

Communication

Imine Reduction with $\text{Me}_2\text{S-BH}_3$

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Abstract: Although there exists a variety of different catalysts for hydroboration of organic substrates such as aldehydes, ketones, imines, nitriles etc., recent evidence suggests that tetra-coordinate borohydride species, formed by activation, redistribution, or decomposition of boron reagents, are the true hydride donors. We then proposed that $\text{Me}_2\text{S-BH}_3$ could also act as a hydride donor for the reduction of various imines, as similar compounds have been observed to reduce carbonyl substrates. This boron reagent was shown to be an effective and chemoselective hydroboration reagent for a wide variety of imines.

Keywords: hydroboration; synthesis; aldimine; ketimine



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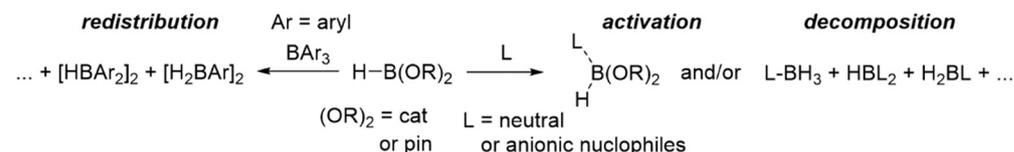
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1. Introduction

Hydroboration can be considered as one of the most powerful methods for reduction of various organic substrates such as aldehydes, ketones, imines, and nitriles under mild reaction conditions [1–3]. Pinacolborane (HBpin) or catecholborane (HBcat) has been predominantly used as the hydroborating agent in these particular transformations, but the boron fragment (i.e., Bcat/Bpin) was normally sacrificed to yield, for example, free alcohols (from carbonyls) or amines (from imines/nitriles). Furthermore, these reduction reactions were mainly performed in the presence of catalytic amounts of a diverse range of (in)organic/organometallic compounds [4–9]. Several of the described hydroboration reactions were efficient as catalyst loadings as low as 0.001 mol%, resulting in excellent substrate conversions [7]. Nevertheless, the exact role of these presumed (pre)catalytic species has been divisive, as several reports provided convincing evidence for the existence of hidden boron catalysis (HBC), i.e., the main role of the species that were introduced in “catalytic” amounts was the formation, via activation, redistribution, or decomposition (Scheme 1) of HBcat/HBpin, of boron-based compounds (e.g., hydroborates and boranes) that then acted as the true catalysts [10–12].



Scheme 1. Observed activation, redistribution and/or decomposition of HBcat/HBpin in presence of nucleophiles (L) or other boranes (BAr_3).

Four-coordinate borohydride compounds (e.g., HBR_3^-) were identified to serve as the (pre)catalysts for hydroboration of a hetero-atom containing unsaturated substrates such as aldehydes, ketones and imines [11,12]. This would then suggest that L-BH_3 (L = THF, SMe_2 , NR_3 (R = alkyl), *N*-heterocyclic carbene (NHC), etc.) could not only act as adequate reagents for reduction of these types of substrates but also deliver more cost-effective

hydroboration protocol(s) as certain BH_3 -containing species act as synthetic precursors to HBpin/HBcat [13,14]. However, there appears to be a limited number of published works that use these particular reagents (i.e., L-BH_3) for this specific purpose, with THF- BH_3 being the preferred choice for hydroboration of mainly carbonyl substrates [15–20]. Furthermore, NHC- BH_3 adducts were shown to be adequate reduction agents for $\text{C}=\text{X}$ fragments ($\text{X}=\text{N}$, O , etc.), but an addition of an activator (e.g., silica gel, *p*-toluenesulfonic acid) was required [21,22]. The presence of protic activators (e.g., Al_2O_3) and/or protic solvent media (e.g., MeOH) were also required for efficient reduction of these substrates with, for example, NaBH_4 and NaBH_3CN [23–27]. Lastly, although ammonia borane ($\text{NH}_3\text{-BH}_3$) has been used for reduction of various aldehydes, ketones, imines, etc. [28–31], experimental and computational studies suggested that these particular reduction reactions underwent a concerted (double) hydrogen transfer mechanism [28,31], which is not typical for hydroboration reactions (see below). Therefore, herein we disclose chemoselective hydroboration of imines using solely $\text{Me}_2\text{S-BH}_3$ as the reducing agent in the absence of any activators and/or a protic solvent medium.

