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# Highly Chemoselective Reductive Amination of Carbonyl Compounds Promoted by $InCl_3/Et_3SiH/MeOH$ System

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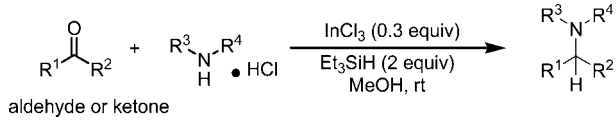
*Received July 20, 2008*

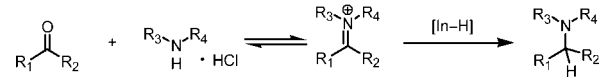



A new strategy has been developed for reductive amination of aldehydes and ketones with the $InCl_3/Et_3SiH/MeOH$ system, which is a nontoxic system with highly chemoselective and nonwater sensitive properties. The methodology can be applied to a variety of cyclic, acyclic, aromatic, and aliphatic amines. Functionalities including ester, hydroxyl, carboxylic acid, and olefin are found to be stable under our conditions. The reaction shows a first-order kinetics profile with respect to both $InCl_3$ and $Et_3SiH$. Spectroscopic techniques such as NMR and ESI-MS have been employed to probe the active and resulting species arising from $InCl_3$ and $Et_3SiH$ in MeOH, which are important in deriving a mechanistic proposal. In the ESI-MS studies, we have first discovered the existence of stable methanol-coordinated indium(III) species which are presumably responsible for the gentle generation of indium hydride at room temperature. The solvent attribution was crucial in tuning the reactivity of [In−H] species, leading to the establishment of mild reaction conditions. The system is superior in flexible tuning of hydride reactivity, resulting in the system being highly chemoselective.

## Introduction

Over the past decade, the growing use of catalytic indium(III) halides in organic synthesis has attracted considerable attention. With the advantage of indium(III) halides' stability in air, their combination with appropriate reducing agents has demonstrated excellent degrees of chemoselective reducing activity toward various functional groups. Extensive use of indium(III) halides in different reaction types including selective double-bond reduction,[1] radical cyclization and radical addition,[2] cleavage of 2,3-epoxybromides,[3] cyclization of enynes,[4] Friedel−Crafts alkylation,[5] reduction of alkyl halides[6] and aldehydes,[7] reductive aldol reaction,[8] and other specific reactions[9] has been reported. Although indium(III) halides have been proven to be an excellent catalyst for reduction, the application of the system in iminium ion reduction has not yet been investigated. As reductive amination[10] is an important protocol in the construction of the carbon−nitrogen bond, we launch research on the application of indium(III) halide as a catalyst in the area of reductive amination.

**SCHEME 1**




(1) (a) Ranu, B. C.; Samanta, S. *Tetrahedron* **2003**, *59*, 7901. (b) Ranu, B. C.; Samanta, S. *J. Org. Chem.* **2003**, *68*, 7130. (c) Ranu, B. C.; Samata, S. *Tetrahedron Lett.* **2002**, *43*, 7405.

(2) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.

(3) Ranu, B. C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* **2004**, *45*, 8579.

(4) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981.

(5) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 6291.

(6) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4661.

(7) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929.

(8) (a) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711. (b) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985.

(9) For other selected reactions involving indium(III) halides, see: (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414. (b) Yamada, M.; Tanaka, K.; Araki, S.; Butsugan, Y. *Tetrahedron Lett.* **1995**, *36*, 3169. (c) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685. (d) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212. (e) Miura, K.; Fujisawa, N.; Hosomi, A. *J. Org. Chem.* **2004**, *69*, 2427. (f) Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13690. (g) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363. (h) Lu, J.; Ji, S-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (i) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414. (j) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539. (k) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743.

(10) Baxter, E. W.; Reitz, A. B. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: Singapore, 2002; Vol. 59.

10.1021/jo8016082 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/22/2008

Organosilanes are mild and environmentally benign reducing agents, which have applications in many kinds of reactions.[11] In recent years, only a small number of studies in the literatures have reported the use of organosilanes in reductive amination[12−17] and demonstrated relative success in addressing some of the inherent disadvantages of traditional reducing agents.[18] Unfortunately, they, too, suffer from their own drawbacks: the TFA/$Et_3SiH$[12] system is not compatible with acid labile functional groups; applicability of $TiCl_4$/PHMS[14] is restricted to aromatic aldehydes; $Bu_2SnCl_2/PhSiH_3$[15] is highly toxic; $Ti(OiPr)_4$/PMHS[16] is water-sensitive; and $IrCl_3/Et_3SiH$[17] is not compatible with substrates containing double bonds.

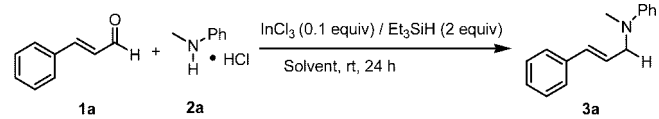
Here we first report a study on mild and highly chemoselective reductive amination of carbonyl compounds with secondary amine salts using a reducing system of triethylsilane in the presence of indium(III) chloride, as shown in Scheme 1. $InCl_3$/$Et_3SiH$ generates [In−H] species in situ,[4,6] which reduces iminium ion in a chemoselective manner. This is the first method that utilizes [In−H] in reducing iminium ion.

## Results and Discussion

**I. Optimization of Reaction Conditions.** Our studies began with screening of various solvents for reductive amination between *trans*-cinnamaldehyde and *N*-methylaniline·HCl salt. We conducted the reactions by adding the corresponding amine·HCl salt (0.5 mmol) to a stirred solution of carbonyl substrate (0.5 mmol) in 1.7 mL of solvent at room temperature. After being stirred for 1 h, $Et_3SiH$ (0.15 mL, 1.0 mmol) was added to the reaction mixture via a syringe, followed by the addition of $InCl_3$ (10 mol %). The results are summarized in Table 1.

