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Base-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes – Scope, Limitations and Computational Studies

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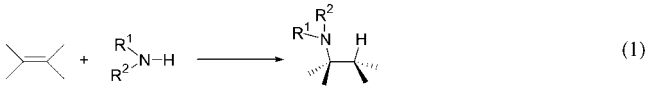
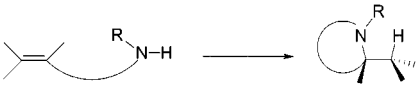
The hydroamination of vinylarenes with primary and secondary amines was studied with catalytic amounts as low as 2 mol-% of $LiN(SiMe_3)_2$/TMEDA. Reactions proceeded readily at 120 °C in the absence of solvent to give selective anti-Markovnikov addition. Slow addition was observed at 25 °C with either electron-deficient *p*-chlorostyrene or secondary cyclic amines such as pyrrolidine, piperidine, or morpholine. Primary amines were prone to a second hydroamination reaction to form tertiary amine byproducts. The selectivity for the mono(hydroamination) products could be improved with a two-fold excess of the amine. $KN(SiMe_3)_2$ showed higher catalytic activity but lower selectivity in comparison to that of $LiN(SiMe_3)_2$, resulting in undesired C–H-activation byproducts. The mechanism of the lithium-catalyzed hydroamination and the influence of TMEDA was studied with density functional theory.

Introduction

The importance of nitrogen-containing compounds in biological systems, as pharmaceuticals and industrially relevant basic and fine chemicals, has led to significant research efforts toward their efficient syntheses. Although many synthetic methods have been devised over the last century, one of the simplest synthetic approaches, hydroamination, has only become the focus of attention with the advent of transition-metal catalysts. The addition of amines to unsaturated carbon–carbon bonds, either in an intermolecular [Equation (1)] or intramolecular [Equation (2)] fashion, generates amines in a waste-free, highly atom-economical manner, starting from simple and inexpensive precursors.[1]



(1)



(2)

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Despite its high synthetic value, hydroamination has found significant attention only in recent years with the development of more efficient transition-metal-based catalyst systems.[2] Although alkali metals have been used as hydroamination catalysts for more than fifty years,[3] the overall number of reports is limited.[1,4] Base-catalyzed hydroamination reactions have been reported predominantly for activated olefins such as vinylarenes and 1,3-dienes,[5] and to some extent, simple unactivated olefins.[6–8] Industrial applications have remained scarce, with one prominent example being the base-catalyzed hydroamination of myrcene with diethylamine as part of the industrial-scale synthesis of (–)-menthol.[5b,9] The anti-Markovnikov addition of amines to vinylarenes leads to β-arylethylamines, which are lead structures for psychodysleptics, strong analgesics, analeptics, antihistaminics, and anorectics (Figure 1).[5e,10–13] However, there have only been a few reports on the scope and limitations of this base-catalyzed process.

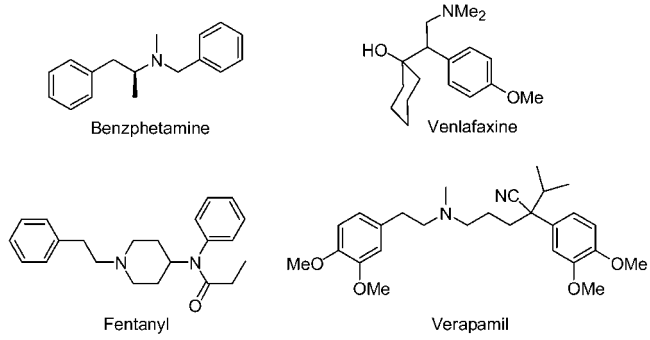


Figure 1. Pharmaceutically active β-arylethylamines.

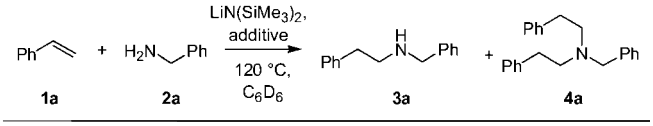
Herein, we wish to report a more detailed investigation on the scope and limitations of the alkali-metal-catalyzed hydroamination of vinylarenes, as well as the influence of additives such as TMEDA on catalyst activity. Furthermore, the mechanism and effect of the additive was studied with computational methods.

Results and Discussion

Scope and Limitations of Alkali-Metal-Catalyzed Hydroamination of Vinylarenes

As a model system for the application of alternative base catalysts, we investigated the reaction of styrene and benzylamine, catalyzed by $LiN(SiMe_3)_2$ in the presence or absence of chelating diamine donor additives such as TMEDA and (–)-sparteine (Table 1). A 1.5:1 styrene/benzylamine mixture was allowed to react at 120 °C in the presence of 2–15 mol-% of precatalyst and a small amount of C_6D_6 as an NMR lock solvent.[14] A slight excess of styrene was employed in these initial experiments in order to compensate for polystyrene formed as a byproduct. It is important to note that hexamethyldisilazane itself did not add to styrene [5 mol-% $LiN(SiMe_3)_2$, 150 °C, 16 h; only the formation of polystyrene was observed].

Table 1. Variation of the base-catalyzed intermolecular hydroamination of styrene and benzylamine.[a]

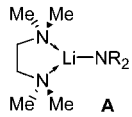


Entry	Catalyst (mol-%)	Additive	**1a/2a**	*t* (h)	Yield (%)[b]	Ratio (**3a/4a**)[c]
1	15	–	3:2	19	51	1.5:1
2	2.5	–	3:2	13	67	2:1
3	2	–	3:2	2	44	1.6:1
4	2	TMEDA	3:2	1	73[d]	2.6:1
5	2	TMEDA	1:1	2.5	62	5:1
6	2	TMEDA	1:2	0.75	67[d]	20:1
7	2	(–)-sparteine	1:1	1.25	74	6:1

[a] Reaction conditions: 2–3 mmol of styrene, 2–4 mmol of amine, and 0.1 mL of C_6D_6 at 120 °C. [b] Determined by GC chromatography with octadecane as an internal standard. [c] Determined by ^1H NMR spectroscopy. [d] Determined by column chromatography.

The reaction gave predominantly the secondary amine mono(adduct) **3a**, as well as the tertiary amine bis(adduct) **4a** as a byproduct. Both hydroamination products were formed exclusively as anti-Markovnikov adducts. The ratio between secondary and tertiary amine could be improved by increasing the amine/styrene ratio (Table 1, Entries 4–6).

The addition of TMEDA or (–)-sparteine resulted in a ligand-accelerated catalytic reaction (Table 1, Entries 4 and 7), in which the formation of a lithium–TMEDA chelate complex, $R_2NLi{\cdot}TMEDA$ (**A**), has been postulated.[6,15–17]



Several substituted vinylarenes were hydroaminated with 2 mol-% of $LiN(SiMe_3)_2$ at 120 °C in a similar fashion with primary (Table 2) or secondary amines (Table 3). Reactions were generally monitored until the vinylarene had been consumed completely; however, in some cases, the isolated yields suffered from the formation of the bis(adduct) and/or formation of poly(vinylarenes).

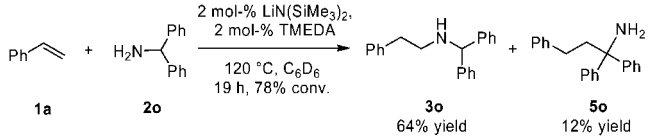
As before, the addition of TMEDA resulted in improved reaction rates and conversions. The reactions could be performed in bulk without additional solvent (Table 2, Entries 8, 10, and 15 and Table 3, Entries 1, 7, and 10).[14] Electron-deficient *p*-chlorostyrene reacted slowly but selectively at room temperature, while catalyst deactivation and low conversion was observed at elevated temperatures. Electron-donating substituents in the vinylarene decreased turnover rates (Table 2, Entry 1 vs. Entries 5 and 9). The effect is opposite for benzylamines, leading to increased rates for *p*-methoxybenzylamine (Table 1, Entry 4 vs. Table 2, Entry 2), especially in the presence of TMEDA. As observed earlier in lithium-catalyzed intermolecular hydroaminations,[5c,5d,5l] the reactions displayed a first-order rate dependence on styrene concentration (see the Supporting Information).

The reaction of 2-vinylnaphthalene with benzylamine required 10 mol-% of $LiN(SiMe_3)_2$/TMEDA and resulted in a 7.5:1 ratio of the mono- and bis(adducts) **3e** and **4e**, respectively (Table 2, Entry 6). However, this ratio improved to 12:1 when the reaction was carried out with a two-fold excess of the amine (Table 2, Entry 7). The addition of benzylamines to α- and β-methylstyrene produced selectively the mono(adducts), though only in moderate yields.

Attempts to perform asymmetric hydroamination reactions with chiral additives have been rather unsuccessful so far. Reactions involving (–)-sparteine[18] or α-isosparteine[18–20] proceeded with slightly slower rates than with TMEDA; however, little or no enantioselectivity was observed (≤ 14% *ee*, see Table 2, Entries 14, 16, 17, 19, and 20). Another commonly applied additive for lithium-catalyzed asymmetric reactions, (*R*,*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline),[20b,21] displayed strong binding to $LiN(SiMe_3)_2$ (as observed by NMR spectroscopy); however, no catalytic hydroamination reaction was observed.

Aniline added rather sluggishly to styrene even at 150 °C (Table 2, Entry 21), but the more nucleophilic *N*-methylaniline reacted faster (Table 3, Entry 10).

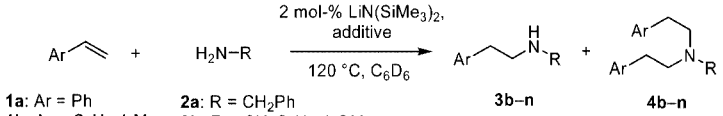
The reaction of styrene with benzhydrylamine (**2o**) in the presence of 2 mol-% of $LiN(SiMe_3)_2$/TMEDA proceeded to 78% conversion at 120 °C within 19 h. However, C–H activation of benzhydrylamine produced a small amount of the primary amine **5o** as a byproduct [Equation (3)].