2. Results & Discussion

Instead of generating an “optimized” reaction condition with one of the examined imines and then implementing this procedure for the rest of the substrates, we decided to optimize each transformation in order to maximize the substrate conversions. Thus, the reactions were screened by varying the amount of $\text{Me}_2\text{S-BH}_3$ and the reaction temperature while the reactants were mixed in about 1 mL of CDCl_3 in a sealed J. Young NMR tube. The most important outcomes and observations are summarized in Table 1. In a vast majority of examined transformations, heating to 60 °C was necessary to obtain quantitative substrate conversions with $\text{Me}_2\text{S-BH}_3$ loadings varying between 0.75 and 1.50 equiv. For example, most of the reaction mixtures showed negligible reactivity at room temperature, while imine substrates with enhanced steric properties (entries 5 and 6, Table 1) required, in general, 1.50 equiv loadings of $\text{Me}_2\text{S-BH}_3$ with respect to the imine. Reductions of imines that contain a 2,6-disopropylaniline fragment (e.g., entry 5) have been rarely examined, presumably due to low conversions of these particular substrates under the reported reaction conditions [32,33]. Furthermore, reduction of the imines that contained *N*-aryl substituents (entries 4 and 12) required not only a lower $\text{Me}_2\text{S-BH}_3$ loading (e.g., 0.75 vs. 1.10 mmol) but also a shorter reaction time (e.g., 6 vs. 12 h) in comparison to their *N*-alkyl containing analogues (e.g., entries 2 and 3 vs. entry 12). This can be potentially explained by the presence of the resonance structures involving the *N*-aryl fragment pulling the electron density away from the $\text{N}=\text{C}$ fragment and hence allowing hydride transfer to the carbon atom of this fragment (see below). It was then not surprising to observe that the presence of an electron withdrawing group (CF_3) had a rate-enhancing effect (entry 7) while an electron donating group (OMe) had an opposite effect (entry 8). These observations suggested that the rate limiting step for the examined reactions was nucleophilic in nature (i.e., hydride transfer from a B-H fragment to the imine substrate; see below) and not electrophilic (i.e., formation of an imine- BH_3 adduct) [20].

More importantly, according to $^1\text{H-NMR}$ spectroscopy, all reactions resulted exclusively or solely in the anticipated reduction of the $\text{C}=\text{N}$ double bond. This was particularly important for the reduction of the imine substrates that also contained an alkenyl group (i.e., α,β -unsaturated imines; entries 13 and 14, Table 1). Quantitative substrate conversions with excellent chemoselectivities (>98%) were achieved with these particular imines, while, at the same time, generating the fastest reaction rates among the examined substrates, despite the transformations performing at -78 °C (for the selectivity purposes). Lastly, according to the results summarized in Table 1, it appeared that this reduction protocol favored, in terms of reaction rates, ketimines over aldimines, which is not typically observed in the literature [10,32–45]. At the moment, the precise reason(s) for this observation is(are) not known but it may suggest that the electrophilic step i.e., coordination of imine to BH_3

(see below) was rate determining, as one would expect that the hydride transfer (i.e., the nucleophilic step) would be less favored for ketimines over aldimines.

Table 1. Summary of reaction conditions to achieve quantitative conversion of imines ¹.