We employed polar solvents to facilitate the dissolution of starting materials as well as the formation of iminium ion. As shown in Table 1, among the solvents tested, alcoholic solvents were generally more efficient (up to 100% conversion, 100% yield; entries 1−5) than polar aprotic solvents (up to 72% conversion, <20% yield; entries 6 and 7). Notably, the best conversion and yield were achieved with MeOH as the solvent (100% conversion, 100% yield; entry 1). In addition, we found that sterically more hindered alcohols as solvents are associated with lower substrate conversion and yield (cf. entry 1 and entries 2−4).

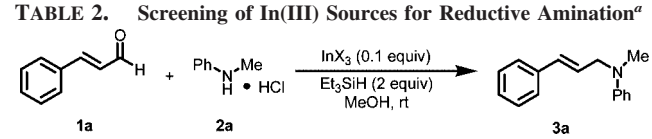
**TABLE 1. Solvent Screening for Reductive Amination**[a]




| entry | solvent | conv (%)[b] | yield (%)[b] |
|---|---|---|---|
| 1 | MeOH | 100 | 100 |
| 2 | EtOH | 50 | 49 |
| 3 | *i*-PrOH | 30 | 2 |
| 4 | *t*-BuOH | 10 | 0 |
| 5 | $CF_3CH_2OH$ | 82 | 47 |
| 6 | $CH_3NO_2$ | 61 | 12 |
| 7 | MeCN | 72 | 13 |

[a] All reactions were performed at room temperature for 24 h with 0.5 mmol of *trans*-cinnamaldehyde, 0.5 mmol of *N*-methylaniline·HCl salt, 0.1 equiv of indium(III) chloride, and 2.0 equiv of $Et_3SiH$ in 1.7 mL of the indicated solvent. [b] Determined by $^1H$ NMR with DMF as an internal standard.

**TABLE 2. Screening of In(III) Sources for Reductive Amination**[a]




| entry | $InX_3$ | time (h) | conv (%)[b] | yield (%)[b] |
|---|---|---|---|---|
| 1 | $InF_3$ | 72 | 100 | 57 |
| 2 | $InCl_3$ | 24 | 100 | 99 |
| 3 | $InBr_3$ | 12 | 100 | 73 |
| 4 | $InI_3$ | 18 | 100 | 79 |
| 5 | $In(OTf)_3$ | 12 | 100 | 72 |
| 6 | − | 72 | 0 | n.d.[c] |

[a] All reactions were performed at room temperature with 0.5 mmol of *trans*-cinnamaldehyde, 0.5 mmol of *N*-methylaniline·HCl salt, 0.1 equiv of indium(III) halide, and 2.0 equiv of $Et_3SiH$ in 1.7 mL of methanol. [b] Determined by $^1H$ NMR with DMF as an internal standard. [c] Not determined.

Next, various In(III) sources were examined and the results are summarized in Table 2. Among the In(III) sources tested, a trend can be observed in the In(III) catalysts of different halide counterions. $InCl_3$ gave the highest yield (entry 2). $InF_3$ was ineffective, with which the reaction was complete after 3 days in low yield (57%, entry 1). The reaction rate increased upon going down the series from $InF_3$ to $InBr_3$ (cf. entries 1−3). $In(OTf)_3$ displayed similar performance as $InBr_3$ and complete conversion was achieved in 12 h in 72% yield (entry 5). No reaction was found in the absence of In(III) species (entry 6).

We then investigated the effect of loading $InCl_3$ and $Et_3SiH$. In our observations, the reaction rate increased proportionally with increasing amount of $InCl_3$ (Table 3, entries 1−4), which resembles a first-order kinetics profile. In addition, a similar resemblance of a first-order kinetics profile was also found with respect to the amount of $Et_3SiH$ administered (Table 3, entries 5−7). In a study by Ishii and colleagues[17] on the use of Ir(III)/$Et_3SiH$ in reductive alkylation of secondary amines, it was proposed that the hydrogen source comes from both silane and water in an equimolar ratio. Thus, the required amount of silane would be only half of the essential hydrogen atoms delivered. Our experimental findings revealed a nonresemblance between

(11) For reviews on the use of organosilanes as reducing agents, see: (a) Chatgilialoglu, C. In *Organosilanes in Radical Chemistry*; Wiley-VCH: Chichester, UK, 2004; Chapters 3 and 4. (b) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633. (c) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. For other references, see: (d) Ballestri, M.; Chatgilialoglu, C.; Guerra, M.; Guerrini, A.; Lucarini, M.; Seconi, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 421. (e) Chatgilialoglu, C.; Guerra, M.; Guerrini, A.; Seconi, G. *J. Org. Chem.* **1992**, *57*, 2427. (f) Kamal, A.; Rao, N. V.; Laxman, E. *Tetrahedron Lett.* **1997**, *38*, 6945. (g) Lesage, M.; Simoes, J. A. M.; Griller, D. *J. Org. Chem.* **1990**, *55*, 5413. (h) Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3829. (i) Chatilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* **1993**, *58*, 249.

(12) (a) Chen, B.-C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245. (b) Dube, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295. (c) Webb, R. R.; Barker, P. L.; Baier, M.; Reynolds, M. E.; Robarge, K. D.; Blackburn, B. K.; Tischler, M. H.; Weese, K. J. *Tetrahedron Lett.* **1994**, *35*, 2113.

(13) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.

(14) Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett* **2001**, *10*, 1617.