(3)

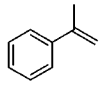
Secondary amines reacted cleanly and efficiently at 120 °C with 5 mol-% of $LiN(SiMe_3)_2$/TMEDA to produce the desired anti-Markovnikov tertiary amines **6a**–**j** in moderate to excellent yields (Table 3).[5j] Loss of product in these cases resulted primarily from polymeric byproducts or catalyst deactivation. The addition of cyclic secondary amines proceeded slowly at 25 °C with significantly improved yields for piperidine and morpholine (Table 3, Entries 2 and 6). It is noteworthy that benzylmethylamine and benzylamine add to styrene at similar rates, despite the increased steric demand of the secondary amine. Note also that dibenzylamine adds significantly more rapidly to styrene than diethylamine, most likely due to the higher volatility of diethylamine under the reaction conditions employed.

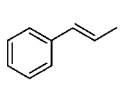
Table 2. $LiN(SiMe_3)_2$-catalyzed intermolecular hydroamination of vinylarenes with primary amines.[a]



1a: Ar = Ph
1b: Ar = C_6H_4-4-Me
1c: Ar = 2-naphthyl
1d: Ar = C_6H_4-4-OMe
1e: Ar = C_6H_4-4-Cl

2a: R = CH_2Ph
2b: R = $CH_2C_6H_4$-4-OMe
2c: R = Ph
2d: R = *n*Pr

1f: 

1g: 

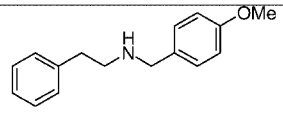
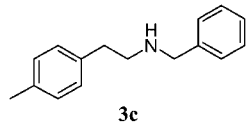
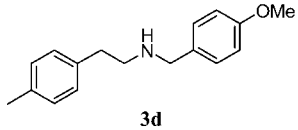
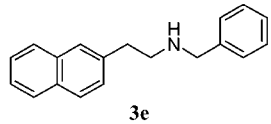
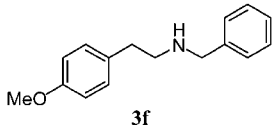
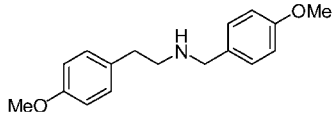
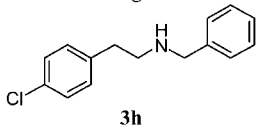
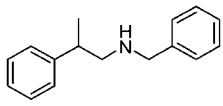
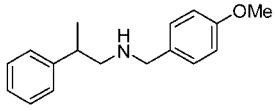
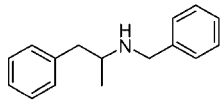
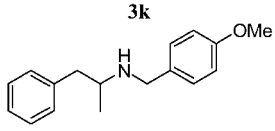
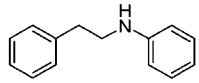
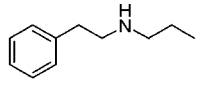
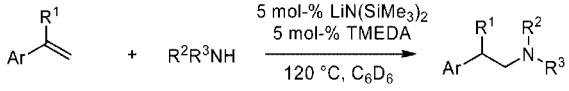
Entry	Alkene	Amine	Additive	*t* (h)	Product **3**	Yield (%)[b]	Ratio (**3**/**4**)[c]
1	**1a**	**2b**[d]	–	2.5	 **3b**	52	2.6:1
2	**1a**	**2b**[d]	TMEDA	0.55		50	2.8:1
3	**1a**	**2b**[e]	TMEDA	1.9		78	13:1
4	**1b**	**2a**	TMEDA	19	 **3c**	54	7:1
5	**1b**	**2b**[d]	–	21	 **3d**	44	4:1
6	**1c**	**2a**	TMEDA[f]	0.83	 **3e**	57	7.5:1
7	**1c**	**2a**[c]	TMEDA[f]	0.75		69	12:1
8	**1d**	**2a**	TMEDA[g]	19	 **3f**	36	3.5:1
9	**1d**	**2b**[d]	–	22	 **3g**	34	1:0
10	**1d**	**2b**	TMEDA[g]	163		29	1:0
11	**1e**	**2a**	TMEDA	1	 **3h**	33	1:0
12	**1e**	**2a**	TMEDA	188[h]		50	1:0

Table 2. *(continued)*

Entry	Alkene	Amine	Additive	*t* (h)	Product **3**	Yield (%)[b]	Ratio (**3**/**4**)[c]
13	**1f**	**2a**	TMEDA	21		48	1:0
14	**1f**	**2a**	(–)-sparteine	37	**3i**	57[i]	1:0
15	**1f**	**2b**	TMEDA[g]	163		38	1:0
16	**1f**	**2b**	(–)-sparteine	65	**3j**	40[i]	1:0
17	**1f**	**2b**	α-isosparteine	70		38[i]	1:0
18	**1g**	**2a**	TMEDA	21		74	1:0
19	**1g**	**2a**	(–)-sparteine	13.5	**3k**	71[i]	1:0
20	**1g**	**2b**	(–)-sparteine	18		60[k]	1:0
					3l		
21	**1a**	**2c**	TMEDA	113		58[l]	1:0
					3m		
22	**1a**	**2d**	TMEDA	5.5		58	4:1
					3n		

[a] Reaction conditions: 2 mmol of vinylarene, 2 mmol of amine, 2 mol-% of $LiN(SiMe_3)_2$, 2 mol-% of additive, and 0.1 mL of C_6D_6 at 120 °C. [b] Isolated yield by column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Vinylarene/amine = 3:2. [e] Vinylarene/amine = 1:2. [f] 10 mol-% of $LiN(SiMe_3)_2$ and 10 mol-% of TMEDA. [g] Using a sealed capillary of C_6D_6. [h] Reaction at 25 °C. [i] Racemic product. [j] 7% *ee*. [k] 14% *ee*. [l] Reaction at 150 °C.

Table 3. Lithium amide catalyzed intermolecular hydroamination of vinylarenes with secondary amines.[a]



1a: Ar = Ph, R^1 = H
1e: Ar = C_6H_4-4-Cl, R^1 = H
1f: Ar = Ph, R^1 = Me

6a–j

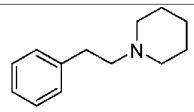
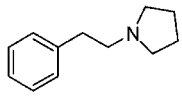
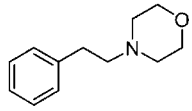
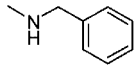
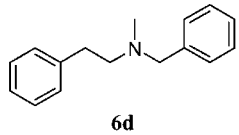
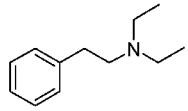
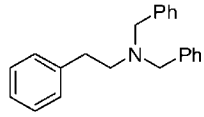
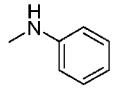
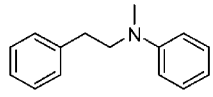
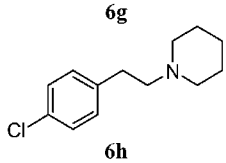
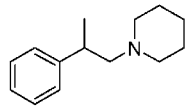
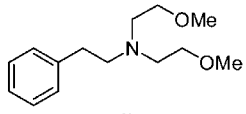
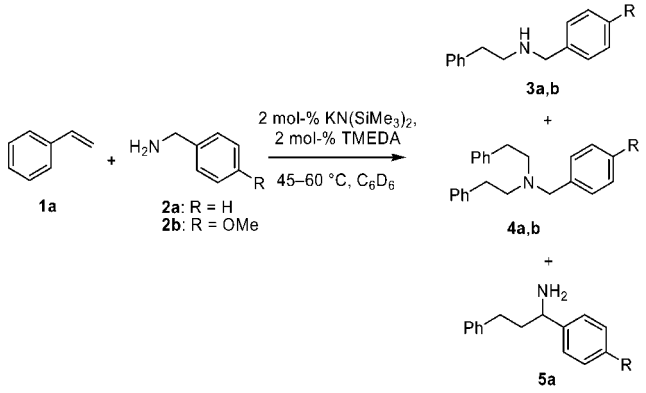
Entry	Alkene	Amine	*t* (h)	Product	Yield (%)[b]
1	**1a**		1[c]		62
2	**1a**		371[d]	**6a**	68
3	**1a**		1.5		82
4	**1a**		107[d]	**6b**	79
5	**1a**		3.2[e]		61
6	**1a**		107[d]	**6c**	96
7	**1a**		1[c]		64
				6d	

Table 3. *(continued)*

Entry	Alkene	Amine	*t* (h)	Product	Yield (%)[b]
8	**1a**	Et_2NH	78	 **6e**	47
9	**1a**	$(PhCH_2)_2NH$	5.5	 **6f**	39
10	**1a**		92[c]	 **6g**	50
11	**1e**		137[e]	 **6h**	36
12	**1f**		48[e,f]	 **6i**	53
13	**1a**	$HN(CH_2CH_2OMe)_2$	5.5	 **6j**	68

[a] Reaction conditions: 2 mmol of vinylarene, 2 mmol of amine, 5 mol-% of $LiN(SiMe_3)_2$, 5 mol-% of TMEDA, and 0.1 mL of C_6D_6 at 120 °C. [b] Isolated yield by column chromatography. [c] Using a sealed capillary of C_6D_6. [d] Reaction at 25 °C. [e] 2 mol-% of $LiN(SiMe_3)_2$ and 2 mol-% of TMEDA. [f] Reaction at 150 °C.

Table 4. $KN(SiMe_3)_2$-catalyzed intermolecular hydroamination of styrene.[a]



Entry	Alkene	Amine	*t* (h)	*T* (°C)	Conversion (%)[b]	Ratio (**3**/**4**/**5**)[b]
1	**1a**	**2a**	1.5	45	99	2.3:1:1.5
2	**1a**	**2b**	16.5	60	99	2:1:0

[a] Reaction conditions: 2 mmol of vinylarene, 2 mmol of amine, 2 mol-% of $KN(SiMe_3)_2$, 2 mol-% of TMEDA, and 0.1 mL of C_6D_6. [b] Determined by ^1H NMR spectroscopy.