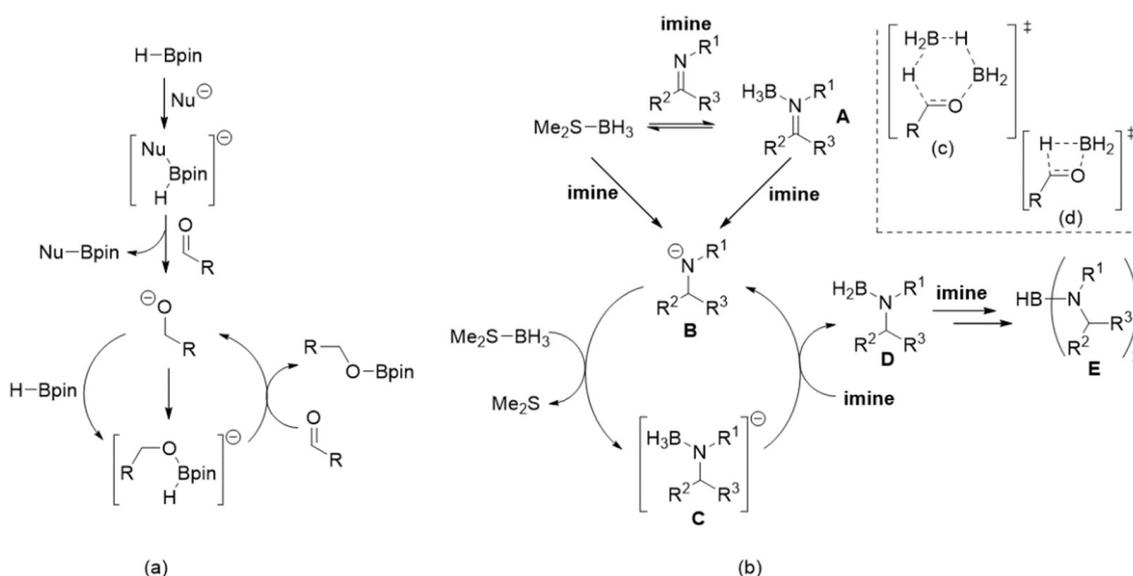
Entry	R ¹	R ²	R ³	Me ₂ S-BH ₃ (Equiv)	Time (h)	Conversion (Isolated Yields)
1 ²	Me	Ph	H	0.75	30	>99% (65%)
2	<i>i</i> Pr	Ph	H	1.10	72	>99% (81%)
3 ³	<i>t</i> Bu	Ph	H	1.10	24	>99% (71%)
4	Ph	Ph	H	0.75	2	>99% (87%)
5 ³	2,6- <i>i</i> Pr ₂ -C ₆ H ₃	Ph	H	1.50	6	>99% (88%)
6	<i>i</i> Pr	2,6-Me ₂ -C ₆ H ₃	H	1.50	12	>99% (84%)
7	<i>i</i> Pr	4-CF ₃ -C ₆ H ₄	H	1.10	30	>99% (76%)
8	<i>i</i> Pr	4-OMe-C ₆ H ₄	H	1.10	96	>99% (80%)
9 ³	<i>i</i> Pr	Ph	Ph	1.10	18	>99% (44%)
10	<i>i</i> Pr	Ph	Me	1.10	6	>99% (61%)
11	<i>i</i> Pr	(CH ₂) ₅		1.10	12	>99% (52%)
12	Ph	(CH ₂) ₅		0.75	6	>99% (81%)
13 ^{3,4}	<i>i</i> Pr	CH=CHPh (trans)	H	0.75	1	>99% (78%)
14 ⁴	<i>i</i> Pr	CH=CHPh (trans)	Me	0.75	1	>99% (65%)

¹ Reactions were performed using 1.0 mmol of imines. ² This reaction was also preformed using 1.0 g (8.4 mmol), resulting in 66% product yield. ³ These reactions were performed at least three times. ⁴ Reaction performed at -78 °C in DCM.