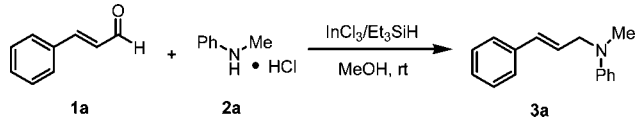
(15) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.

(16) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, *11*, 1655.

(17) Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 2195.

(18) For reviews using sodium cyanoborohydride, see: (a) Lane, C. F. *Synthesis* **1975**, 135. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *91*, 2897. (c) Hutchins, R. O.; Hutchins, M. K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 8, p 25. For reviews using sodium triacetoxyborohydride, see: (d) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (e) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. Sodium cyanoborohydride requires large quantities of excess amine. Moreover, the reagent is highly toxic and cyanides are generated as byproducts after reaction. Sodium triacetoxyborohydride is not compatible with aromatic and unsaturated ketones.

**TABLE 3. Effect of $InCl_3/Et_3SiH$ Loading in the Reductive Amination System**[a]




**1a** **2a** **3a**

| entry | equiv of $InCl_3/Et_3SiH$ | time (h) | conv (%)[b] | yield (%)[b,c] |
|---|---|---|---|---|
| 1 | 1.0/2.0 | 3 | 100 | 100 |
| 2 | 0.5/2.0 | 6 | 100 | 100 |
| 3 | 0.25/2.0 | 12 | 100 | 100 |
| 4 | 0.1/2.0 | 24 | 100 | 100 |
| 5 | 0.1/3.0 | 18 | 100 | 100 |
| 6 | 0.1/1.5 | 36 | 100 | 100 |
| 7 | 0.1/1.0 | 48 | 100 | 100 |
| 8 | 0.1/0.5 | 72 | 88 | 42 |
| 9 | 0.1/0.2 | >96 | <5 | n.d.[d] |

[a] All reactions were performed at room temperature for the indicated reaction time with 0.5 mmol of *trans*-cinnamaldehyde, 0.5 mmol of *N*-methylaniline HCl salt, and the indicated amount of $InCl_3$ and $Et_3SiH$ in 1.7 mL of MeOH. [b] Determined by integrating $^1H$ NMR spectra relative to an internal standard (DMF). [c] Based on conversion. [d] Not determined.

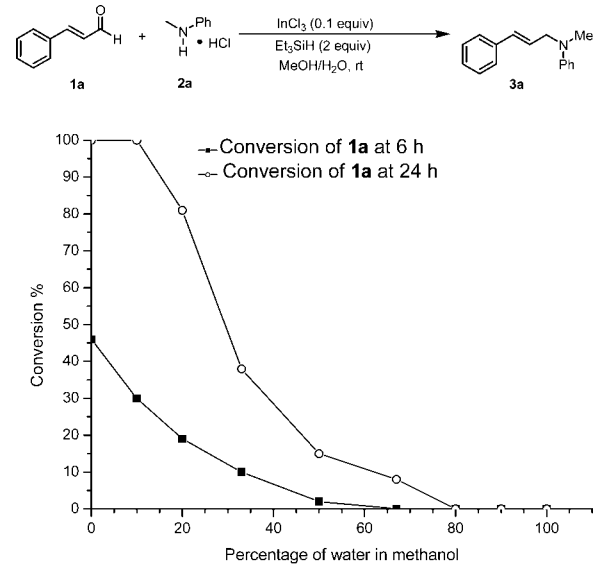



**FIGURE 1.** Investigation on the effect of water content on the reductive amination reaction.

In(III)- and Ir(III)-catalyzed reductive amination, which was confirmed by incomplete conversion observed for loadings of $Et_3SiH$ below 1.0 equiv (entries 8 and 9). These experimental observations provide an important clue to the reaction mechanism.

As hydride ion reacts with water rapidly, many of the hydride reduction reactions require strict anhydrous conditions.[18a−c,19] A strict anhydrous reaction system created extra demands on reagent quality as well as reaction handling. As a logical alternative, the use of nonwater-sensitive reducing agents would confer an advantage. We have also noticed that a considerable number of silane reactions occur in aqueous media,[20,21] and that water is generated in situ during the formation of iminium salt in reductive amination. It would be interesting to investigate the possibility of a MeOH/water cosolvent system. As shown in Figure 1, we found that the reaction between *trans*-cinnamaldehyde and *N*-methylaniline·HCl salt displayed satisfactory conversion with a cosolvent system of up to 10% water in MeOH. Further increase in water content led to reduction in yield due to the reduced solubility of starting materials in water. Nevertheless, this result reveals the superiority of the $InCl_3/Et_3SiH$ system as a nonwater-sensitive reducing agent.

**II. Reductive Amination of Various Carbonyl Compounds.** After gaining some initial insights about the reaction conditions, we moved on to examine the reductive amination of *trans*-cinnamaldehyde with various amine salts (Table 4). To achieve higher catalytic efficiency, we increased the loading of $InCl_3$ to 30 mol % and the reaction concentration to 0.5 M. Apart from *N*-methylaniline·HCl salt, reactions with aliphatic amine·HCl salts were also successful (entries 2−9).

