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Bisulfite Addition Compounds as Substrates for Reductive Aminations in Water

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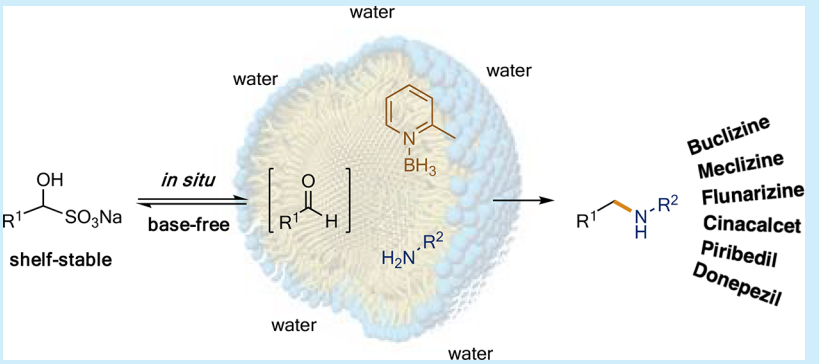
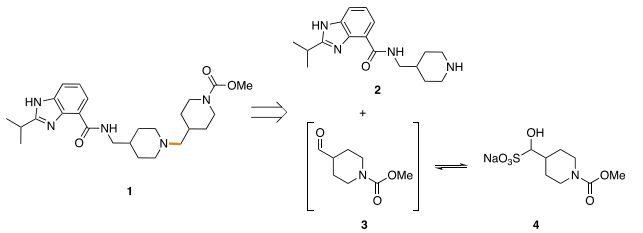


ABSTRACT: Highly valued products resulting from reductive aminations utilizing shelf-stable bisulfite addition compounds of aldehydes can be made under aqueous micellar catalysis conditions. Readily available α-picolineborane serves as the stoichiometric hydride source. Recycling of the aqueous reaction medium is easily accomplished, and several applications to targets in the pharmaceutical industry are documented.

A multistep synthesis of the 5-HT4 receptor agonist TAK-954 (**1**) recently appeared,[1] showcasing use of water as the reaction medium in each reaction. The overall evaluation led, as stated, to "77% less material inputs, 94% less organic solvent, and surprisingly, 48% less water, while improving overall yield from 35% to 56%." Included among this award-winning[2] report was a reductive amination (i.e., **2** + **3**; Scheme 1) that relied on an aldehyde precursor bisulfite addition compound **4**, in equilibrium with its aldehyde equivalent (**3**), which together underwent a very efficient conversion in aqueous micellar media using α-picolineborane (1.5 equiv) as the reducing agent. Such educts are very attractive given their inherent stability, as well as their usual crystallinity allowing for facile purification.[3] Noteworthy was the observation that added base was not needed to convert bisulfite addition complex **4** to its required aldehyde form prior to reductive amination; the aqueous conditions sufficed for this purpose, unlike prior runs in organic solvents.[3] The mild conditions under which this transformation occurred, together with this unprecedented approach in water, suggested that a more detailed evaluation be made of this new technology. In this *Letter* we describe such a study leading to both a general procedure and its application to several targets in the pharmaceutical industry.

Scheme 1. Key Reductive Amination Involving Bisulfite Addition Compound 4; Reducing Agent = α-Picolineborane



Using the conditions established for TAK-954[1] that involved an aqueous solution containing 2 wt % TPGS-750-M,[4] together with MeOH (20% v/v) as cosolvent[5] and α-picolineborane[6] as the hydride source (1.5 equiv), several functionalized bisulfite addition compounds and primary amines were examined to establish the scope of these reductive aminations. As shown in Table 1, most combinations afforded the desired products, isolated in typically ≥70% to quantitative yields. Importantly, a wide variety of reaction partners was