As mentioned in the introduction, catalytic hydroboration of unsaturated C=X fragments (X=O, N, etc., but X≠C) has been a controversial topic. However, there is a significant body of evidence suggesting that four-coordinate B-H containing compound(s) (usually anionic), generated by activation, decomposition, or redistribution of boron reagents, act as initial hydride donors and hence as initiators of catalytically active species [11,12]. Clark and co-workers suggested a mechanism (Scheme 2a) that involved “activation” of HBpin (or HBCat) by coordination of a nucleophile (the electrophilic step), followed by hydride transfer (the nucleophilic step) from boron to the substrate (e.g., aldehyde), to yield the corresponding anion (e.g., alkoxide) [46]. This anion would then bind to another molecule of H-Bpin to generate the catalytically active species (e.g., [HBpin(alkoxy)][−]). Thus, we propose that for reduction of imines with Me₂S-BH₃, initial hydride transfer occurs from either Me₂S-BH₃ or imine-BH₃ (A, Scheme 2b) to produce amide anion B. This anion then displaces Me₂S from Me₂S-BH₃ to generate the catalytically active species C, which acts as a hydride donor to another imine completing the cycle while also yielding reduced species D.

Recently, Abe and Yamataka proposed that reduction of carbonyl compounds using BH₃ (in THF), the first step was H₃B-carbonyl adduct formation (similar to A, Scheme 2b), followed by a hydride transfer step via a BH₃-assisted transition state (Scheme 2c) [20]. However, although a majority of our examined hydroboration reactions require excess Me₂S-BH₃, it was still possible to achieve quantitative imine reduction with sub-stoichiometric amounts (0.75 mol%) of this boron reagent for several transformations (entries 1, 4, 13 and 14; Table 1). This suggested that, at least in certain instances, it was not only possible to reduce more than one imine substrate with one equivalent of Me₂S-BH₃ but also that the

BH_3 -catalysed hydride transfer step (in our case going from **A** to **D**) step was less likely to occur. Furthermore, it was also suggested that the hydride transfer step (e.g., **A** \rightarrow **D** in our case) occurred via a bimolecular transition state (Scheme 2d) [19]. This would help explain our observation that more than one equivalent of imine was reduced by $\text{Me}_2\text{S-BH}_3$ but a recent theoretical study indicated that a similar transition was high in energy [47]. Regardless of the nature of the hydride transfer step(s), it is still important to mention that we identified, via $^{11}\text{B}\{^1\text{H}\}$ -NMR spectroscopy, several proposed intermediates described in Scheme 2b. After mixing $\text{Me}_2\text{S-BH}_3$ and *N*-benzylideneaniline in a 1:1 mol ratio at room temperature for 6 h, it was possible to detect respective intermediates **A** ($\delta_{\text{B}} \sim -9$ (*cis*) and -14 (*trans*) ppm, Figure 1; [48]), **D** ($\delta_{\text{B}} \sim 41$ ppm; [49]) and **E** ($\delta_{\text{B}} \sim 31$ ppm; [50,51]). The fact that unreacted $\text{Me}_2\text{S-BH}_3$ ($\delta_{\text{B}} \sim -20$ ppm) was also present strongly suggested the existence of an equilibrium process between this reagent and intermediate **A** as indicated in Scheme 2b.



Scheme 2. (a) The Clark mechanism; (b) the proposed mechanism for hydroboration of imines with $\text{Me}_2\text{S-BH}_3$; (c) and (d) proposed transition states for the hydride step in reduction of carbonyl compounds.

