Enantioenriched BCP Benzylamine Synthesis via Metal Hydride Hydrogen Atom Transfer/Sulfinimine Addition to [1.1.1]Propellane

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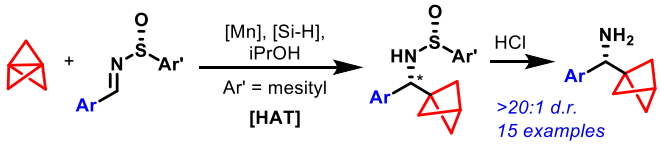
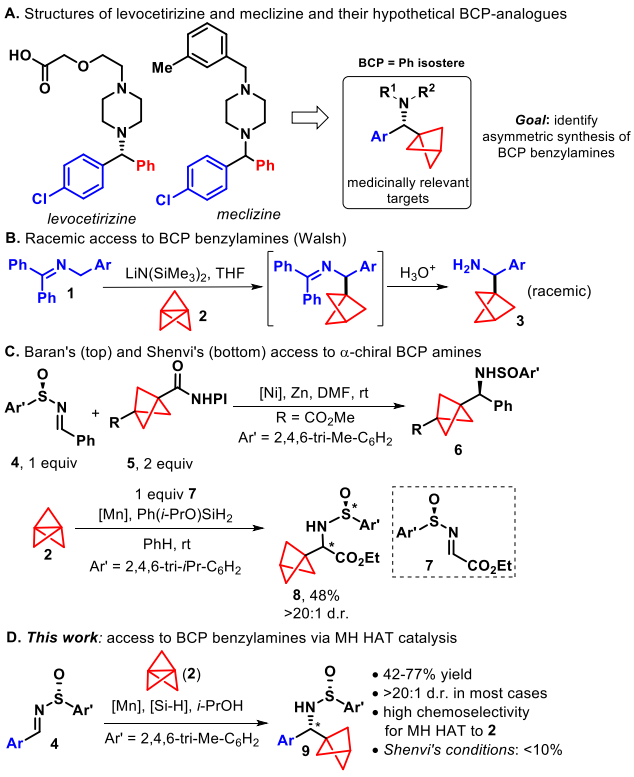
Supporting Information Placeholder



ABSTRACT: The stereoselective synthesis of BCP benzylamine derivatives from [1.1.1]propellane and mesityl sulfinimines via metal hydride hydrogen atom transfer (MH HAT) is reported. Medicinally relevant heterocyclic BCP methanamines are prepared with high diastereoselectivity. The strategic impact of the method is demonstrated via the streamlined synthesis of the BCP analogue of a key levocetirizine intermediate. Mechanistic evidence for a competitive H_2 evolution pathway and the importance of controlled silane addition during reaction initiation are disclosed.

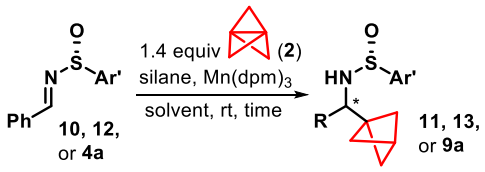
Diarylmethanamines are a common motif in bioactive molecules and represent the core structures of numerous FDA-approved drugs, including antihistamines levocetirizine and meclizine.[1] Given the importance of diarylmethanamines, synthetic access to their bioisostere-containing analogues is vital to enabling structure activity relationship (SAR) exploration during drug discovery. For instance, replacement of an aryl ring with a bicyclo[1.1.1]pentane (BCP) to generate a BCP benzylamine analogue might represent a favorable structural modification given the well-established pharmacokinetic benefits of these bioisosteres (Scheme 1A).[2] With this in mind, we previously developed methods to access both mono- and di-substituted BCP benzylamines via a two-step sequence from *N*-benzyl imines **1** and [1.1.1]propellane (**2**) (Scheme 1B), albeit as racemic mixtures.[3,4] While significant inroads in complex BCP synthesis have been made recently, the stereoselective construction of medicinally relevant BCPs remains relatively underdeveloped,[5-11] syntheses of enantioenriched α-chiral BCP amines are virtually unreported.[12,13] Given the importance of the diarylmethanamine motif in bioactive compounds, the development of a method for the stereoselective construction of BCP benzylamines would benefit the medicinal chemistry community.