The addition of piperidine to α-methylstyrene (Table 3, Entry 12) required a more forcing reaction temperature (150 °C). Although the addition of *N*-methylaniline to styrene (Table 3, Entry 10) proceeded more smoothly than did the addition of aniline (Table 2, Entry 21), the reaction was significantly slower than the addition of more nucleophilic secondary alkylamines.

It has been observed previously that potassium bases commonly exhibit higher reactivity in base-catalyzed hydroamination reactions.[5e] Indeed, $KN(SiMe_3)_2$/TMEDA displayed improved catalytic activity in the intermolecular hydroamination of styrene (Table 4) than did $LiN(SiMe_3)_2$/TMEDA, and reactions could be performed under milder reaction conditions. However, selectivity towards the secondary amine products **3a**,**b** decreased, and a significant amount of the C–H activation byproduct **5a** was formed (Table 4, Entry 1).

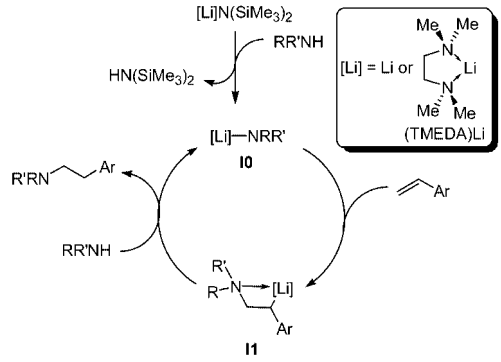
Computational Study of the Catalytic Cycle

The proposed catalytic cycle for the base-catalyzed hydroamination of vinylarenes is based on an ionic mecha-

nism (Scheme 1).[1,4] Alkali metals, their alkyl and aryl salts, hydrides, and amides deprotonate the reacting amine to give strongly nucleophilic metal amides (**I0**), which can add to the olefin more easily. Nevertheless, the activation energy for this step is large due to the unfavorable interaction between the nitrogen lone pair and the π-system of the alkene. The resulting polar (2-aminoalkyl)metal complexes (**I1**) are highly reactive and form the product immediately upon protonation by the starting amine, regenerating the metal amide.

There are several thermodynamic and kinetic aspects that restrain the direct nucleophilic addition of amines across C–C multiple bonds.[1a,1b] One of them is low exothermicity, and these reactions are sometimes even thermoneutral.

In this study, the lithium-catalyzed addition of benzylamine to styrene was investigated in the presence and absence of TMEDA with DFT methods. As noted above, the catalytic cycle of our reaction begins with [Li]NHBn (**I0**), which is generated from $[Li]N(SiMe_3)_2$ and benzylamine by



Scheme 1.

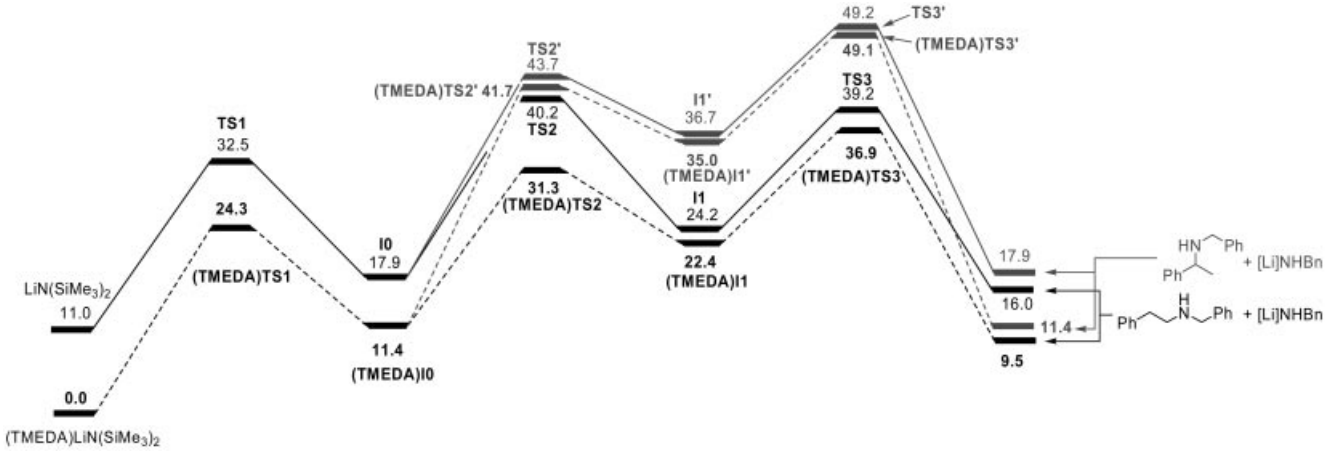
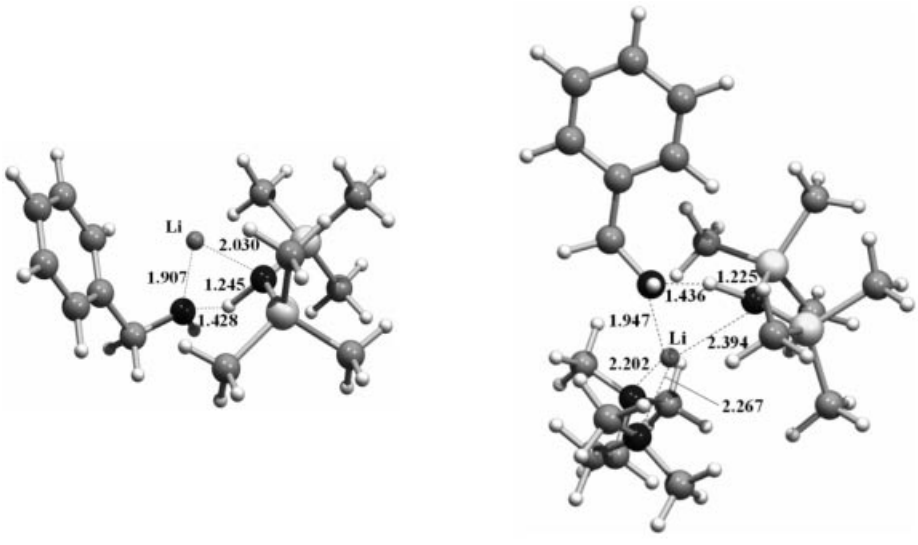


Figure 2. Gibbs energy profile in benzene solution for the catalytic anti-Markovnikov hydroamination of styrene with benzylamine, catalyzed by $LiN(SiMe_3)_2$ (solid line) or $(TMEDA)LiN(SiMe_3)_2$ (dashed line). The relative Gibbs energies at 298.15 K and 1 mol L^{-1} in kcal mol^{-1} are given. The corresponding profile for the Markovnikov addition is given in grey.



TS1 **(TMEDA)TS1**

Figure 3. Transition states [**TS1** and **(TMEDA)TS1**] for the lithium/proton exchange between $LiN(SiMe_3)_2$ and benzylamine in the absence (left) and presence of TMEDA (interatomic distances in Å).

proton/lithium exchange (Scheme 1). Taking this into account, the whole catalytic cycle has been found slightly exergonic (Figure 2), in agreement with results found previously.[1a,1b]

The calculated Gibbs energy profile for the hydroamination reaction of styrene with benzylamine with either LiN(SiMe$_3$)$_2$ or the TMEDA adduct (TMEDA)LiN(SiMe$_3$)$_2$ as the catalyst is depicted in Figure 2. The global process involves three elementary steps. The first consists of a proton transfer from benzylamine to [Li]N(SiMe$_3$)$_2$ {[Li] = Li or (TMEDA)Li} to form [Li]NHBn and HN(SiMe$_3$)$_2$. In the second step, [Li]NHBn undergoes nucleophilic attack on styrene to form the intermediate **I1**. This nucleophilic attack can be Markovnikov or anti-Markovnikov and determines the regioselectivity of the process. Both possibilities have been studied in the Gibbs energy profile of Figure 2, and it is observed that anti-Markovnikov structures are more stable than the Markovnikov ones in all cases. Thus,