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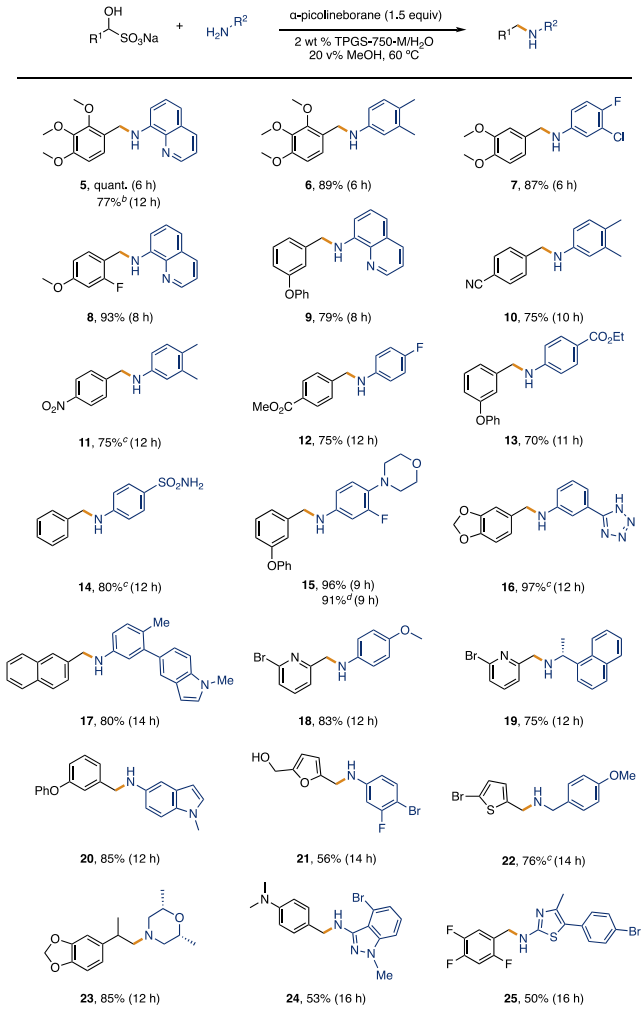
Table 1. Representative Products from Reductive Aminations in Aqueous Nanoreactors[a]

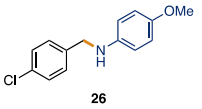
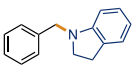
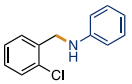
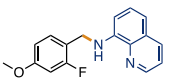


[a]Reaction conditions unless otherwise noted: 0.20 mmol of amine, 0.30 mmol of bisulfite adduct, 0.30 mmol α-picolineborane, stirred in 2 wt % TPGS-750-M/H_2O and 20 v % MeOH, 60 °C. Yields are for isolated purified products. [b]Free aldehyde instead of bisulfite adduct. [c]Run with 20 mol % HOAc present. [d]Without 20 v % MeOH as cosolvent.

found to be amenable to this method. Given the compatibility with nitrogen-containing substrates and heterocycles, as well as the breadth of scope (including aryl-, heteroaryl-, and aliphatic aldehydes, etc.) this process is expected to be especially applicable to production of pharmaceuticals. Using the free aldehyde, rather than its bisulfite addition adduct, as in the case leading to product **5**, required 12 h to reach completion and afforded a lower isolated yield, mainly due to competing reduction to the corresponding undesired alcohol. Repeating the conversion to highly functionalized secondary amine **15** in the absence of cosolvent[5] (i.e., 20% MeOH) still gave a high yield of product (91%) within the same time frame, suggesting that its presence is not essential in all cases. Occasionally, HOAc was needed to assist in shifting the equilibrium enhancing desired product formation (see products **11**, **14**, **16**, and **22**).

It is also important to place this approach in perspective, relative to existing technologies of late, even though these tended to involve far simpler target amines (Table 2). As the

Table 2. Comparison Cases: Representative Literature Methods vs This Work

2° amines from reductive aminations	literature conditions:	our conditions (yield, %)
 **26**	4 mol% $Fe_3(CO)_{12}$ 50 bar H_2 toluene, 65 °C **73% yield**[5]	quant.
 **27**	5 mol% nanoporous Au 8 atm H_2 EtOH, 90 °C **53% yield**[6]	88%
 **28**	Pd/ImS3-14 (540 ppm Pd) 5 equiv HCOOH 5 equiv NaCOOH iPrOH/H_2O, 70 °C **35% yield**[7]	quant.
 **8**	8000 ppm 1 wt% Pd/C 1.5 equiv Et_3SiH 2 wt% TPGS-750-M, 45°C **75% yield**[8]	93%