Since most biologically interesting organic compounds contain multiple functionalities, the reaction system will be valuable if it demonstrates high chemoselectivity. We further tested the system's applicability with respect to different functional groups. Morpholine·HCl salt reacted smoothly with *trans*-cinnamaldehyde to furnish **3c** in 88% yield (entry 3), while the reaction with proline methyl ester gave **3g** in 80% yield (entry 7), demonstrating the system's compatibility with ether and ester groups. Interestingly, reactions with 3-hydroxypiperidine and prolinol gave products **3e** and **3f**, respectively, suggesting the inertness of the OH functionality toward the reaction system (entries 5 and 6). Notably, carboxylic acid was also compatible with the system, as indoline-2-carboxylic acid gave product **3h** in 67% yield (entry 8). Furthermore, indoline-2-carboxylic acid could be administered directly without preforming HCl salt presumably because it contains a carboxylic acid group. Apart from cyclic amines, acyclic dibenzylamine HCl salt was also efficient in furnishing **3i** in 80% yield (entry 9). The wide scope of amines and excellent tolerance of functionalities underscore the robustness and high value of the system in organic synthesis applications in which a protecting group may well be redundant.

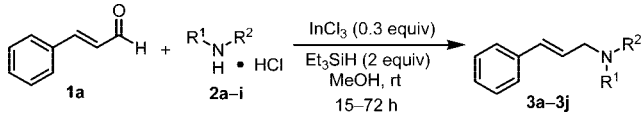
We next explored the reductive amination of different carbonyl compounds with various amine·HCl salts (Table 5). The $InCl_3/Et_3SiH$/MeOH system was specific to 1,2-reduction. Clean reactions in excellent yields (entries 1−4) were achievable with a variety of substituted $\alpha,\beta$-unsaturated aldehydes. Notably, the reaction of methacrolein (**1b**), which contains an unsubstituted terminal double bond, proceeded smoothly with **3j** as the only detectable product in 95% yield, further highlighting the remarkably chemoselective character of the system toward $\alpha,\beta$-unsaturated iminium ions. Reactions with aliphatic aldehydes were also satisfactory in generating the products **3n−q** (entries 5−8). In addition, the system could also be applied to less reactive aromatic aldehydes. The reaction of 4-methyoxybenzaldehyde with various amine·HCl salts proceeded efficiently to afford benzylic tertiary amines **3r**, **3s**, and **3t** (entries 9−11). One aspect of the superiority of the $InCl_3/Et_3SiH$ system is that it is so highly compatible with acid labile double bonds that neither hydrolysis nor reduction of olefin results. While many existing reductive amination methods require strongly acidic conditions[12,18] or highly reactive catalysts[17] by which the structural integrity of isolated olefin is often destroyed, we have demonstrated the intactness of such isolated double bonds under the reaction system. The trisubstituted double bond in citral **1e** was not protonated, affording the product **3m** (entry 4). Furthermore, unlike transition metals, indium metal did not

(19) For reviews on the use of zinc borohydride in reduction, see: Ranu, B. C. *Synlett* **1993**, 885.

(20) Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2519.

(21) (a) Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3821. (b) Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3835. (c) Doyle, M. P.; DeBruyn, D. J.; Donnelly, S. J.; Kooistra, D. A.; Odubela, A. A.; West, C. T.; Zonnebelt, S. M. *J. Org. Chem.* **1974**, *39*, 2740.

**TABLE 4. Reductive Amination with Various Amine Salts To Give Tertiary Amines[a]**




| entry | substrate | product | time (h) | conv. (%)[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **2a** | **3a** | 24 | 100 | 99 |
| 2 | **2b** | **3b** | 48 | 95 | 66 |
| 3 | **2c** | **3c** | 15 | 100 | 88 |
| 4 | **2d** | **3d** | 48 | 100 | 68 |
| 5 | **2e** | **3e** | 48 | 80 | 66 |
| 6 | **2f** | **3f** | 48 | 95 | 75 |
| 7 | **2g** | **3g** | 48 | 100 | 80 |
| 8[d,e] | **2h** | **3h** | 72 | 100 | 67 |
| 9 | **2i** | **3i** | 48 | 100 | 80 |

[a] All reactions were conducted at room temperature with 0.5 mmol of *trans*-cinnamaldehyde, 0.5 mmol of amine·HCl salt, 0.3 equiv of $InCl_3$, and 2.0 equiv of $Et_3SiH$ in 1 mL of MeOH. [b] Determined by $^1H$ NMR with DMF as an internal standard. [c] Isolated yield. [d] The concentration was 0.13 M owing to low solubility of starting materials. [e] Indole 2-carboxylic acid was directly used instead of its HCl salt.

promote reduction of isolated olefins. Thus, both *cis*- and *trans*-disubstituted double bonds in substrates **1f** and **1g**, which furnished the products **3n** and **3o** (entries 5 and 6), respectively, were intact against reduction.

Apart from aldehydes, ketones were also found to undergo reductive amination to give tertiary amines. Cyclic ketones underwent reaction in the manner that more rigid cyclopentanone **1j** and cyclohexanone **1k** reacted faster to give the products **3u** and **3v** (Table 5; entries 12 and 13), respectively, while the reaction of cycloheptanone was less efficient (entry 14). The trend in reactivity may be contributed by a higher steric shield from adjacent hydrogen atoms to carbonyl group owing to a more flexible ring structure upon increasing ring size. The rigid 2-indanone also presented excellent reactivity, furnishing product

**TABLE 5. Reductive Amination with Various Aldehydes and Amine·HCl Salts Promoted by the $InCl_3/Et_3SiH$/MeOH System[a]**

| entry | carbonyl | amine HCl salt | time (h) | product | conv. (%)[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **1b** | **2a** | 48 | **3j** | 100 | 95 |
| 2 | **1c** | **2a** | 24 | **3k** | 100 | 99 |
| 3 | **1d** | **2a** | 24 | **3l** | 95 | 95 |
| 4 | **1e** | **2a** | 7 | **3m** | 94 | 41 |
| 5 | **1f** | **2a** | 48 | **3n** | 100 | 100 |
| 6 | **1g** | **2d** | 48 | **3o** | 100 | 70 |
| 7 | **1g** | **2g** | 48 | **3p** | 100 | 44 |
| 8 | **1h** | **2a** | 48 | **3q** | 100 | 99 |
| 9 | **1i** | **2a** | 24 | **3r** | 100 | 80 |
| 10 | **1i** | **2c** | 48 | **3s** | 100 | 90 |
| 11 | **1i** | **2d** | 48 | **3t** | 100 | 83 |
| 12 | **1j** | **2a** | 48 | **3u** | 100 | 100 |
| 13 | **1k** | **2a** | 48 | **3v** | 100 | 100 |
| 14 | **1l** | **2a** | 48 | **3w** | 100 | 68 |
| 15 | **1m** | **2a** | 24 | **3x** | 100 | 91 |
| 16 | **1j** | **2j** | 48 | **3y** | 100 | 88 |