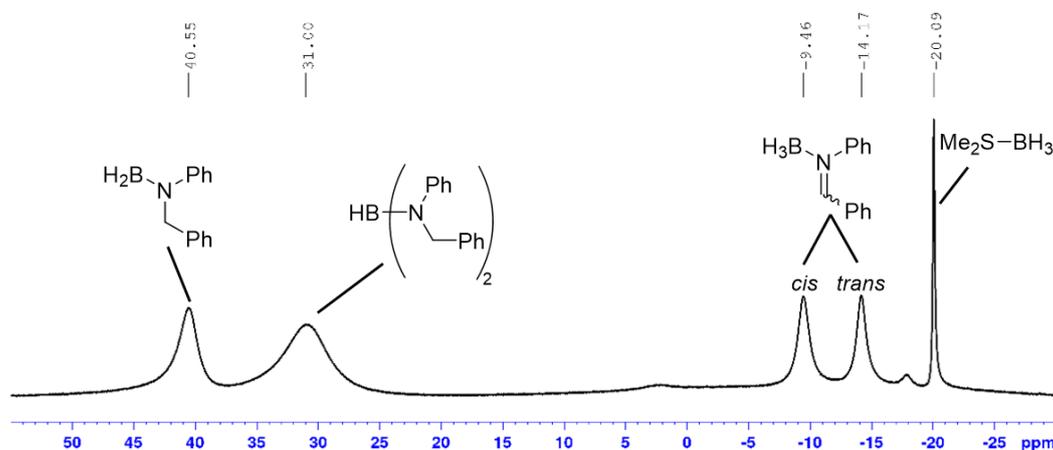


Figure 1. $^{11}\text{B}\{^1\text{H}\}$ -NMR spectrum of a mixture (1:1) between $\text{Me}_2\text{S-BH}_3$ and *N*-benzylideneaniline after 6 h.

In conclusion, we have shown that $\text{Me}_2\text{S-BH}_3$ could also be used for reduction of a number of imines under mild reaction conditions and excellent chemoselectivity control. We have also managed to detect several key intermediates in the overall reaction pathway, which should aid in a better understanding of the overall hydroboration mechanism.

3. Materials and Methods

All imines were synthesized according to the literature reports (Table 2), while Me₂S-BH₃ was purchased from a commercial source and used as received. CDCl₃ was dried by distilling it over CaSO₄, while CH₂Cl₂ was dried by distilling over CaH₂. Reduction of imines was performed using standard Schlenk techniques, while subsequent work-up steps (with MeOH) were performed in on a benchtop.

Table 2. Literature references for the synthesis of the examined imines and spectroscopic data for the corresponding amines.

Entry	R ¹	R ²	R ³	References	
				Synthesis of Imines	Spectroscopic Data for Amines
1	Me	Ph	H	[52]	[53]
2	<i>i</i> Pr	Ph	H	[52]	[37]
3	<i>t</i> Bu	Ph	H	[33,52]	[32]
4	Ph	Ph	H	[33,52]	[37,53]
5	2,6- <i>i</i> Pr ₂ -C ₆ H ₃	Ph	H	[33]	[54]
6	<i>i</i> Pr	2,6-Me ₂ -C ₆ H ₃	H	[52]	[54]
7	<i>i</i> Pr	4-CF ₃ -C ₆ H ₄	H	[55]	[37]
8	<i>i</i> Pr	4-OMe-C ₆ H ₄	H	[52]	[37]
9	<i>i</i> Pr	Ph	Ph	[33,55]	[56]
10	<i>i</i> Pr	Ph	Me	[33]	[57]
11	<i>i</i> Pr	(CH ₂) ₅		[58]	[59]
12	Ph	(CH ₂) ₅		[58]	[59]
13	<i>i</i> Pr	CH=CHPh (trans)	H	[34,52,55]	[34,60]
14	<i>i</i> Pr	CH=CHPh (trans)	Me	[55]	[60]