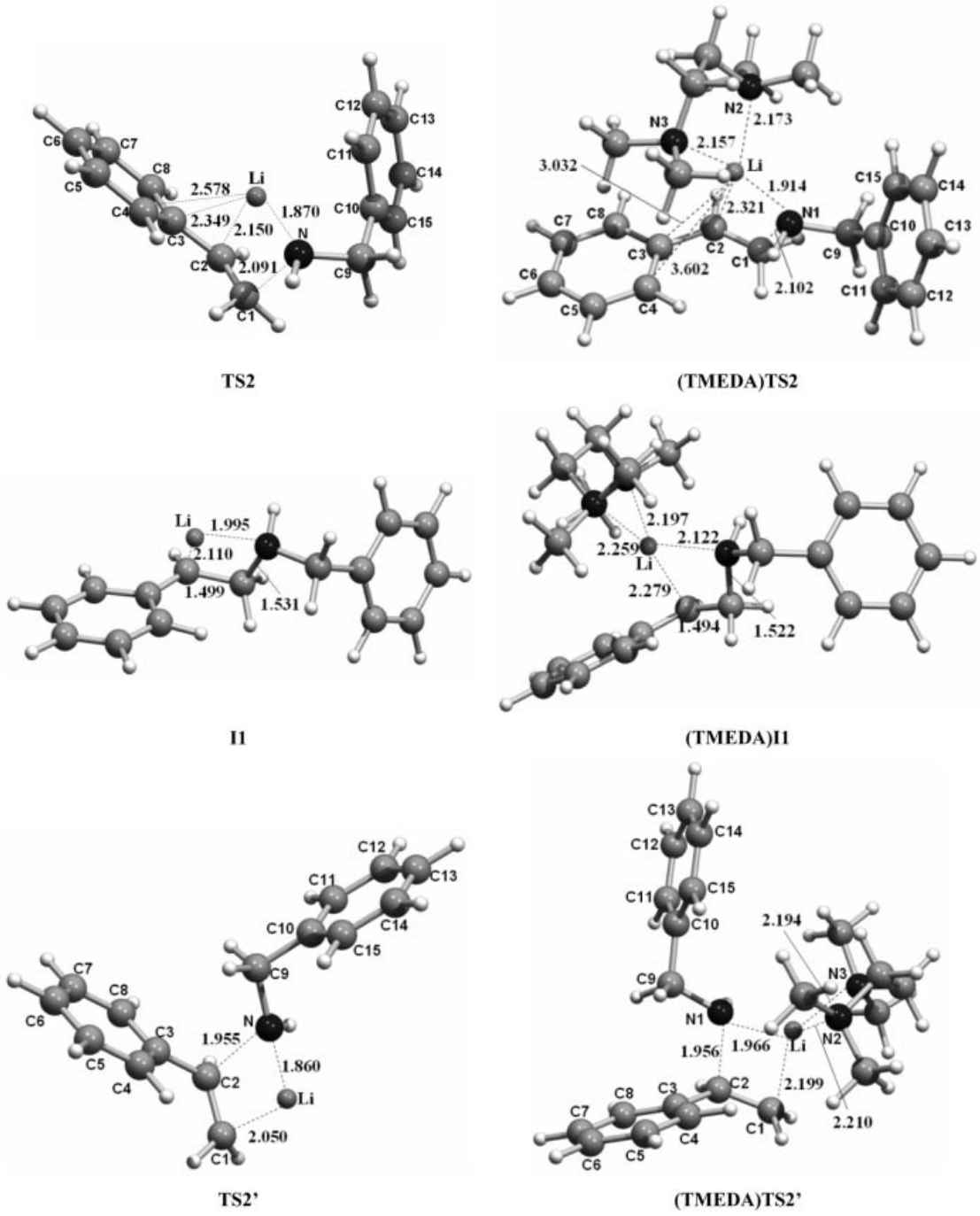


Figure 4. Transition states [**TS2** and **(TMEDA)TS2**] of the anti-Markovnikov nucleophilic attack of the lithium amide on styrene (top) as well as the resulting anti-Markovnikov intermediates [**I1** and **(TMEDA)I1**] formed in this attack (center). The transition states for the Markovnikov nucleophilic attack [**TS2′** and **(TMEDA)TS2′**] are depicted in the bottom row (all interatomic distances in Å).

the discussion below will be mainly based on the anti-Markovnikov pathway. The third and final step involves an exchange of lithium in **I1** by a proton from free benzylamine, releasing the hydroamination product and regenerating the lithium benzylamide catalyst. The coordination by TMEDA stabilizes all stationary points.

The first step is endergonic and involves the late transition states **TS1** and **(TMEDA)TS1**, respectively (Figure 3). The proton of benzylamine has already been transferred to the nitrogen atom of [Li]N($SiMe_3$)$_2$, whereas the lithium cation is halfway between both nitrogen atoms. The N–H distances are similar for both transition states, while the Li–N distances are larger for **(TMEDA)TS1** than they are for **TS1**.

The nucleophilic attack of [Li]NHBn on styrene is assisted by the lithium cation, as indicated by the coordination of the lithium ion to both reactants observed in the structures of the stationary points corresponding to the transitions states **TS2** and **(TMEDA)TS2** (Figure 4). The resulting intermediates **I1** and **(TMEDA)I1** are stabilized by an intramolecular amine coordination to the lithium ion, thereby increasing the stiffness of the molecule (Figure 4). This second step is also thermodynamically unfavorable, especially in the presence of TMEDA, and has a Gibbs free energy cost of ΔG = 11.0 kcal mol^{-1} (with TMEDA) or ΔG = 6.3 kcal mol^{-1} (in the absence of TMEDA). Thus, the coordination of TMEDA does not seem to have any role from a thermodynamic point of view. Moreover, as observed in Figure 4, TMEDA has almost no effects in the N–C distance since this distance is almost the same in both transition states (2.091 Å in the absence of TMEDA and 2.102 Å in the presence of TMEDA).

As observed in Figure 2, in the absence of TMEDA the activation energies for the transition states **TS1** (21.5 kcal mol^{-1}) and **TS2** (22.3 kcal mol^{-1}) differ by only 0.8 kcal mol^{-1} when looking at the entire process. When considering only the catalytic cycle (involving only **TS2** and **TS3**), the rate-determining step of the catalytic cycle is **TS2**. In the presence of TMEDA, **(TMEDA)TS1** has the largest Gibbs activation energy (24.3 kcal mol^{-1}) in the whole process. However, the rate-determining step considering only the catalytic cycle is the formation of **(TMEDA)TS2** (19.9 kcal mol^{-1}). Therefore, coordination of TMEDA decreases the Gibbs activation energy for the rate-determining step by 2.4 kcal mol^{-1} for the formation of **(TMEDA)TS2** versus that for **TS2**.

In the third and final step, the hydroamination product is formed in another proton/lithium exchange reaction, in which benzylamine acts as an acid. We have also considered the possibility that **I1** is protonated by HN($SiMe_3$)$_2$, formed in the first step, instead of benzylamine. This process is thermodynamically more favorable (ΔG = –15.1 kcal mol^{-1}) than the protonation involving benzylamine (ΔG = –8.2 kcal mol^{-1}). However, the Gibbs activation energies for the reactions of **I1** and **(TMEDA)I1** with HN($SiMe_3$)$_2$ are $\Delta G^{\ddagger}$ = 20.9 kcal mol^{-1} and $\Delta G^{\ddagger}$ = 24.8 kcal mol^{-1}, respectively. These Gibbs activation energies are clearly larger than those corresponding to protonation by benzylamine ($\Delta G^{\ddagger}$ = 15 kcal mol^{-1} and $\Delta G^{\ddagger}$ = 14.5 kcal mol^{-1}), which is due to the large steric congestion in the transition state of the proton transfer involving HN($SiMe_3$)$_2$. Therefore, kinetic control predominates in this process over thermodynamic control, and the proton is transferred from benzylamine via the transition state depicted in Figure 5. From a thermodynamic point of view, this last step is more favorable in the presence of TMEDA (ΔG = –12.9 kcal mol^{-1}) than in the absence of TMEDA (ΔG = –8.2 kcal mol^{-1}). From a kinetic point of view, coordination of TMEDA decreases the Gibbs activation energy by only 0.5 kcal mol^{-1} (Figure 2). The most important geometrical parameters for the transition state are the C–H distance, which is shorter by 0.083 Å in the presence of TMEDA (1.469 Å vs. 1.552 Å, Figure 5), and the C–Li distance, which is longer in the absence of TMEDA (2.985 Å vs. 3.275 Å).

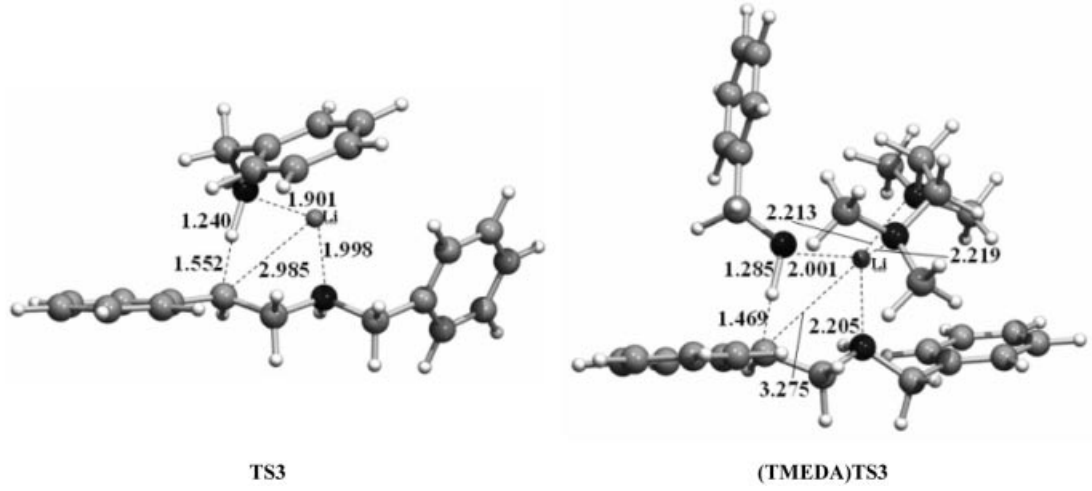


Figure 5. Transition states [**TS3** and **(TMEDA)TS3**] for the lithium/proton exchange between **I1** and **(TMEDA)I1**, respectively, and benzylamine in the absence (left) and presence of TMEDA (right). Interatomic distances are given in Å.

Regioselectivity of Base-Catalyzed Hydroamination of Vinylarenes

One important aspect of base-catalyzed hydroamination of vinylarenes is the high anti-Markovnikov regioselectivity observed.[22] The regioselectivity is determined in the second step of the global process involving the addition of [Li]-$NHCH_2Ph$ (**I0**) to styrene. Therefore, the bonding of the lithium ion was analyzed through Wiberg indexes[23] for the anti-Markovnikov and Markovnikov transition states **TS2** and **TS2′** (see Figure 4) and were evaluated with the natural bond orbital (NBO)[24] method.

All Markovnikov stationary points (Figure 2, grey profile) are higher in energy than the corresponding anti-Markovnikov points (Figure 2, black profile) in the presence of TMEDA (dashed lines) as well as in the absence of TMEDA (solid lines). In the nucleophilic attack, the lithium ion has a tendency to interact with the aromatic ring of styrene in the anti-Markovnikov transition state **TS2** in the absence of TMEDA (Figure 4, top), as confirmed by the bond-order values for Li–C3 (0.0134) and Li–C4 (0.0133), which are similar to the bond-order value of Li–C2 (0.0181).[25] The Markovnikov transition state **TS2′** (Figure 4, bottom), on the other hand, shows significantly larger distances between lithium and the aromatic ring carbon atoms, and the bond orders are smaller due to the orientation of the system. Coordination of TMEDA to the lithium ion in the anti-Markovnikov transition state **(TMEDA)TS2** and the Markovnikov transition state **(TMEDA)TS2′** (Figure 4) results in longer Li–C(aryl) distances and reduced bond orders in comparison to **TS2** and **TS2′**, respectively.