[a]Reaction conditions unless otherwise noted: 0.20 mmol of amine, 0.30 mmol of bisulfite adduct, 0.30 mmol of α-picolineborane, stirred in 2 wt % TPGS-750-M/H_2O and 20 v % MeOH, 60 °C, 16 h. Yields are for isolated purified products. [b]Run with 20 mol % HOAc present.

top three examples illustrate, a moderate yield is characteristic of each,[7−9] notwithstanding the choice of metal involved or the conditions used. The last case, utilizing our earlier set of conditions,[9] still led to only a 75% yield of secondary amine. Thus, these results obtained under aqueous micellar conditions relative to those using traditional conditions of organic solvent, elevated temperatures, and oftentimes special equipment to accommodate the pressures involved are indicative of the far milder, more selective, and more efficient outcome to be expected when such reactions are run within nanoreactors solubilized in water.[11]

Several secondary and tertiary amines were also prepared that correspond to subsections found in various known drugs and drug intermediates (**29** and **30**). As shown in Figure 1, pharmaceuticals prepared via reductive aminations include the following: (a) Buclizine, an antihistamine and antiemetic;[12] (b) Meclizine, used to treat or prevent nausea, vomiting, and dizziness caused by motion sickness;[13] (c) Flunarizine, a selective calcium entry blocker;[14] (d) Cinacalcet, a calcium sensing receptor agonist;[15] (e) Piribedil, used in the treatment of Parkinson's disease;[16] and (f) Donepezil, used to treat the behavioral and cognitive effects of Alzheimer's Disease and other types of dementia.[17] The preparation of intermediate **29** serves as the precursor to both Bamipine, an antipruritic ointment,[18] and Antazoline, an antihistamine.[19] Product **30** functions as a precursor to Fipexide, used as a nootropic drug mainly for the treatment of senile dementia.[20] Taken together, these are suggestive of the potential for this technology to apply to "real world" (i.e., more complex) targets.

As usually associated with chemistry in water, the opportunity to recycle the aqueous medium[21] was studied for these reductive aminations. Hence, following the initial conversion (96%) shown in Scheme 2 to secondary amine **15**, product isolation via decantation was followed by use of the aqueous reaction mixture for four additional reactions. The isolated yields obtained for each of the five conversions were virtually identical, all within the 93−97% range. Thus, using

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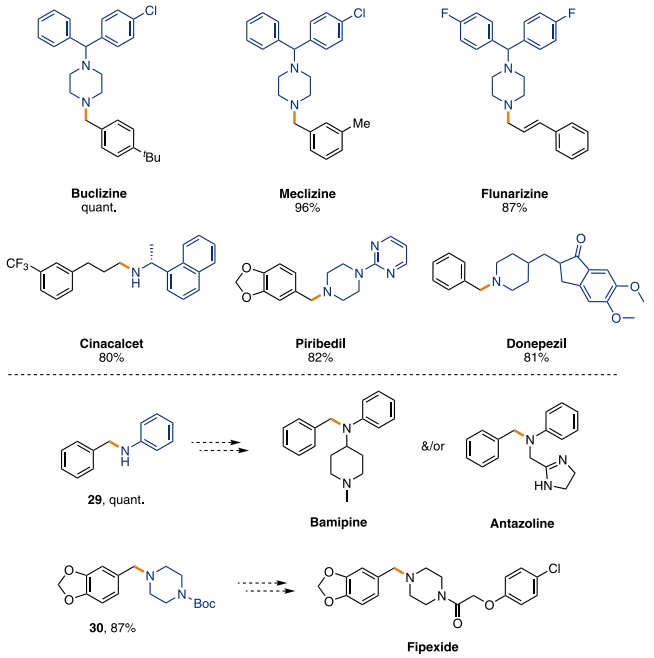
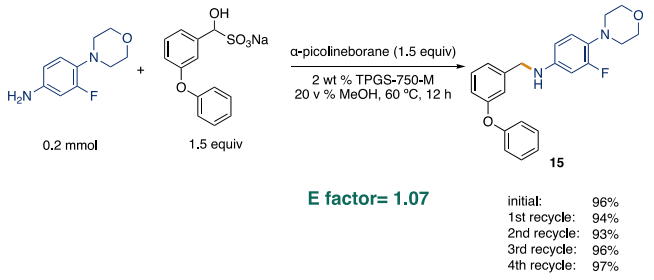


Figure 1. Reductive aminations used to prepare several known pharmaceutical targets.