[a] All reactions were conducted at room temperature for the indicated reaction time with 0.5 mmol of carbonyl compound, 0.5 mmol of amine·HCl salt, 0.3 equiv of $InCl_3$, and 2.0 equiv of $Et_3SiH$ in 1 mL of MeOH. [b] Determined by $^1H$ NMR with DMF as an internal standard. [c] Isolated yield.

**3x** (entry 15). Similarly, cyclopentanone also reacted with 1,2,3,4-tetrahydroquinoline·HCl salt to produce **3y** (entry 16).

**III. Mechanistic Studies.** Although isolation of the intermediates was not possible, it could be conjectured that indium

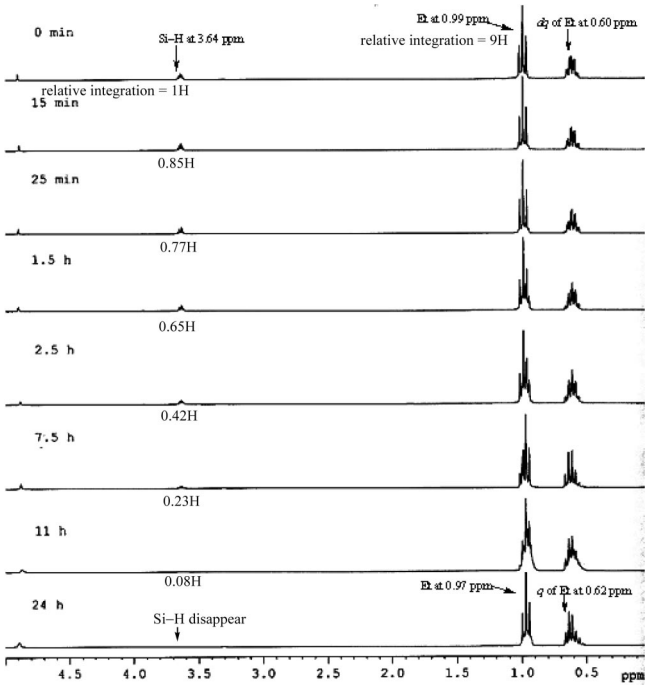



**FIGURE 2.** $^{1}$H NMR studies on the reaction between $InCl_3$ (0.15 mmol) and $Et_3SiH$ (1 mmol) in $CD_3OD$ (1 mL).

hydride, formed by the combination of indium(III) chloride and triethylsilane, is a likely candidate responsible for the reduction. Recently, Baba et al. proposed radical behavior of the $InCl_3$/$Et_3SiH$ system with $Et_3SiCl$ as an end species.[4] In addition, in their study of reductive aldol condensation,[8] they proposed direct transmetalation between $InCl_3$ and $Et_3SiH$ in acetonitrile, which generates reactive indium hydride species and $Et_3SiCl$ as a byproduct. To make comparisons with our system, we carried out a series of experiments to elucidate the underlying mechanism.

We scrutinized the indirect evidence for indium hydride species by observing silane end species in NMR studies. First, we conducted $^{1}$H NMR experiments to determine the silane end species. $InCl_3$ (0.15 mmol) was dissolved in 1 mL of $CD_3OD$, followed by the addition of 1 mmol of $Et_3SiH$. Upon mixing of the reagents, the $^{1}$H NMR spectrum was recorded at several time intervals (0 min, 15 min, 25 min, 1.5 h, 2.5 h, 7 h, 11 h, and 24 h) as shown in Figure 2.[22] The $^{1}$H NMR data revealed that the signals of Si−H at 3.64 ppm and the ethyl group at 0.99 ($CH_3$) and 0.60 ppm ($CH_2$) gradually decreased over a period of 24 h, while a new set of peaks at 0.97 ($CH_3$) and 0.62 ppm ($CH_2$) developed. The coupling pattern of the $CH_2$ unit of the Et group gradually changed from a *doublet of quartets* to a *quartet*. The above observations served as strong evidence for the consumption of organosilane under the actions of $InCl_3$. A control experiment was carried out with $InCl_3$ being replaced by $Sc(OTf)_3$, and $Et_3SiH$ was found to be inert. This provides further support to the hypothetical existence of a transmetalation process that involves the generation of indium hydride as an active intermediate. The absence of an extra peak in $^{1}$H NMR might be due to the low concentration of this active intermediate. Furthermore, this suggests that the properties of $InCl_3$/$Et_3SiH$ in MeOH is different from that in MeCN as reported by Baba et al.

(22) Field, L. D.; Messerle, B. A.; Rehr, M.; Soler, L. P.; Hambley, T. W. *Organometallics* **2003**, *22*, 2387.

