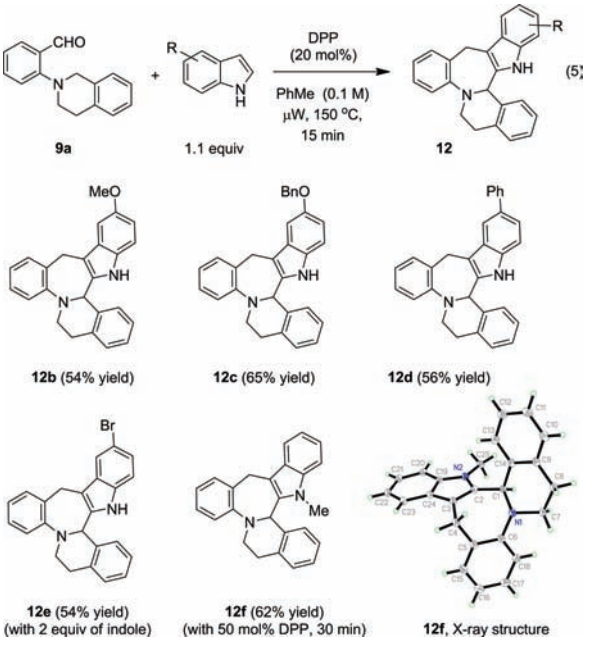
Table 1. Evaluation of Reaction Parameters[a]



entry	catalyst (equiv)	solvent	yield of **12a** (%)	yield of **11a** (%)
1	*p*-TSA (0.1)	PhMe	56	13
2	CF_3COOH (1.2)	PhMe	20	30
3	CH_3SO_3H (0.2)	PhMe	trace	trace
4	CSA (0.1)	PhMe	54	9
5	$HBF_4 \cdot OEt_2$ (0.1)	PhMe	trace	trace
6	4-Br-pyr·HCl (0.1)	PhMe	0	0
7	H_3PO_4(1.2)	PhMe	0	0
8	PhCOOH (0.2)	PhMe	0	0
9	DPP (0.1)	PhMe	81	4
10[b]	DPP (0.1)	xylenes	69	4
11	DPP (0.1)	$C_2H_4Cl_2$	40	4
12[c]	DPP (0.1)	PhMe	79	6
13[d]	DPP (0.1)	PhMe	73	6
14	DPP (0.2)	PhMe	83	4

[a] Reactions were performed on a 0.25 mmol scale. [b] Reaction was run at 170 °C. [c] Reaction was run with 1.1 equiv of indole. [d] Reaction was run with 1.3 equiv of indole.

Chart 1. Scope of the Indole Component[a]



[a] Reactions were performed on a 0.25 mmol scale.

The new cascade reaction was successfully extended to double nucleophiles other than indole. As shown in eq 7, reaction of aminobenzaldehyde **9a** with 2,5-dimethylpyrrole resulted in formation of the 3,4-pyrrole annulated benzazepine **15** in 59% yield.[16]

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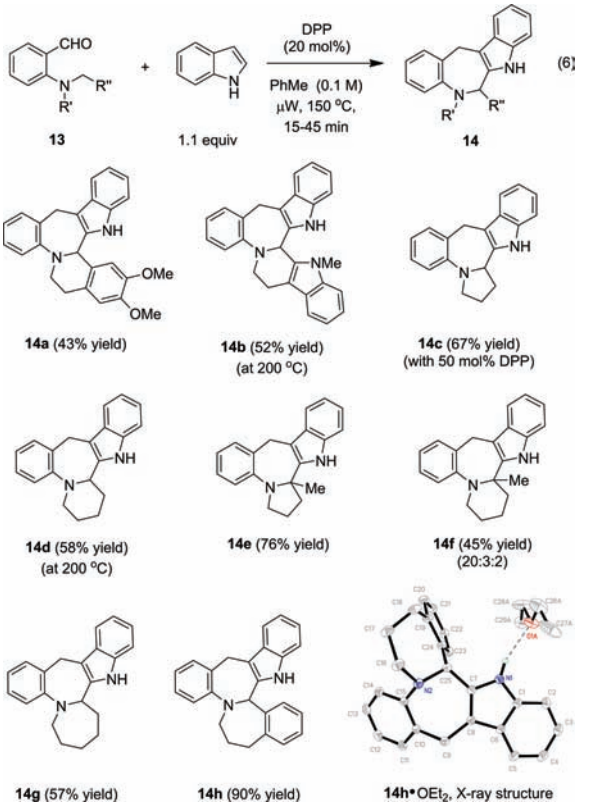
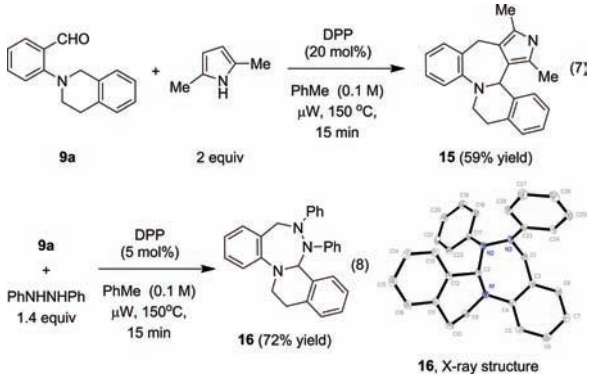
Chart 2. Scope of the Aminobenzaldehyde Component[a]