The Gibbs energy difference between **(TMEDA)TS2** and **(TMEDA)TS2′** is 10.4 kcal mol^{-1}, with the anti-Markovnikov transition state **(TMEDA)TS2** being more stable. On the other hand, in the absence of TMEDA the difference between **TS2** and **TS2′** is only 3.5 kcal mol^{-1}. This is due to a solvent effect, because lithium is more accessible to the solvent in **TS2′** than it is in **TS2** (Figure 4). This increased solvent–ion interaction results in a larger electrostatic term and stabilizes **TS2′**. When TMEDA is introduced, the lithium ion is equally accessible in **(TMEDA)TS2** and **(TMEDA)TS2′**, resulting in similar solvent effects for the Markovnikov and anti-Markovnikov transition states. The anti-Markovnikov intermediates **I1** and **(TMEDA)I1** are both ca. 12.5 kcal mol^{-1} more stable than the corresponding Markovnikov intermediates.

In the last step leading to the hydroamination product, the anti-Markovnikov pathway is clearly favored over the Markovnikov one. Both anti-Markovnikov transition states **TS3** and **(TMEDA)TS3** are ca. 10–12 kcal mol^{-1} more stable than the corresponding Markovnikov transition states. On the other hand, the anti-Markovnikov hydroamination product is also favored by 1.9 kcal mol^{-1} over the Markovnikov hydroamination product. Therefore, thermodynamic as well as kinetic factors favor the anti-Markovnikov products, both in the presence and absence of TMEDA.

Conclusions

$LiN(SiMe_3)_2$/TMEDA is a convenient catalyst system for the intermolecular hydroamination of vinylarenes with primary and secondary alkylamines in a 1:1 ratio. Reactions could be performed effectively in the absence of solvent. While reactions generally required elevated temperatures (120 °C), several activated substrates were shown to react at room temperature. Primary amines were prone to a second hydroamination reaction to give tertiary amine byproducts. However, the secondary amine mono(adducts) could be obtained with good selectivity if a two-fold excess of the amine was employed.

Finally, we have investigated the mechanism of the lithium-catalyzed hydroamination of styrene with benzylamine with computational methods. The anti-Markovnikov addition is favored over the Markovnikov pathway both by thermodynamic and kinetic factors governing the regioselectivity-determining addition step of the addition of the lithium amide to the vinylarene. The aromatic ring plays an important role since its interaction with the lithium ion favors the anti-Markovnikov mechanism. Within the catalytic cycle, coordination of TMEDA decreases the Gibbs activation energy for the rate-determining nucleophilic addition step of [Li]NHBn to styrene by 2.4 kcal mol^{-1} in comparison to that of the reaction in the absence of TMEDA. Therefore coordination of TMEDA results in an increase in the rate of the reaction.

Experimental Section

General Considerations: All operations were carried out with standard Schlenk and glove-box inert-gas techniques under dry nitrogen or argon, unless otherwise stated. Hexane was purified by distillation from sodium/triglyme/benzophenone ketyl. Deuterated benzene was dried with sodium/benzophenone ketyl and distilled in vacuo. *n*BuLi (2.5 M in hexanes) and (*R*)-*O*-acetylmandelic acid were used as received. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA), (–)-sparteine, and other commercially available amines and vinylarenes were distilled from finely powdered CaH_2 and were stored over molecular sieves. α-Isosparteine was prepared according to a published procedure.[26] $LiN(SiMe_3)_2$ was prepared by the addition of *n*BuLi to a solution of hexamethyldisilazane in hexane at 0 °C. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker Avance 300 or Avance 400 spectrometer. Mass spectra were recorded with a Micromass Zabspec instrument (FAB, 3-nitrobenzyl alcohol) and Finnigan MAT 95XP instrument (EI) for High Resolution Mass Spectrum. Gas chromatography was conducted with a ThermoQuest Trace GC 2000 (OPTIMA-5, 0.25 μm capillary column, 25 m × 0.32 mm). Elemental analyses were determined with a Carlo Erba EA1110 CHN instrument by the Microanalytical Laboratory of this department.

Typical Catalytic Intermolecular Hydroamination Reactions: In a glove box, a screw-cap NMR tube was charged with the catalyst precursors (0.04 mmol, 2 mol-%), C_6D_6 (0.1 mL or sealed capillary), TMEDA (0.04 mmol, 2 mol-%) or chiral additive (0.04 mmol, 2 mol-%), the olefin (2.0 mmol), and the amine (2.0 mmol). The NMR tube was then placed in a preheated oil bath (25–150 °C), and conversion was monitored by ^1H and ^{13}C NMR spectroscopy. Final conversions were determined by the disappear-

ance of characteristic olefinic signals. Et_2O (ca. 2 mL) was added to the reaction mixture, and the mixture was then filtered through a pad of silica gel to remove polymeric byproducts, and the pad was washed with Et_2O (2 × 2 mL). The solvent was carefully removed in a rotary evaporator to give the crude products. The products were purified by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, or EtOAc/hexane, 4:1).

Benzyl(phenethyl)amine (3a): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.02). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.19 (m, 10 H, aryl-H), 3.80 (s, 2 H, NHCH_2Ph), 2.91 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, PhCH_2CH_2NH), 2.83 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, PhCH_2CH_2NH), 1.52 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.2, 140.0, 128.7, 128.4, 128.3, 128.0, 126.9, 126.1 (aryl), 53.8 (NH*C*H$_2$Ph), 50.5 (PhCH$_2$*C*H$_2$NH), 36.3 (Ph*C*H$_2$CH$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 212 (100) $[M]^+$, 120 (16) $[M - CH_2Ph]^+$. $C_{15}H_{17}N$ (211.31): calcd. C 85.26, H 8.11, N 6.63; found C 85.24, H 7.87, N 6.39. The spectroscopic data are in agreement with previously published data.[51,27]

(4-Methoxybenzyl)(phenethyl)amine (3b): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.02). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.26 (m, 2 H, aryl-H), 7.21–7.18 (m, 5 H, aryl-H), 6.86–6.83 (m, 2 H, aryl-H), 3.78 (s, 3 H, OMe), 3.73 (s, 2 H, NHCH_2Ar), 2.91–2.87 (m, 2 H, PhCH_2CH_2NH), 2.83–2.80 (m, 2 H, PhCH_2CH_2NH), 1.49 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.5, 140.0, 132.4, 129.2, 128.7, 128.4, 126.1, 113.7 (aryl), 55.2 (OMe), 53.2 (NH*C*H$_2$Ar), 50.4 (PhCH$_2$*C*H$_2$NH), 36.3 (PhCH$_2$*C*H$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 242 (50) $[M]^+$, 150 (22) $[M - CH_2Ph]^+$, 136 (16) $[M - CH_2CH_2Ph]^+$, 121 (100) $[M - NHCH_2CH_2Ph]^+$. HRMS (EI): calcd. for $C_{16}H_{19}NO$ 241.1461; found 241.1466. The spectroscopic data are in agreement with previously published data.[51,28]

Benzyl[2-(*p*-tolyl)ethyl]amine (3c): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.06). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.23 (m, 5 H, aryl-H), 7.09 (s, 4 H, aryl-H), 3.80 (s, 2 H, NHCH_2Ph), 2.89 (m, 2 H, MePhCH_2CH_2NH), 2.79 (m, 2 H, MePhCH_2CH_2NH), 2.32 (s, 3 H, CH_3C$_6$H$_4$), 1.34 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.4, 136.9, 135.5, 128.9, 128.6, 128.3, 128.0, 126.8 (aryl), 53.9 (NH*C*H$_2$Ph), 50.7 (ArCH$_2$*C*H$_2$NH), 35.9 (Ar*C*H$_2$CH$_2$NH), 21.0 (*C*H$_3$C$_6$H$_4$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 226 (100) $[M]^+$, 120 (32) $[M - NHCH_2Ph]^+$. HRMS (EI): calcd. for $C_{16}H_{19}N$ 225.1512; found 225.1501.

(4-Methoxybenzyl)[2-(*p*-tolyl)ethyl]amine (3d): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.15).^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.20 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 7.10 (s, 4 H, aryl-H), 6.85 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, aryl-H), 3.79 (s, 3 H, OCH_3), 3.74 (s, 2 H, NHCH_2Ar), 2.88 (m, 2 H, ArCH_2CH_2NH), 2.79 (m, 2 H, ArCH_2CH_2NH), 2.32 (s, 3 H, CH_3C$_6$H$_4$), 1.46 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.5, 136.9, 135.5, 132.4, 129.2, 129.1, 128.5, 113.7 (aryl), 55.2 (OCH_3), 53.2 (NH*C*H$_2$Ar), 50.5 (ArCH$_2$*C*H$_2$NH), 35.8 (Ar*C*H$_2$CH$_2$NH), 21.0 (*C*H$_3$C$_6$H$_4$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 256 (48) $[M]^+$, 121 (100) $[CH_3OC_6H_4CH_2]^+$. $C_{17}H_{21}NO$ (255.36): calcd. C 79.96, H 8.29, N 5.49; found C 79.94, H 8.35, N 5.61.

Benzyl[2-(naphthalen-2-yl)ethyl]amine (3e): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.04). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.77–7.71 (m, 4 H, aryl-H), 7.60 (s, 1 H, aryl-H), 7.43–7.33 (m, 4 H, aryl-H), 7.31–7.17 (m, 3 H, aryl-H), 3.77 (s, 2 H, NHCH_2Ph), 2.95 (s, 4 H, ArCH_2CH_2NH), 1.49 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 140.0, 137.4, 133.5, 132.1, 128.4, 128.1, 127.6, 127.4, 127.3, 127.0, 126.9, 126.9, 125.9, 125.3 (aryl), 53.8 (NH*C*H$_2$Ph), 50.2 (ArCH$_2$*C*H$_2$NH), 36.4 (Ar*C*H$_2$CH$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 262 (100) $[M]^+$, 120 (38) $[M - C_{10}H_7CH_2]^+$. $C_{19}H_{20}ClN$ (**3e**·HCl) (297.83): calcd. C 76.62, H 6.77, N 4.70; found C 76.13, H 6.82, N 4.79.