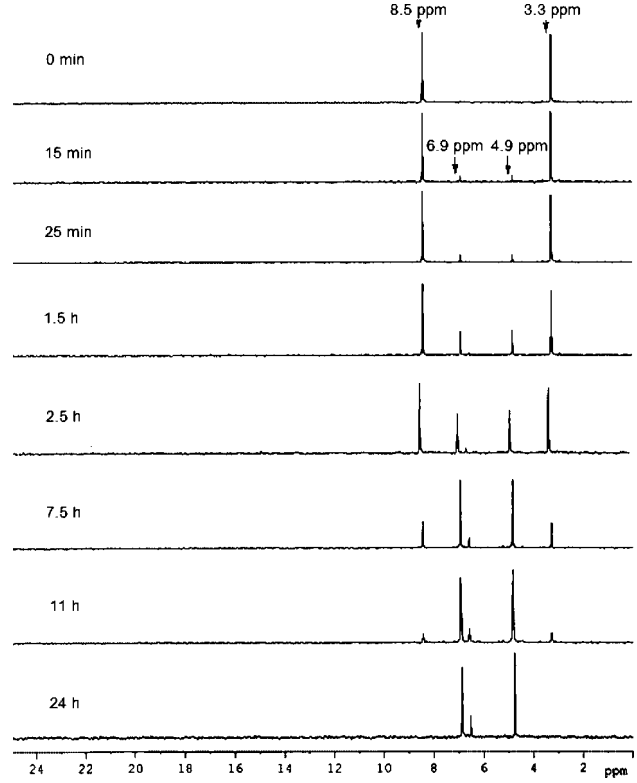



**FIGURE 3.** $^{13}$C NMR studies on the reaction between $InCl_3$ (0.15 mmol) and $Et_3SiH$ (1 mmol) in $CD_3OD$ (1 mL).

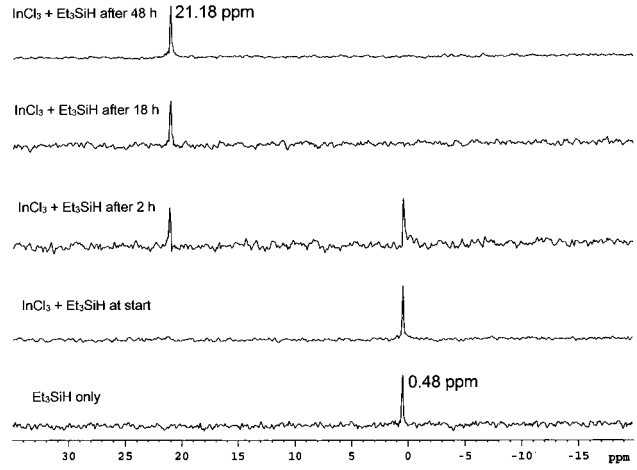



**FIGURE 4.** $^{29}$Si NMR studies on the reaction between $InCl_3$ (0.15 mmol) and $Et_3SiH$ (1 mmol) in $CD_3OD$ (1 mL).

We then turned our attention to investigating the fate of triethylsilane by $^{13}$C NMR analysis, whose results are as shown in Figure 3. Over a period of 24 h, the original peaks corresponding to the Et group of triethylsilane at 8.5 ($CH_3$) and 3.3 ppm ($CH_2$) slowly disappeared, while two new peaks at 6.9 ($CH_3$) and 4.9 ppm ($CH_2$) gradually emerged. This suggests that $Et_3SiH$ slowly reacted with $InCl_3$ to give a stable species as the final product.

The fate of triethylsilane was also probed by $^{29}$Si NMR analysis, and the results are as shown in Figure 4. Over a period of 48 h, the $^{29}$Si chemical shift changed from 0.48 ppm to a more downfield value at 21.18 ppm. This indicates the disappearance of the Si−H bond and the formation of a new bond between silicon and a heteroatom.

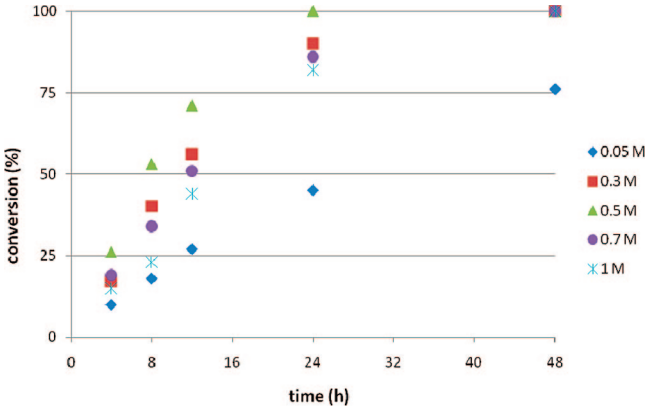



**FIGURE 5.** Conversion upon time at different concentrations of **1a**.

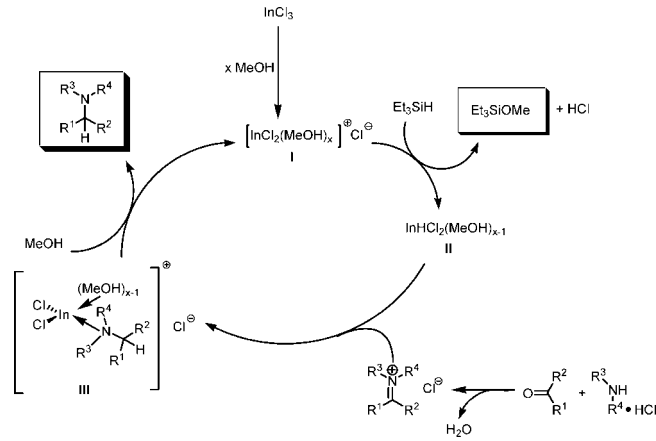
We initially suspected the end-species to be $Et_3SiCl$ as a result of direct transmetalation. However, this was disproved in a control experiment, in which the $^{13}C$ NMR of $Et_3SiCl$ in $CD_3OD$ in the presence of $InCl_3$ displayed peaks at 7.2 and 7.3 ppm. In view of the above, there could be different mechanistic pathways which diverge between our system (in MeOH) and Baba et al.'s system (in MeCN).