Scheme 1. Motivation for MH HAT to [1.1.1]Propellane for BCP Benzylamine Synthesis



Several recent reports describe the stereoselective synthesis of α-chiral BCP amines. Baran and coworkers disclosed a single example of a diastereoselective Ni-catalyzed coupling of enantiopure sulfinimine **4** with BCP redox-active ester **5** (RAE, R = CO_2Me) to produce diastereoenriched BCP benzylamine **6** (Scheme 1C, top).[13] However, this approach relies on the use of pre-functionalized bis-BCP esters. In contrast, an approach that directly utilizes the feedstock chemical [1.1.1]propellane would be more atom- and step-economical. Along these lines, Shenvi reported metal hydride hydrogen atom transfer (MH HAT) to [1.1.1]propellane (**2**), which upon trapping with **7** produced protected amino acid derivative **8** in 48% yield and >20:1 d.r.[12] (Scheme 1C, bottom). Despite the pioneering efforts of Baran and Shenvi, neither work provides broad access to α-chiral BCP amines. Within this *Letter*, we detail the application of MH HAT to a general synthesis of stereoenriched BCP benzylamines, which required substantial reworking of the reported conditions for MH HAT to **2**. We merge MH HAT catalysis with stereoselective sulfinimine addition to access enantioenriched BCP benzylamines via simple deprotection of diastereoenriched BCP sulfinamide products **9** (Scheme 1D). Downstream functionalization of the products is demonstrated and preliminary mechanistic evidence for a competitive side reaction pathway is discussed.

Table 1. Optimization of the MH HAT reaction



Entry	Ar'	Mol % [Mn]	Silane (equiv)	Solvent	T (h)	Conv. (%)	% product AY
1[a]	4-Me-C_6H_4 (**10**)	2	$PhSiH_3$ (1)	DCM/Et_2O/*i*-PrOH (1:1:1)	24	54	36, 2.5:1 d.r.
2[a]	2,4,6-tri-iPr-C_6H_2 (**12**)	2	$PhSiH_3$ (4)	DCM/Et_2O/*i*-PrOH (1:1:1)	24	58	44
3[a,b]	Mesityl (**1a**)	2	$PhSiH_3$ (4)	DCM/Et_2O/*i*-PrOH (1:1:1)	20	70	30
4[c]	Mesityl	2	$PhSiH_3$ (4)	DCM/Et_2O/*i*-PrOH (1:1:1)	24	90	49
5[a,b]	Mesityl	2	Ph(O*i*Pr)SiH_2 (4)	DCM/Et_2O/*i*-PrOH (1:1:1)	18	30	12
6[b]	Mesityl	2	Ph(O*i*Pr)SiH_2 (4)	DCM/Et_2O/*i*-PrOH (1:4:1)	24	55	21
7	Mesityl	2	Ph(O*i*Pr)SiH_2 (4)	Et_2O/*i*-PrOH (1:1)	48	94	77
8	Mesityl	2	Ph(O*i*Pr)SiH_2 (3)	Et_2O/*i*-PrOH (1:1)	48	91	81
9[b]	Mesityl	2	Ph(O*i*Pr)SiH_2 (2)	*n*-pentane/*i*-PrOH (1:1)	48	88	71
10	Mesityl	2	$PhSiH_3$ (2)	Et_2O/*i*-PrOH (1:1)	48	81	59
11[e]	Mesityl	2	Ph(O*i*Pr)SiH_2 (3)	Et_2O/*i*-PrOH (1:1)	72	41	21
12[d,e]	**Mesityl**	**4**	**Ph(O*i*Pr)SiH_2 (3)**	**Et_2O/*i*-PrOH (1:1)**	**48**	**95**	**79 (72% IY)**
13[d,e]	Mesityl	8	Ph(O*i*Pr)SiH_2 (3)	Et_2O/*i*-PrOH (1:1)	48	88	80
14[e]	Mesityl	2	Ph(O*i*Pr)SiH_2 (3)	Et_2O	48	38	23