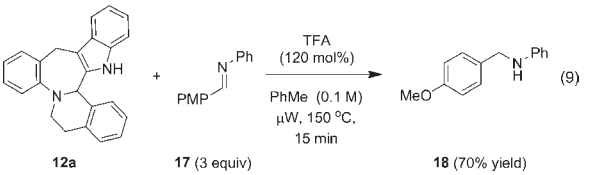


[a] Reactions were performed on a 0.25 mmol scale.

In preliminary work, we considered entirely different double nucleophiles. For instance, substrate **9a** readily underwent reaction with *N*,*N*′-diphenylhydrazine to form the interesting triaza-heterocycle **16** in 72% yield (eq 8). A reduced catalyst loading of 5 mol % was beneficial in this case. The X-ray crystal structure of **16** was also obtained.

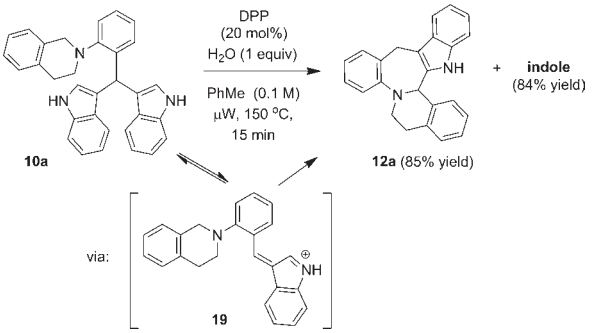


As outlined before, under certain reaction conditions, the formation of the desired annulation products was accompanied by varying amounts of apparently reduced product (i.e., **11a**) which in some cases was the only isolable material. Considering that products such as **12a** could potentially act as hydride donors, we proposed that **12a** might promote its own reduction in an interesting type of disproportionation reaction. In fact, we have observed that prolonged reaction times under microwave irradiation led to reduced yields of annulation products and the buildup of increased amounts of the reduced products. Furthermore, when **12a** was exposed to the reaction conditions outlined in eq 2, the reduced product **11a** was obtained in 33% yield as the only isolable product. As we have thus far been unable to isolate the corresponding oxidation product of **12a**, presumably due to its rapid decomposition, we devised an alternative experiment to establish the potential of **12a** to act as an intermolecular hydride delivery agent. Indeed, as shown in eq 9, **12a** readily promoted the reduction of imine **17** to the corresponding amine **18** in 70% yield (yield based on **12a**).[17] The product resulting from the oxidation of **12a** could not be isolated, and the reduced **11a** was not formed in this process.



Lastly, we wanted to establish that formation of the well-known and easily formed bis(indolyl)methanes[14] (e.g., **10a**) does not necessarily represent a dead end in this reaction. Rather, we speculated that under acid-catalyzed conditions, compounds such as **10a** might be in equilibrium with the corresponding azafulvenium ions (e.g., **19**), presumed intermediates in the formation of the annulation products. Indeed, exposure of **10a** to the original reaction conditions gave rise to the formation of annulation product **12a** in 85% yield, accompanied by the expected recovery of indole in 84% yield (Scheme 1). In addition, **11a** was formed in 5% yield (not shown).

Scheme 1. Transformation of a Bis(indolyl)methane into an Azepinoindole



Here we have shown that reactions of doubly nucleophilic species such as indoles with aminobenzaldehydes lead to unprecedented reaction cascades. In this new redox-neutral process, a 1,5-hydride shift results in formation of seven-membered ring products. The resulting indole-fused benzazepines can be obtained in just two steps from commercially available materials. Current studies are aimed at developing other redox-neutral reaction cascades for rapid buildup of molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information. Complete ref 13e, experimental procedures, characterization data, and X-ray crystal structures of **10a**, **12f**, **14h**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) While the results in Table 1 indicate that the catalyst pK_a is certainly important, there appears to be no direct correlation between catalyst activity and acidity. Acids with similar pK_a's (e.g., DPP and phosphoric acid) gave vastly different results. We thus speculate that catalyst reactivity might be partially dependent on catalyst solubility in the nonpolar reaction medium (or on the corresponding solubility of protonated starting material/product).

(16) Related furan-containing compounds have been prepared from relatively complex starting materials via an intriguing gold-catalyzed cascade reaction that involves a 1,5-hydride shift: Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593.

(17) No reduction of **17** was observed in the absence of **12a**.