We propose the end-species to be $Et_3SiOMe$. In a paper describing the preparation of $Et_3SiOMe$ from $Et_3SiH$ by Field and Messerle,[22] the chemical shifts of the ethyl group were reported to be 0.99 ($CH_3$) and 0.64 ppm ($CH_2$) in $^1H$ NMR spectra and 7.3 ($CH_3$) and 4.7 ppm ($CH_2$) in $^{13}C$ NMR spectra, both taken in $CDCl_3$. In addition, the reported chemical shift in $^{29}Si$ NMR in $CDCl_3$ is 20.92 ppm. Those chemical shift values were similar to our findings, providing compelling evidence for the formation of $Et_3SiOMe$.

**Investigation of the Amount of Methanol vs the Reaction Rate.** To acquire a better understanding of methanol participation, we varied the amount of methanol during our kinetic study in rate. We performed our studies using *trans*-cinnamaldehyde (0.5 mmol), *N*-methylaniline·HCl salt (0.5 mmol), 0.1 equiv of $InCl_3$, and 2 equiv of $Et_3SiH$ in various volumes of MeOH, corresponding to 0.05 to 1 M substrate concentration, and followed the reaction conversion for 48 h by $^1H$ NMR. Throughout the whole concentration range, all the starting materials and reagents were completely soluble in MeOH. The results shown in Figure 5 revealed that an initial increase in substrate concentration up to 0.5 M resulted in a more rapid reaction, which resembled the intermolecular reaction profile; but further increase in substrate concentration caused retardation of the reaction, probably due to the reduced amount of MeOH. This provides strong evidence that MeOH participated in the reaction, which is highly informative in the formulation of the mechanistic proposal.

**Observation of In(III) Complex Using ESI-MS Analysis.** We identified several In(III) complexes by ESI-MS analysis. After mixing 0.5 mmol of $InCl_3$ and 1.0 mmol of $Et_3SiH$ in 1.0 mL of MeOH, the mixture was subjected to ESI-MS experimental procedures. Similar results were obtained throughout the reaction time (15 min to 48 h). Four species were observed as shown in Figure 6. The major species had *m*/*z* at 249, and the three other minor species at 185, 217, and 281, respectively. In addition, an isotope pattern in a ratio of 9:6:1 was observed with 3 discrete peaks each differing by 2 *m*/*z* units. This pattern corresponds to the existence of 2 Cl atoms in each of the four observed species. This finding highlights that the coordination of In(III) species by MeOH is necessary for the observed hydride reactivity and chemoselectivity.

**SCHEME 2. Proposed Mechanism for the $InCl_3$/$Et_3SiH$/MeOH System-Promoted Reductive Amination**




**Proposed Mechanism.** On the basis of the above experimental results, a plausible reaction mechanism is proposed in Scheme 2. Initially, $InCl_3$ exchanges one Cl ligand with MeOH to form the cationic $[InCl_2(MeOH)_x]^+$ complex (**I**). Transmetalation with $Et_3SiH$ results in the active indium hydride species $[InHCl_2(MeOH)_{x-1}]$ (**II**). At the same time, $Et_3SiOMe$ is generated. We have ruled out the generation of $Et_3SiOMe$ from $Et_3SiCl$ and MeOH based on the results of a previously described NMR control experiment in which $Et_3SiCl$ was found to be stable in the presence of $InCl_3$ in $CD_3OD$. This active indium hydride complex then transfers the hydride to the in situ generated iminium ion, formed between the carbonyl compound and secondary amine·HCl salt, to give an intermediate complex (**III**). Finally, the product tertiary amine is released by MeOH displacement of **III** with the regeneration of $[InCl_2(MeOH)_x]^+$ complex (**I**) for another catalytic cycle.

**Significance of Donor Solvent Stabilization.** The existence of a MeOH-coordinated indium hydride complex has never been described in the literature. Therefore, its activity compared to that of the naked indium−hydride complex remains poorly characterized. The highly chemoselective behavior can be accounted for by the formation of MeOH-coordinated In−H complexes which provide a steric shield to the generated indium hydride species. Consequently, this methanol stabilization effect leads to more efficient hydride delivery to iminium ion.

Furthermore, this discovery is consistent with the results of solvent screening described in Table 1. A more sterically hindered alcohol results in less efficient chelation to the In(III) ion, reflected by the relative lower yield (cf. Table 1; entries 1−4). The strong withdrawing $CF_3$ group in $CF_3CH_2OH$ inhibits the donating ability of the oxygen atom, as revealed by the relatively lower yield based on conversion compared to that with EtOH as a solvent (cf. Table 1; entries 2 and 5).