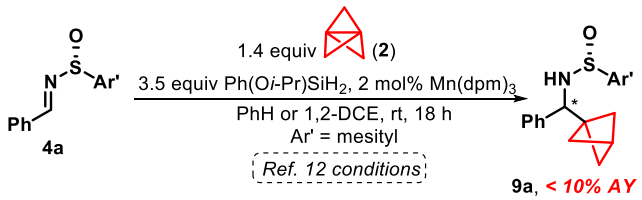
Entries 10–11: Ar' = 4-Me-C_6H_4. Entries 12–13: Ar' = 2,4,6-C_6H_2-*i*Pr. **4a**, **9a**: Ar' = mesityl, 2,4,6-tri-Me-C_6H_2. All reactions on 0.05 mmol scale and d.r. >20:1, unless otherwise noted. (a) Reaction initiated and run at 0 °C. (b) 4 equiv [1.1.1]propellane. (c) Reaction initiated and run at 10 °C. (d) Reaction initiated at 0 °C by dropwise addition of silane, followed by 10 min stirring, then warmed to rt, stirred 48 h. (e) 0.15 mmol imine

To begin our optimization, we tested Bunker's reported conditions for sequential MH HAT/DBAD trapping of [1.1.1]propellane (**2**).[14] Reaction of **2** with 1 equiv $PhSiH_3$, 2 mol% $Mn(dpm)_3$ catalyst in DCM/*i*-PrOH at 0 °C for 24 h in the presence of enantiopure 4-tolyl sulfinimine **10** produced 36% AY of the desired BCP adduct **11** in 2.5 : 1 d.r. In this case, a significant portion of unreacted starting material remained (Table 1, entry 1). With the goal of improving the d.r., we examined 2,4,6-triisopropylbenzene (TRiP, **12**) and 2,4-6-trimethylbenzene (mesityl, **1a**) sulfinimine derivatives, which

gave 44% and 30% AY of **13** and **9a**, respectively, each in >20 : 1 d.r. (entries 2 and 3). However, reaction mixtures derived from TRiP sulfinimine **12** were challenging to purify, leading us to pursue further optimization with mesityl derivative **1a**. Additionally, we tested the Ellman sulfinimine (Ar' = *t*-Bu), which is desirable from a cost perspective, but this substrate gave a complex mixture and no desired BCP adduct. While raising the reaction temperature from 0 °C to 10 °C improved the AY to 49%, most of **1a** had been consumed with much of the mass balance being unaccounted for. We next examined the role of the silane in the reaction. Notably, we found that replacing $PhSiH_3$with isopropoxy(phenyl)silane ($Ph(OiPr)SiH_2$) led to an overall improvement in mass balance (12% AY with 70% **1a** recovered, entry 5).[15] Performing the reaction at room temperature and increasing the concentration from 0.1 M to 0.4 M improved the yield to 21% (entry 6). To address this sluggish reactivity, the reaction time was extended to 48 h, which offered a dramatic improvement to 77% AY (entry 7). Additional experiments showed the role of organic cosolvent (DCM, *n*-pentane) had little effect on the reaction outcome. Further evaluation revealed 3 equiv $Ph(OiPr)SiH_2$ to be optimal (81% AY, entry 8) when compared to the use of 2 equiv. (71% AY, entry 9). The improved reactivity of $Ph(OiPr)SiH_2$ vs. $PhSiH_3$ was confirmed when the latter was evaluated under these more optimized conditions and delivered the product in a lower 59% AY (entry 10).