Benzyl[2-(4-methoxyphenyl)ethyl]amine (3f): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.05). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.22 (m, 5 H, aryl-H), 7.12 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, aryl-H), 6.83 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 3.80 (s, 2 H, NHCH_2Ph), 3.79 (s, 3 H, OCH_3), 2.87 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, ArCH_2CH_2NH), 2.77 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, ArCH_2CH_2NH), 1.42 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.0, 140.3, 132.0, 129.6, 128.4, 128.1, 126.9, 113.9 (aryl), 55.2 (OCH_3), 53.9 (NH*C*H$_2$Ph), 50.8 (ArCH$_2$*C*H$_2$NH), 35.4 (Ar*C*H$_2$CH$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 242 (100) $[M]^+$, 120 (42) $[M - MeOC_6H_4CH_2]^+$. HRMS (EI): calcd. for $C_{16}H_{19}NO$ 241.1461; found 241.1455.

(4-Methoxybenzyl)[2-(4-methoxyphenyl)ethyl]amine (3g): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.91).^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.18 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 7.09 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 6.82 (m, 4 H, aryl-H), 3.78 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.72 (s, 2 H, NHCH_2Ar), 2.84 (m, 2 H, ArCH$_2$CH_2NH), 2.75 (m, 2 H, ArCH_2CH$_2$NH), 1.41 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.6, 158.0, 132.5, 132.1, 129.6, 129.2, 113.8, 113.7 (aryl), 55.2 (OCH_3), 53.3 (NH*C*H$_2$Ar), 50.7 (ArCH$_2$*C*H$_2$NH), 35.4 (Ar*C*H$_2$CH$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 272 (15) $[M]^+$, 121 (100) $[MeOC_6H_4CH_2]^+$. $C_{17}H_{21}NO_2$ (271.36): calcd. C 75.25, H 7.80, N 5.16; found C 75.71, H 7.54, N 4.91.

Benzyl[2-(4-chlorphenyl)ethyl]amine (3h): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.04).^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.21 (m, 7 H, aryl-H), 7.12 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, aryl-H), 3.79 (s, 2 H, NHCH_2Ph), 2.88 (m, 2 H, PhCH_2CH_2NH), 2.79 (m, 2 H, PhCH_2CH_2NH), 1.32 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.2, 138.5, 131.9, 130.0, 128.5, 128.4, 128.0, 126.9 (aryl), 53.8 (NH*C*H$_2$Ph), 50.3 (ArCH$_2$*C*H$_2$NH), 35.7 (Ar*C*H$_2$CH$_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 246 (100) $[M]^+$, 154 (52) $[M - CH_2Ph]^+$, 120 (85) $[M - ClC_6H_4CH_2]^+$. $C_{15}H_{16}ClN$ (245.75): calcd. C 73.31, H 6.56, N 5.70; found C 73.48, H 6.49, N 5.89.

Benzyl(2-phenylpropyl)amine (3i): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.02). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 4 H, aryl-H), 7.22 (m, 6 H, aryl-H), 3.77 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H, NCH_2Ph), 3.72 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H, NCH_2Ph), 3.01–2.93 (m, 1 H, PhCH(CH$_3$)CH$_2$NH), 2.79 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H, PhCH(CH$_3$)-CH_2NH), 1.36 (br. s, 1 H, NH), 1.25 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 145.3, 140.4, 128.5, 128.3, 128.0, 127.4, 127.2, 126.8, 126.3 (aryl), 56.3 (NH*C*H$_2$Ph), 53.8 (PhCH(Me)*C*H$_2$NH), 40.0 (Ph*C*H(Me)-CH$_2$NH), 20.1 (CH_3) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 226 (100) $[M]^+$. The spectroscopic data are in agreement with previously published data.[29]

(4-Methoxybenzyl)(2-phenylpropyl)amine (3j): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.53). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 2 H, aryl-H), 7.24 (m, 3 H, aryl-H), 7.18 (d, $^3J_{H,H}$ =

8.6 Hz, 2 H, aryl-H), 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 3.82 (s, 3 H, OCH_3), 3.75 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, NHCH_2Ar), 3.70 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, NHCH_2Ar), 3.00 (m, 1 H, PhCH(CH_3)-CH_2NH), 2.81 (d, $^3J_{H,H}$ = 4.5 Hz, 2 H, PhCH(CH_3)CH_2NH), 1.45 (br. s, 1 H, NH), 1.29 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.5, 145.4, 132.4, 129.1, 128.5, 127.2, 126.3, 113.7 (aryl), 56.2 (NHCH$_2$Ar), 55.2 (OCH_3), 53.2 (PhCH(CH_3)CH$_2$NH), 40.0 (PhCH(CH_3)CH_2NH), 20.1 (CH_3) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 256 (18) $[M]^+$, 121 (100) $[CH_3OC_6H_4CH_2]^+$. $C_{17}H_{21}NO$ (255.36): calcd. C 79.96, H 8.29, N 5.49; found C 80.00, H 8.01, N 5.42.

Benzyl(1-methyl-2-phenylethyl)amine (3k): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.02). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.15 (m, 10 H, aryl-H), 3.85 (d, $^2J_{H,H}$ = 13.3 Hz, 1 H, NCH_2Ph), 3.74 (d, $^2J_{H,H}$ = 13.3 Hz, 1 H, NCH_2Ph), 3.01–2.90 (m, 1 H, PhCH_2CH(CH_3)-NH), 2.78 (m, 1 H, PhCH_2CH(CH_3)NH), 2.65 (m, 1 H, PhCH_2CH(CH_3)NH), 1.63 (br. s, 1 H, NH), 1.10 (d, $^3J_{H,H}$ = 6.2 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.4, 139.4, 129.3, 128.3, 127.9, 126.8, 126.1 (aryl), 53.7 (NHCH$_2$Ph), 51.2 (PhCH$_2$$C$H($CH_3$)NH), 43.5 (Ph$CH_2$CH($CH_3$)NH), 20.2 ($CH_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 226 (100) $[M]^+$, 134 (52) $[M - CH_2Ph]^+$. The spectroscopic data are in agreement with previously published data.[5h,13c]

(4-Methoxybenzyl)(1-methyl-2-phenylethyl)amine (3l): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.42). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 2 H, aryl-H), 7.23 (m, 1 H, aryl-H), 7.17 (m, 4 H, aryl-H), 6.84 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, aryl-H), 3.82 (d, 1 H, NCH_2Ar, obscured by another signal), 3.80 (s, 3 H, OCH_3), 3.69 (d, $^2J_{H,H}$ = 12.9 Hz, 2 H, NHCH_2Ar), 3.00–2.92 (m, 1 H, PhCH$_2$CH(CH_3)NH), 2.79 (m, 1 H, PhCH_2CH(CH_3)NH), 2.66 (m, 1 H, PhCH_2CH(CH_3)NH), 1.51 (br. s, 1 H, NH), 1.11 (d, $^3J_{H,H}$ = 6.2 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.5, 139.4, 132.6, 129.1, 129.0, 128.3, 126.1, 113.7 (aryl), 55.2 (OCH_3), 53.6 (PhCH$_2$$C$H($CH_3$)NH), 50.6 (NH$CH_2$Ar), 43.5 (Ph$CH_2$CH($CH_3$)-NH), 20.1 ($CH_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 256 (38) $[M]^+$, 121 (100) $[CH_3OC_6H_4CH_2]^+$. $C_{17}H_{21}NO$ (255.36): calcd. C 79.96, H 8.29, N 5.48; found C 79.87, H 8.38, N 5.42. The spectroscopic data are in agreement with previously published data.[13d]

(Phenethyl)phenylamine (3m): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.65). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.34 (m, 2 H, aryl-H), 7.29–7.20 (m, 5 H, aryl-H), 6.75 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, aryl-H), 6.65 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, aryl-H), 3.69 (br. s, 1 H, NH), 3.43 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, PhCH$_2$CH_2N), 2.95 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, PhCH_2CH$_2$N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 147.9, 139.3, 129.2, 128.7, 128.5, 126.4, 117.4, 112.9 (aryl), 45.0 (PhCH$_2$$CH_2$N), 35.5 (Ph$CH_2CH_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 198 (98) $[M]^+$, 197 (100) $[M - H]^+$. The spectroscopic data are in agreement with previously published data.[12b,13b]

(Phenethyl)propylamine (3n): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.1). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.21–7.15 (m, 2 H, aryl-H), 7.11–7.08 (m, 3 H, aryl-H), 2.77 (m, 2 H, PhCH$_2$CH_2NH), 2.70 (m, 2 H, PhCH_2CH$_2$NH), 2.48 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, NHCH_2CH$_2$CH$_3$), 1.43–1.33 (m, 2 H, NHCH$_2$CH_2CH$_3$), 1.00 (br. s, 1 H, NH), 0.78 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, NHCH$_2$CH$_2$CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.2, 128.7, 128.4, 126.1 (aryl), 51.8 (CH_2NH), 51.2 (CH_2NH), 36.5 (PhCH$_2$), 23.2 (NHCH$_2$$CH_2CH_3$), 11.8 (NHCH$_2CH_2$$CH_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 164 (100) $[M]^+$. $C_{11}H_{17}N$ (163.26): calcd. C 80.93, H 10.50, N 8.58; found C 80.77, H 10.28, N 8.39. The spectroscopic data are in agreement with previously published data.[11]

(Benzhydryl)(phenethyl)amine (3o): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.45). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.34 (m, 4 H, aryl-H), 7.28–7.24 (m, 6 H, aryl-H), 7.20–7.16 (m, 5 H, aryl-H), 4.82 (s, 1 H, NHCHPh$_2$), 2.84–2.80 (s, 4 H, PhCH_2CH_2NH), 1.57 (br. s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 144.1, 140.1, 128.7, 128.43, 128.37, 127.2, 126.9, 126.0 (aryl), 67.3 (NHCHPh$_2$), 49.3 (PhCH$_2$$CH_2$NH), 36.5 (Ph$CH_2CH_2$NH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 288 (22) $[M]^+$, 210 (10) $[M - Ph]^+$, 167 (100) $[M - NHCH_2CH_2Ph]^+$. $C_{21}H_{21}N$ (287.40): calcd. C 87.76, H 7.36, N 4.87; found C 87.76, H 7.41, N 4.78.