General procedure for reduction of imines: After 1.0 mmol of an imine (entries 1–12) and Me₂S-BH₃ (amounts according to Table 1) were mixed in a sealed J. Young NMR tube using about 1 mL of CDCl₃, the reaction mixture was left at 60 °C for the time duration indicated in Table 1. For α,β-unsaturated imines (entries 13 and 14), the reactants were mixed in CH₂Cl₂ at −78 °C. After the reaction was completed (via ¹H-NMR spectroscopy), it was quenched with 5 mL of MeOH, followed by removal of all volatiles under reduced pressure. The crude product mixture was then dissolved in 10 mL ethyl acetate, washed three times with 10 mL of water/brine, and dried with MgSO₄. All amine samples were collected as oils after removal of solvent apart from benzylmethylamine (entry 1) and N-benzylaniline (entry 4), which were obtained as solids. The spectroscopic data for all amines matched those reported (Table 2).

Purity was assessed by ¹H and ¹³C[¹H]-NMR spectroscopy and all samples were >95% pure. ¹H (400.2 MHz), ¹³C[¹H] (100.6 MHz), and/or ¹¹B[¹H] (128.6 MHz) NMR spectra of reactions and/or isolated amines in CDCl₃ were recorded on a Bruker Avance III 400.

¹H and ¹³C[¹H]-NMR spectroscopic data for isolated amines (Supplementary Materials):

N-methyl-1-phenylmethanamine (Entry 1): ¹H-NMR (400.2 MHz, CDCl₃): δ 7.31 (m, 2H), 7.25 (m, 3H), 3.86 (s, 2H), 3.05 (s, br, 1H), 2.32 (s, 1H), 2.31 (s, 2H). ¹³C-NMR (CDCl₃, 100.6 MHz): δ 136.5, 136.3, 129.8, 129.5, 128.3, 128.2, 127.7, 127.7, 66.8, 66.2, 48.4, 47.7.

N-benzylpropan-2-amine (Entry 2): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.25 (m, 4H), 7.17 (m, 1H), 3.71 (s, 2H), 2.79 (hept, $^3J = 6.2$ Hz, 1H), 1.57 (s, br, 1H), 1.03 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 140.6, 128.4, 128.2, 126.9, 51.6, 48.1, 22.9.

N-benzyl-2-methylpropan-2-amine (Entry 3): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.25 (m, 4H), 7.15 (m, 1H), 3.66 (s, 2H), 1.11 (s, 9H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 140.1, 127.4, 127.3, 125.8, 49.9, 46.2, 28.0, 27.3.

N-benzylaniline (Entry 4): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.26 (m, 5H), 7.10 (m, 2H), 6.67 (m, 1H), 6.59 (m, 2H), 4.64 (s, br, 1H), 4.25 (s, 2H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 146.4, 137.9, 128.3, 127.6, 126.7, 126.3, 117.1, 112.4, 47.7.

N-benzyl-2,6-diisopropylaniline (Entry 5): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.29 (m, 5H), 7.04 (m, 3H), 4.00 (s, 2H), 3.24 (hept, $^3J = 6.8$ Hz, 2H), 1.16 (d, $^3J = 6.8$ Hz, 12H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 142.9, 128.6, 128.1, 127.5, 123.7, 56.0, 27.8, 24.3.

N-(2,6-dimethylbenzyl)propan-2-amine (Entry 6): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 6.93 (m, 3H), 3.66 (s, 2H), 2.84 (hept, $^3J = 6.2$ Hz, 1H), 2.32 (s, 6H), 1.05 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 135.9, 127.2, 125.9, 48.6, 44.6, 21.9, 18.5.

N-(4-(trifluoromethyl)benzyl)propan-2-amine (Entry 7): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.59 (d, $^3J = 8.0$ Hz, 2H), 7.47 (d, $^3J = 8.0$ Hz, 2H), 3.86 (s, 2H), 2.87 (hept, $^3J = 6.2$ Hz, 1H), 1.78 (s, br, 1H), 1.13 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 144.7, 129.3, 129.0, 128.3, 125.6, 125.3, 122.9, 50.9, 48.2, 22.8.