At this stage of optimization, we applied our optimal conditions (Table 1, entry 8) to a 0.15 mmol scale reaction. Surprisingly, this 3x increase in scale led to a disappointing 21% AY of **9a** with 59% unreacted starting material remaining. Through extensive reevaluation of reaction parameters, we discovered a dependence on the initial reaction temperature and found that dropwise addition of the silane at 0 °C, followed by warming to rt, was critical for reaction success across scales (78% AY, entry 12). Additionally, increasing the catalyst loading from 2 to 4 mol % resulted in the most consistent, reproducible yields. Further increasing catalyst loading to 8 mol% did not improve the yield (entry 13). We confirmed the necessity of *i*-PrOH as a cosolvent in the reaction; omission of *i*-PrOH gave 23% AY **1a** and 62% unreacted SM (entry 14). Poor reactivity in the absence of *i*-PrOH could possibly be explained by low solubility of reaction components (e.g. the metal catalyst) in organic solvents. Throughout the course of optimization, we evaluated other alcohols, including MeOH and *t*-AmOH. These alcohols produced 0% AY of the desired product and, in the case of MeOH, vigorous gas evolution (presumed to be H_2) was observed upon silane addition. This result highlights the importance of the size of the R group of ROH, which has a meaningful impact on the course of the reaction. Lastly, it is important to note that application of Shenvi's previously disclosed literature conditions for MH HAT to [1.1.1]propellane[12] (3.5 equiv $Ph(OiPr)SiH_2$, benzene or 1,2-DCE with no alcohol cosolvent and room temperature silane addition), did not produce any detectable product and returned 95% of unreacted sulfinimine starting material (Scheme 2).

Scheme 2. Application of literature conditions to MH HAT/sulfinimine addition of [1.1.1]propellane