Benzylbis(phenethyl)amine (4a): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.09). Isolated yield: 21% (based on the amine for Table 1, Entry 4). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.29–7.12 (m, 10 H, aryl-H), 3.73 (s, 2 H, NCH_2Ph), 2.79 (s, 8 H, PhCH_2CH_2N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.6, 139.6, 128.8, 128.7, 128.3, 128.1, 126.8, 125.8 (aryl), 58.5 (NCH$_2$Ph), 55.7 (PhCH$_2$$CH_2$N), 33.6 (Ph$CH_2CH_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 316 (76) $[M]^+$, 224 (100) $[M - CH_2Ph]^+$. HRMS (EI): calcd. for $C_{23}H_{25}N$ 315.1982; found 315.1950. The spectroscopic data are in agreement with previously published data.[5l]

(4-Methoxybenzyl)bis(phenethyl)amine (4b): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.07). Isolated yield: 20% (based on the amine for Table 2, Entry 2). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28 (t, $^3J_{H,H}$ = 7.4 Hz, 4 H, aryl-H), 7.22–7.18 (m, 4 H, aryl-H), 7.16–7.14 (m, 4 H, aryl-H), 6.84 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 3.82 (s, 3 H, OMe), 3.69 (s, 2 H, NCH_2Ar), 2.80 (s, 8 H, PhCH_2CH_2N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 158.5, 140.6, 131.5, 129.8, 128.8, 128.2, 125.8, 113.5 (aryl), 57.7 (NCH$_2$Ar), 55.4 (OMe), 55.2 (PhCH$_2$$CH_2$N), 33.5 (Ph$CH_2CH_2$N-) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 346 (8) $[M]^+$, 344 (24) $[M - H_2]^+$, 254 (24) $[M - CH_2Ph]^+$, 121 (100) $[CH_3C_6H_4CH_2]^+$. $C_{24}H_{27}NO$ (345.49): calcd. C 83.44, H 7.88, N 4.05; found C 83.21, H 7.96, N 3.91. The spectroscopic data are in agreement with previously published data.[5l]

Benzylbis[2-(*p*-tolyl)ethyl]amine (4c): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.05). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.20 (m, 5 H, aryl-H), 7.07 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H, aryl-H), 7.02 (d, $^3J_{H,H}$ = 8.0 Hz, 4 H, aryl-H), 3.73 (s, 2 H, NCH_2Ph), 2.76 (s, 8 H, CH_2CH_2N), 2.32 (s, 3 H, CH_3C$_6$H$_4$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 139.7, 137.5, 135.3, 129.0, 128.7, 128.6, 128.1, 126.7 (aryl), 58.5 (NHCH$_2$Ph), 55.8 (CH$_2$$CH_2$N), 33.2 ($CH_2CH_2$N), 21.0 ($CH_3C_6H_4$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 344 (32) $[M]^+$, 342 (52) $[M - H_2]^+$, 238 (100) $[M - CH_2C_6H_4$-$CH_3]^+$, 119 (48) $[CH_3C_6H_4CH_2CH_2]^+$. HRMS (EI): calcd. for $C_{25}H_{27}N$ $[M - 2\ H]^+$ 341.2138; found 341.2125.

(4-Methoxybenzyl)bis[2-(*p*-tolyl)ethyl]amine (4d): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.79). Isolated yield: 19% (based on the amine for Table 2, Entry 5). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.20 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, aryl-H), 7.09–7.01 (m, 8 H, aryl-H), 6.82 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, aryl-H), 3.80 (s, 3 H, OCH_3), 3.67 (s, 2 H, NCH_2Ar), 2.75 (s, 8 H, ArCH_2CH_2N), 2.32 (s, 6 H, CH_3C$_6$H$_4$) ppm. $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 158.5, 137.5, 135.3, 131.4, 129.9, 129.0, 128.6, 113.5 (aryl), 57.7 (NCH$_2$Ar), 55.6 (ArCH$_2$$CH_2$N), 55.2 ($OCH_3$), 33.0 (Ar$CH_2CH_2$N), 21.0 ($CH_3$)

ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 374 (20) $[M]^+$, 121 (100) $[CH_3OC_6H_4CH_2]^+$. $C_{26}H_{31}NO$ (373.54): calcd. C 83.60, H 8.37, N 3.75; found C 83.52, H 8.31, N 3.39.

Benzylbis[2-(naphthalen-2-yl)ethyl]amine (4e): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.2). Isolated yield: 9% (based on the amine for Table 2, Entry 7). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79–7.77 (m, 2 H, aryl-H), 7.70–7.68 (m, 4 H, aryl-H), 7.52 (s, 2 H, aryl-H), 7.44–7.35 (m, 5 H, aryl-H), 7.26 (br. s, 2 H, aryl-H), 7.21 (br. s, 4 H, aryl-H), 3.78 (s, 2 H, NCH_2Ph), 2.93–2.90 (m, 8 H, ArCH_2CH_2N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 133.6, 132.0, 128.8, 128.2, 127.8, 127.6, 127.4, 126.9, 126.8, 125.8, 125.1 (aryl), 58.6 (N*C*H_2Ph), 55.5 (ArCH$_2$*C*H_2N), 33.8 (Ar*C*H_2CH$_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 416 (42) $[M]^+$, 274 (100) $[M - C_{10}H_7CH_2]^+$. $C_{31}H_{29}N$ (415.58): calcd. C 89.60, H 7.03, N 3.37; found C 89.41, H 7.03, N 3.24.

Bis(phenethyl)propylamine (4n): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.33). Isolated yield: 17% (based on the amine for Table 2, Entry 22). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.22 (m, 4 H, aryl-H), 7.14–7.11 (m, 6 H, aryl-H), 2.71 (s, 8 H, PhCH_2CH_2N), 2.48 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, NCH_2CH$_2$CH$_3$), 1.50–1.38 (m, 2 H, NCH$_2$CH_2CH$_3$), 0.84 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, NCH$_2$CH$_2$CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.7, 128.7, 128.3, 125.8 (aryl), 56.1 (PhCH$_2$*C*H$_2$N), 56.0 (N*C*H$_2$CH$_2$CH$_3$), 33.7 (Ph*C*H$_2$CH$_2$N), 20.4 (NCH$_2$*C*H$_2$CH$_3$), 11.9 (NCH$_2$CH$_2$*C*H$_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 268 (54) $[M]^+$, 176 (100) $[M - PhCH_2]^+$. $C_{19}H_{25}N$ (267.41): calcd. C 85.34, H 9.42, N 5.24; found C 85.74, H 9.54, N 5.38.

(1,3-Diphenylpropyl)amine (5a): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.07). Isolated yield: 30% (based on the amine for Table 4, Entry 1).^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.27–7.21 (m, 4 H, aryl-H), 7.19–7.13 (m, 3 H, aryl-H), 7.09–7.05 (m, 3 H, aryl-H), 3.80 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, C*H*NH$_2$), 2.58–2.43 (m, 2 H, PhCH$_2$CH_2CH), 1.95–1.86 (m, 2 H, PhCH_2CH$_2$CH), 1.48 (br. s, 2 H, NH$_2$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 146.3, 141.9, 128.5, 128.3, 127.0, 126.4, 125.8 (aryl), 55.8 (*C*HNH$_2$), 41.0 (PhCH$_2$*C*H$_2$CH), 32.8 (Ph*C*H$_2$CH$_2$CH) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 212 (100) $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{17}N$ 211.1356; found 211.1360.

(1,1,3-Triphenylpropyl)amine (5o): Purification by column chromatography on silica gel (CH_2Cl_2 + a few drops of Et_3N, R_f = 0.15). Isolated yield: 12% (based on the amine). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.35 (m, 4 H, aryl-H), 7.29–7.25 (m, 4 H, aryl-H), 7.22–7.08 (m, 7 H, aryl-H), 2.48 (s, 4 H, PhCH_2CH_2), 1.75 (br. s, 2 H, NH$_2$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 148.6, 142.5, 128.4, 128.3, 128.2, 126.5, 126.4, 125.8 (aryl), 61.1 (*C*NH$_2$), 44.7 (PhCH$_2$*C*H$_2$), 30.7 (Ph*C*H$_2$CH$_2$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 288 (20) $[M]^+$, 271 (100) $[M - NH_2]^+$, 183 (98) $[M - PhCH_2CH_2]^+$. $C_{21}H_{21}N$ (287.40): calcd. C 87.76, H 7.36, N 4.87; found C 87.71, H 7.33, N 4.89.