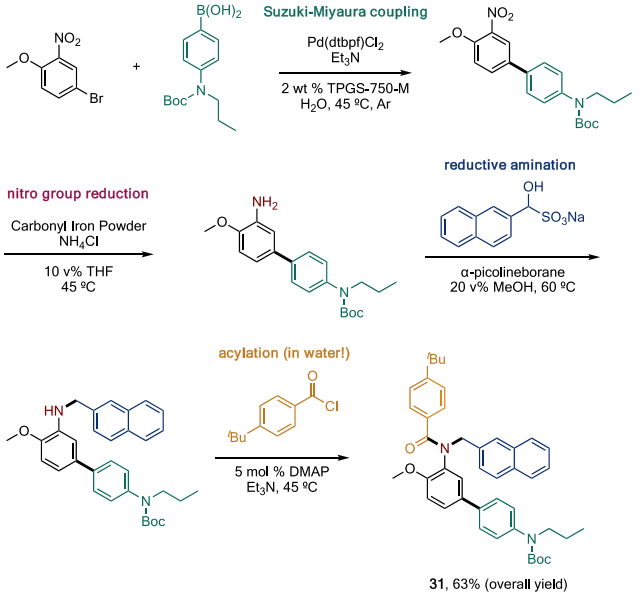
Scheme 2. Recycling Study and E Factor Evaluation



Sheldon's associated E Factor as a measure of greenness,[22] and doing the calculation based on the solvents involved (MeOH and water, which make up 88% of the waste typically seen in drug syntheses),[23] the value of 1.07 is indicative of the environmentally responsible nature of this process. Eventually, of course, the water becomes part of the waste stream containing the surfactant; however, recent work by Novartis has outlined the path for dealing with this aspect of the technology.[24]

As the toolbox of technologies associated with chemistry in water continues to expand,[25] so do the combinations now possible for sequential, one-pot processes that involve a variety of reactions in both the chemo- and, most recently, biocatalysis regimes.[26] The sequence shown in Scheme 3 is illustrative of the dramatic increases of complexity now possible in a single-pot operation, taking advantage of each step being run in the same, aqueous medium. Thus, following an initial Suzuki–Miyaura coupling, the resulting nitro-group-containing biaryl was reduced, without isolation, applying carbonyl iron powder (CIP)[27] to the corresponding aniline. This primary amine then participated readily in a reductive amination, the resulting secondary amine being acylated to afford the final product **31**, all done in water, in an overall yield of 63%. Such possibilities for "telescoping" reactions offer several benefits, including

Scheme 3. Four-Step, One-Pot Sequence Run in Water without Isolation of Intermediates



minimization of waste due to individual product processing and purification, as well as both time[28] and pot[29] economy.

In summary, reductive amination utilizing shelf-stable bisulfite addition compounds has been shown to be a generally applicable technology amenable to use under micellar conditions, run in recyclable water. TPGS-750-M serves as the designer surfactant that, in the presence of water, enables use of these educts to form their reactive aldehydes and, together with the amine present, react to generate the imine that undergoes reduction in the presence of the α-picolineborane as the stoichiometric hydride source. Several targets in the pharma area were prepared using this technology, which has been shown to minimize waste creation. Lastly, it was demonstrated that a reductive amination could be smoothly utilized as part of a multistep sequence performed in water without isolation of reaction intermediates. Several additional new technologies that, likewise, are respectful of their environmental footprints will be forthcoming from these laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02604.

Experimental procedures, analytical data, and copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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