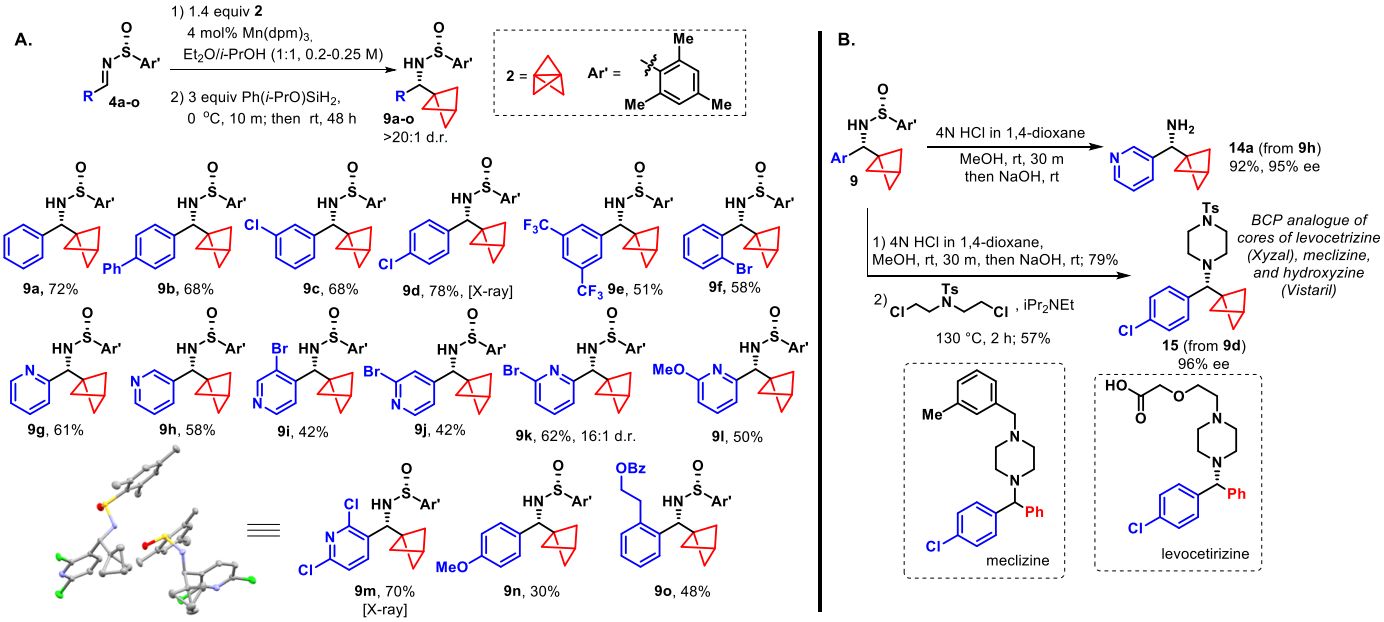


With optimized conditions in hand, we turned to exploration of the reaction scope (Scheme 3A). Electron neutral and electron poor sulfinimines were well-tolerated, producing the desired BCP products as single diastereomers (**9a–f**, 51-77%). Notably, **9f** bears a bulky *ortho*-bromo group, which did not have an adverse effect on the diastereoselectivity of BCP addition. Owing to the importance of nitrogen-containing heterocycles in medicinal chemistry,[16] we were pleased to see a variety of pyridines tolerated, enabling access to 2- and 3-pyridyl BCPs **9g** and **9h** (61 and 58%, respectively). Bromo-substituted pyridines underwent the MH HAT reaction to produce **9i** and **9j** in modest yields of 42% and 44%, respectively. Further substitution of the pyridines was also permitted, as demonstrated by the successful formation of products **9k–m** (50–70%). The 2-halo-pyridine substrates (**9j**, **9k**, **9m**) are of note for their utility in downstream functionalizations (e.g. cross-coupling or S_NAr). Additionally, these activated halides are unlikely to survive the strongly reducing conditions (Ni, Zn) employed by Baran and coworkers[13] and could not be prepared via our previously described racemic azaallyl anion addition chemistry,[3] highlighting the advantages of this MH HAT method to access novel BCP benzylamine building blocks.

Electron-rich substrates, such as **1n** and **1o**, afforded lower yields in the reaction but still produced products as single diastereomers and in yields suitable for medicinal chemistry settings (**9n** and **9o**, 30% and 48%, respectively). Extensive screening of reaction temperature, time, and Lewis acid additives did not further improve the reaction yields for electron rich substrates (see SI). Additionally, unsaturated and aliphatic sulfinimine substrates derived from 4-chloro cinnamaldehyde and isovaleraldehyde were not tolerated, producing only traces of BCP adducts (not depicted). The MH HAT reaction could also be scaled up: in the case of substrate **1d**, scaling to 1.0 mmol of imine produced the product **9d** in 72% yield with excellent d.r. On this scale, the silane was added over a longer period of 90 minutes rather than the typical 3–5 minutes employed on 0.1 mmol scale. This was crucial to obtaining high yields, presumably by minimizing a deleterious exotherm. Lastly, X-ray crystallographic analysis enabled unambiguous assignment of the benzylamine configuration of substrates **9d** and **9m** to each be (*R*). MH HAT to *ent*-**1m** produced *ent*-**9m** in 64% yield, and crystallographic analysis confirmed that the opposite diastereomer was formed (see SI).

BCP sulfinamides **9** are readily deprotected to their enantioenriched BCP benzylamine derivatives, as demonstrated through the conversion of **9h** to **14a** (95% ee) (Scheme 3B, top).

Scheme 3. Scope of the diastereoselective propellylation of sulfinimines and application to drug analogue