***N*-Phenethylpiperidine (6a):** Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.14). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.26 (m, 2 H, aryl-H), 7.17 (m, 3 H, aryl-H), 2.80 (m, 2 H, PhCH$_2$CH_2N), 2.54 (m, 2 H, PhCH_2CH$_2$N), 2.45 (br. s, 4 H, ring α-CH$_2$), 1.64–1.58 (m, 4 H, ring β-CH$_2$) 1.45 (m, 2 H, ring γ-CH$_2$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.7, 128.7, 128.3, 125.9 (aryl), 61.4 (PhCH$_2$*C*H$_2$N), 54.5 (ring α-CH$_2$), 33.7 (Ph*C*H$_2$CH$_2$N), 26.0 (ring β-CH$_2$), 24.4 (ring γ-CH$_2$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 190 (100) $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{19}N$ 189.1512; found 189.1508. The spectroscopic data are in agreement with previously published data.[12a,12c]

***N*-Phenethylpyrrolidine (6b):** Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.34). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28–7.24 (m, 2 H, aryl-H), 7.20–7.15 (m, 3 H, aryl-H), 2.84–2.80 (m, 2 H, PhCH_2CH_2N), 2.70–2.66 (m, 2 H, PhCH_2CH_2N), 2.58–2.53 (m, 4 H, ring α-CH$_2$), 1.81–1.75 (m, 4 H, ring β-CH$_2$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.4, 128.6, 128.3, 125.9 (aryl), 58.3 (ArCH$_2$*C*H$_2$N), 54.2 (ring α-CH$_2$), 35.8 (Ar*C*H$_2$), 23.4 (ring β-CH$_2$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 176 (100) $[M]^+$. The spectroscopic data are in agreement with previously published data.[30]

***N*-Phenethylmorpholine (6c):** Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.05). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.27 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, aryl-H), 7.20–7.16 (m, 3 H, aryl-H), 3.73 (m, 4 H, PhCH_2CH_2N), 2.79 (m, 2 H, NCH$_2$CH_2O), 2.58 (m, 2 H, NCH$_2$CH_2O), 2.52 (br. m, 4 H, NCH_2CH$_2$O) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.1, 138.1, 128.7, 128.4, 126.1 (aryl), 67.0 (NCH$_2$*C*H$_2$O), 60.9 (PhCH$_2$*C*H$_2$N), 53.7 (N*C*H$_2$CH$_2$O), 33.3 (Ph*C*H$_2$CH$_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 192 (100) $[M]^+$. $C_{12}H_{17}NO$ (191.27): calcd. C 75.35, H 8.96, N 7.32; found C 75.03, H 8.98, N 7.28. The spectroscopic data are in agreement with previously published data.[12a,12c,31]

Benzyl(methyl)(phenethyl)amine (6d): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.28 (m, 7 H, aryl-H), 7.21 (m, 3 H, aryl-H), 3.58 (s, 2 H, NCH_2Ph), 2.86 (m, 2 H, PhCH$_2$CH_2N), 2.68 (m, 2 H, PhCH_2CH$_2$N), 2.30 (s, 3 H, NCH$_3$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.5, 139.0, 129.0, 128.7, 128.3, 128.2, 126.9, 125.9 (aryl), 62.2 (N*C*H$_2$Ph), 59.2 (PhCH$_2$*C*H$_2$N), 42.2 (NCH$_3$), 33.9 (Ph*C*H$_2$CH$_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 226 (80) $[M]^+$, 134 (100) $[M - PhCH_2]^+$. $C_{16}H_{19}N$ (225.33): calcd. C 85.29, H 8.50, N 6.22; found C 85.21, H 8.41, N 6.32. The spectroscopic data are in agreement with previously published data.[12d]

Diethyl(phenethyl)amine (6e): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.36). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28–7.24 (m, 2 H, aryl-H), 7.18 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, aryl-H), 2.77–2.67 (m, 4 H, PhCH_2CH_2N), 2.60 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, NCH_2CH$_3$), 1.06 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, NCH$_2$CH_3) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.7, 128.6, 128.3, 125.9 (aryl), 54.8 (PhCH$_2$*C*H$_2$N), 46.8 (N*C*H$_2$CH$_3$), 33.3 (Ph*C*H$_2$CH$_2$N), 11.7 (NCH$_2$*C*H$_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 178 (100) $[M]^+$. The spectroscopic data are in agreement with previously published data.[32]

Dibenzyl(phenethyl)amine (6f): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.19). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.22 (m, 13 H, aryl-H), 7.10–7.08 (m, 2 H, aryl-H), 3.65 (br. s, 4 H, NCH_2Ph), 2.82–2.80 (m, 2 H, PhCH_2CH_2N), 2.74–2.70 (m, 2 H, PhCH_2CH_2N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.6, 139.7, 128.8, 128.7, 128.2, 128.1, 126.8, 125.8 (aryl), 58.2 (N*C*H$_2$Ph), 55.1 (PhCH$_2$*C*H$_2$N), 33.5 (Ph*C*H$_2$CH$_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 302 (26) $[M]^+$, 300 (44) $[M - H_2]^+$, 210 (100) $[M - CH_2Ph]^+$. $C_{22}H_{23}N$ (301.43): calcd. C 87.66, H 7.69, N 4.65; found C 87.83, H 7.83, N 4.65. The spectroscopic data are in agreement with previously published data.[32]

Methyl(phenethyl)(phenyl)amine (6g): Purification by column chromatography on silica gel (CH_2Cl_2/EtOAc, 1:1 + a few drops of Et_3N, R_f = 0.88). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.26 (m, 7 H, aryl-H), 6.81–6.75 (m, 3 H, aryl-H), 3.62 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, PhCH$_2$CH_2N), 2.95 (s, 3 H, NCH$_3$), 2.91 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, PhCH_2CH$_2$N) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 148.8, 139.8, 129.2, 128.8, 128.5, 126.2, 116.1, 112.1 (aryl), 54.7 (*C*H$_2$N), 38.4 (Ph*C*H$_2$), 32.9 (NCH$_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 212 (34) $[M]^+$, 120 (100) $[M - PhCH_2]^+$. $C_{15}H_{17}N$ (211.31): calcd. C 85.26, H 8.11, N 6.63; found C 85.19, H 8.24, N 6.49. The spectroscopic data are in agreement with previously published data.[31]

1-[2-(4-Chlorophenyl)ethyl]piperidine (6h): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.07). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.19 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, aryl-H), 7.08 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, aryl-H), 2.75 (m, 2 H, ArCH$_2$CH_2N), 2.50 (m, 2 H, ArCH_2CH$_2$N), 2.43 (br. m, 4 H, ring α-CH$_2$), 1.62–1.56 (m, 4 H, ring β-CH$_2$), 1.45–1.40 (m, 2 H, ring γ-CH$_2$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 138.9, 131.6, 129.9, 128.3 (aryl), 61.0 (ArCH$_2$*C*H$_2$N), 54.4 (ring α-CH$_2$), 32.8 (Ar*C*H$_2$), 25.8 (ring β-CH$_2$), 24.2 (ring γ-CH$_2$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 224 (100) $[M]^+$. $C_{13}H_{18}ClN$ (223.75): calcd. C 69.79, H 8.11, N 6.26; found C 69.39, H 8.29, N 6.13.

***N*-(2-Phenylpropyl)piperidine (6i):** Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.06). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.29–7.26 (m, 2 H, aryl-H), 7.20–7.15 (m, 3 H, aryl-H), 2.93 (sext., $^3J_{H,H}$ = 7.0 Hz, 1 H, PhC*H*), 2.46–2.38 (m, 4 H, ring α-CH$_2$), 2.28 (br. d, 2 H, PhCH(CH$_3$)CH_2N), 1.60–1.47 (m, 4 H, ring β-CH$_2$), 1.42–1.36 (m, 2 H, ring γ-CH$_2$) 1.26 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH$_3$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 146.7, 128.2, 127.2, 125.9 (aryl), 67.1 (PhCH(CH$_3$)CH_2N), 55.0 (ring α-CH$_2$), 37.5 (Ph*C*H), 26.1 (ring β-CH$_2$), 24.5 (ring γ-CH$_2$), 20.0 (CH$_3$) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 204 (100) $[M]^+$. $C_{14}H_{21}N$ (203.33): calcd. C 82.70, H 10.41, N 6.89; found C 82.40, H 10.39, N 6.80. The spectroscopic data are in agreement with previously published data.[33]

Bis(2-methoxyethyl)(phenethyl)amine (6j): Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 + a few drops of Et_3N, R_f = 0.14). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23–7.20 (m, 2 H, aryl-H), 7.14–7.10 (m, 3 H, aryl-H), 3.42 (t, $^3J_{H,H}$ = 6.1 Hz, 4 H, NCH$_2$CH_2OCH$_3$), 3.29 (s, 6 H, OCH$_3$), 2.78–2.69 (m, 8 H, PhCH_2CH_2NCH_2CH$_2$OCH$_3$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 140.5, 128.7, 128.3, 125.8 (aryl), 71.1 (*C*H$_2$OCH$_3$), 58.8 (OCH$_3$), 57.2 (PhCH$_2$*C*H$_2$N), 53.8 (N*C*H$_2$CH$_2$OCH$_3$), 33.3 (Ph*C*H$_2$CH$_2$N) ppm. MS (FAB, 3-NBA): *m*/*z* (%) = 238 (100) $[M]^+$, 236 (45) $[M - H_2]^+$, 192 (35) $[M - CH_2OCH_3]^+$. HRMS (EI): calcd. for $C_{14}H_{23}NO_2$ 237.1723; found 237.1715.

General Procedure for the Determination of the Enantiomeric Excess: The amine (0.05 mmol) and (*R*)-*O*-acetylmandelic acid (0.06 mmol) were dissolved in $CDCl_3$ or C_6D_6, and their ^1H NMR spectrum was recorded either at room temperature or at 0 °C. The enantiomeric excess was determined by ^1H NMR spectroscopy through the integration of diastereomeric protons in proximity to the nitrogen atom.

Computational Details: All calculations were performed with the nonlocal hybrid Becke 3-parameter Lee–Yang–Parr density functional (B3LYP)[34] with the 6-31+G(d) basis set.[35] Harmonic vibrational frequencies have been calculated for all structures in order to characterize the stationary points as energy minima (all frequencies are real) or transition states (only one imaginary frequency). Thermal corrections to Gibbs free energies were also obtained by these unscaled harmonic vibrational frequencies. All calculations were carried out with the GAUSSIAN03 package.[36] The effect of solvation by benzene was estimated by means of single-point calculations on the gas-phase-optimized geometries with the CPCM method.[37] Gibbs energies in solution have been referred to 298.15 K and 1 mol L^{-1}. Due to the fact that the product of reaction presents many more degrees of freedom than the reactants, a Monte Carlo Multiple Minimum conformational search[38] was carried out for it with the MMFF94s force field[39] implemented in the Macromodel 7.0 package.[40]

Supporting Information (see footnote on the first page of this article): Complete list of Cartesian coordinates for all optimized intermediates and transition states, and all bond orders determined for **TS2**, **TS2′**, **(TMEDA)TS2**, and **(TMEDA)TS2′**, and ^1H and ^{13}C NMR spectra of all hydroamination products.

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