N-(4-methoxybenzyl)propan-2-amine (Entry 8): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.18 (d, $^3J = 8.4$ Hz, 2H), 6.78 (d, $^3J = 8.4$ Hz, 2H), 3.71 (s, 3H), 3.64 (s, 2H), 2.78 (hept, $^3J = 6.2$ Hz, 1H), 1.66 (s, broad, 1H), 1.02 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 158.6, 132.6, 129.4, 113.8, 55.3, 50.9, 48.0, 22.8.

N-benzhydrylpropan-2-amine (Entry 9): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.21 (m, 10H), 4.89 (s, 1H), 2.67 (hept, $^3J = 6.2$ Hz, 1H), 1.40 (s, br, 1H), 1.00 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 144.5, 128.4, 127.4, 126.9, 64.3, 46.2, 23.1.

N-(1-phenylethyl)propan-2-amine (Entry 10): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.20 (m, 4H), 7.13 (m, 1H), 3.80 (q, $^3J = 6.4$ Hz, 1H), 2.54 (hept, $^3J = 6.2$ Hz, 1H), 1.25 (d, $^3J = 6.4$ Hz, 3H), 0.94 (d, $^3J = 6.2$ Hz, 3H), 0.91 (d, $^3J = 6.2$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 145.1, 127.4, 125.7, 125.4, 54.0, 44.5, 23.8, 23.0, 21.1.

N-isopropylcyclohexanamine (Entry 11): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 2.89 (hept, $^3J = 6.2$ Hz, 1H), 2.43 (m, 1H), 1.81 (m, 2H), 1.65 (m, 2H), 1.54 (m, 2H), 1.10 (m, 4H), 0.97 (d, $^3J = 6.2$ Hz, 6H), 0.95 (m, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 53.5, 44.8, 34.0, 26.2, 25.3, 23.4.

N-cyclohexylaniline (Entry 12): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.08 (t, $^3J = 7.8$ Hz, 2H), 6.55 (m, 3H), 3.75 (br s, 1H), 3.17 (m, 1H), 1.98 (m, 2H), 1.67 (m, 2H), 1.57 (m, 1H), 1.27 (m, 2H), 1.10 (m, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 147.1, 129.3, 117.1, 113, 4, 52.0, 33.4, 25.9, 25.0.

(*E*)-*N*-isopropyl-3-phenylprop-2-en-1-amine (Entry 13): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.24 (m, 5H, Phenyl), 6.50 (d, $^3J = 15.8$ Hz, 1H), 6.29 (dt, $^3J = 15.8$ Hz, $^3J = 6.4$ Hz, 1H), 3.39 (d, $^3J = 6.4$ Hz, 2H), 2.87 (hept, $^3J = 6.2$ Hz, 1H), 1.39 (s, broad, 1H), 1.08 (d, $^3J = 6.2$ Hz, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 137.1, 131.1, 128.6, 128.5, 127.3, 126.2, 48.4, 48.1, 22.9.

(*E*)-*N*-isopropyl-1,3-diphenylprop-2-en-1-amine (Entry 14): $^1\text{H-NMR}$ (400.2 MHz, CDCl_3): δ 7.26 (m, 10H, phenyl), 6.53 (d, $^3J = 15.8$ Hz, 1H), 6.31 (dd, $^3J = 15.8$ Hz, $^3J = 7.3$ Hz, 1H), 4.51 (d, $^3J = 7.3$ Hz, 1H), 2.83 (hept, $^3J = 6.2$ Hz, 1H), 1.11 (d, $^3J = 6.2$ Hz, 3H), 1.08 (d, $^3J = 6.2$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz): δ 143.1, 136.98, 132.9, 130.0, 128.5, 128.4, 127.4, 127.3, 127.1, 126.4, 62.4, 45.6, 23.2, 22.8.

Supplementary Materials: This information is available online. Copies of ^1H and ^{13}C -NMR spectra of isolated amines (Figures S1–S28).

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