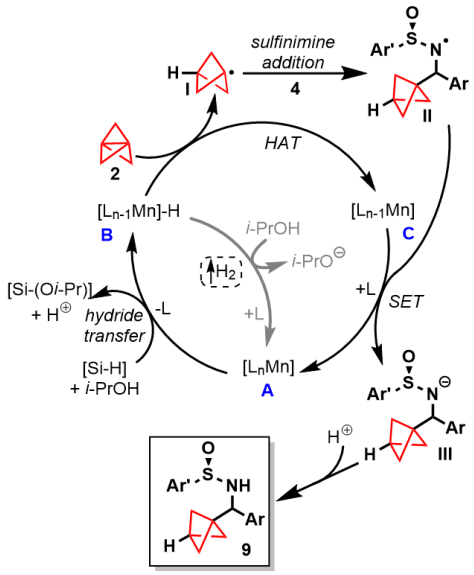


Additionally, 4-Cl-substituted substrate **9c** could be further functionalized to access the core of numerous analogues of important pharmaceuticals, such as levocetirizine, meclizine, and hydroxyzine (Scheme 3B, bottom).[17] Specifically, hydrolysis of **9d** proceeded in 79% yield to form the enantioenriched BCP benzylamine (structure not shown) and subsequent bis-alkylation produced piperazine **15** in 60% yield and 96% ee.

As noted above, slow addition of the silane reagent to a solution held at 0 °C was critical for achieving good yields above 0.05 mmol reaction scale.[18] To explain this phenomenon, we hypothesized that competitive reaction of the Mn–H intermediate with protic sources leads to unproductive consumption of the silane through H_2 evolution. This hypothesis was tested via ^{1}H NMR of a reaction mixture in *i*-PrOH-d_8, which revealed HD gas evolution as a major byproduct (see SI, Figs. S4-S6, for details).[19] We hypothesize that this competitive gas evolution, and thus competitive consumption of the silane, does not occur when the reaction is initiated at lower temperatures.

A possible reaction mechanism is depicted in Figure 1. Catalyst **A** is converted to the manganese hydride **B** via silane methathesis, forming manganese hydride **B** and an alkoxy silane. Hydride **B** engages [1.1.1]propellane in HAT, producing reduced catalyst **C** and the BCP radical **I**. Radical **I** reacts with sulfinimine **4** to produce radical **II**, which is then reduced to anion **III** by **C**, effectively regenerating catalyst **A**.[20] Protonation of **III** produces BCP sulfinamine **9**. We propose the evolution of H_2 to be off-cycle, as the result of protonation of hydride **B** (gray arrows inside cycle), favored by initiating the reaction at room temperature. This proposed H_2 evolution cycle requires no reoxidation of the catalyst and could propagate independently of MH HAT to consume the silane and reduce the yields of the BCP product.[21]

Figure 1. Proposed reaction mechanism



In conclusion, we report a new diastereoselective synthesis of BCP sulfanamines via MH HAT catalysis. These products are readily converted to enantioenriched BCP benzylamines, including medicinally relevant building blocks. The utility of these BCP products was demonstrated through the synthesis of an enantioenriched BCP analogue of a top-selling antihistamine, levocetirizine. Additionally, mechanistic studies indicate an H_2 formation pathway may compete with the MH HAT cycle, necessitating the slow addition of silane to a cooled reaction mixture and reflecting a complex reaction manifold.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data for all new compounds (PDF)

Crystallographic data (.cif)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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(18) See S7 of Supporting Information for Green, S.A.; Huffman, T.R.; McCourt, R.O.; van der Puyl, V., Shenvi, R.A. Hydroalkylation Of Olefins To Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709-7714.

(19) To our knowledge, other reports on the use of Ph(O*i*Pr)SiH_2 as a reductant have not specifically identified H_2 generation as a major competitive pathway, nor do most reactions with Ph(OiPr)SiH_2 require reaction cooling to achieve good yields. Additionally, the observation of HD suggest that H_2 formation does not proceed through a bimolecular interaction of two manganese hydrides, as has been proposed previously; see Green, S.A.; Crossley, S.W.M; Matos, J.L.M.; Vásquez-Céspedes, S.; Shevick, S.L.; Shenvi, R.A. The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628–2640.

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(21) As noted in the optimization above, MeOH as reaction solvent produces vigorous bubbling, while bulkier solvents such as *t*-AmOH produce no reaction. These empirical observations indicate that parameters such as steric profile and acidity of the alcohol are critical for facilitating hydride transfer to the catalyst while avoiding H_2 evolution.