## Conclusion

In conclusion, we have developed an $InCl_3$/$Et_3SiH$/MeOH system and explored its applications in reductive amination. We have discovered the existence of stable methanol-coordinated indium(III) species, which are presumably responsible for the gentle generation of indium hydride at room temperature. The system's superiority is underscored by its mild reducing

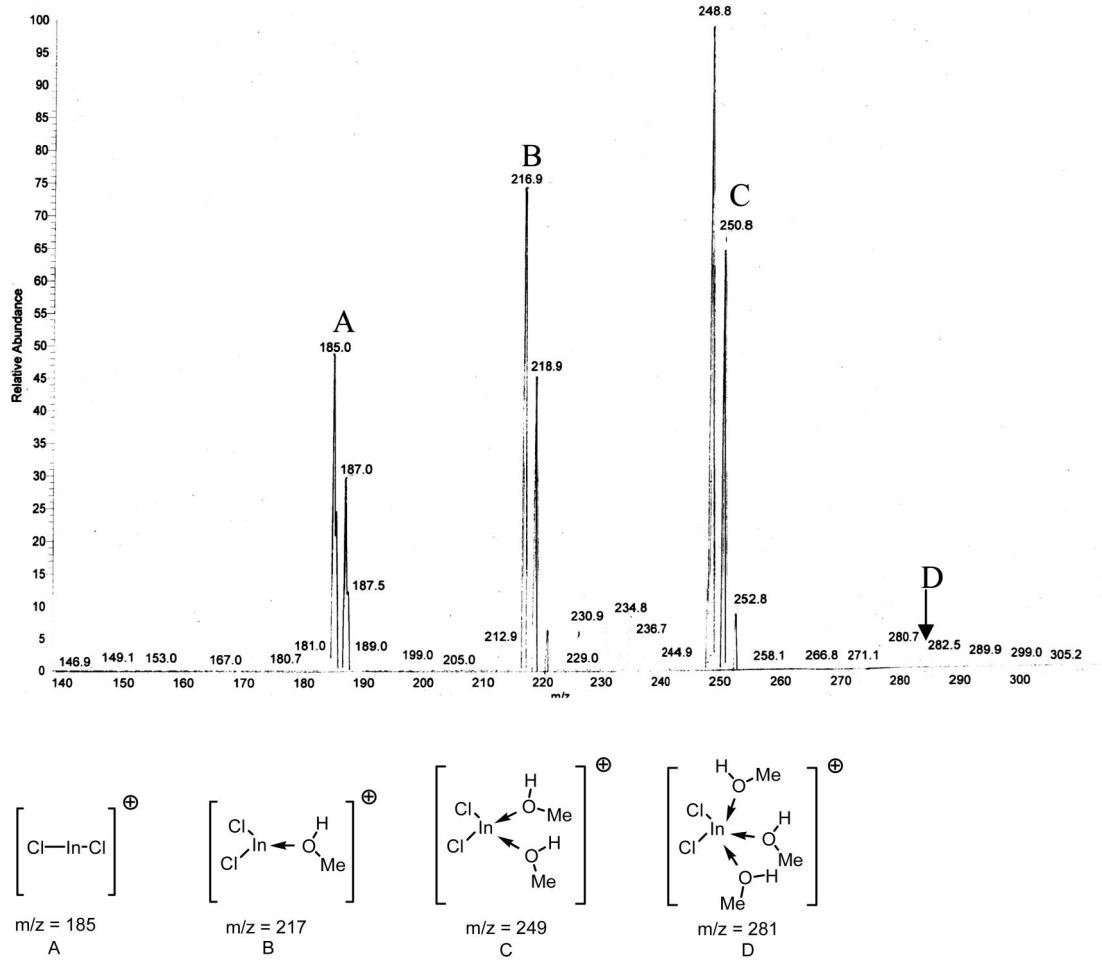



**FIGURE 6.** ESI-MS spectra of the reaction mixture of $InCl_3$ and $Et_3SiH$ in MeOH.

properties, functional group compatibility, and high chemoselectivity, which are desirable for efficient amine synthesis.

## Experimental Section

**Typical Procedure for Reductive Amination Catalyzed by the $InCl_3$/$Et_3SiH$/MeOH System: Formation of 3a−y.** To a stirred solution of carbonyl substrate (0.5 mmol) in methanol (1.0 mL) was added the corresponding amine·HCl salt (0.5 mmol) at room temperature. The mixture was stirred for 1 h. $Et_3SiH$ (0.15 mL, 1.0 mmol) was added by syringe and followed by $InCl_3$ (33 mg, 0.15 mmol). The reaction was allowed to stir at room temperature and was monitored by TLC. When the reaction was completed, the mixture was quenched by saturated $K_2CO_3$ solution (1.0 mL). The mixture was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layer was washed with brine (5.0 mL) and finally was dried over $Na_2SO_4$. The crude product was purified by flash column chromatography to afford product.

***N*-Cinnamyl-*N*-methylbenzenamine (3a):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.63; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.34 (m, 2H), 7.32−7.28 (m, 2H), 7.27−7.21 (m, 3H), 6.78 (dd, $J$ = 8.8, 0.8 Hz, 2 H), 6.72 (td, $J$ = 7.3, 0.8 Hz, 1H), 6.51 (d, $J$ = 15.9 Hz, 1H), 6.25 (dt, $J$ = 15.9, 5.5 Hz, 1H), 4.08 (dd, $J$ = 5.5, 1.6 Hz, 2H), 3.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 149.9, 137.2, 131.6, 129.5, 128.9, 127.7, 126.6, 126.1, 116.9, 112.9, 55.2, 38.4; IR ($CH_2Cl_2$) 3025, 2925, 1673, 1597, 1485 cm$^{-1}$; LRMS (EI) 223 ($M^+$, 19), 120 (49), 117 (100); HRMS (EI) calcd for $C_{16}H_{17}N$ ($M^+$) 223.1361, found 223.1360.

**1-Cinnamylpiperidine (3b):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.17; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.36 (m, 2H), 7.32−7.26 (m, 2H), 7.23−7.20 (m, 1H), 6.50 (d, $J$ = 15.9 Hz, 1H), 6.31 (dt, $J$ = 15.9, 6.7 Hz, 1H), 3.12 (d, $J$ = 6.7 Hz, 2H), 2.43 (br s, 4H), 1.64−1.58 (m, 4H), 1.45 (br s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 137.1, 132.6, 128.5, 127.4, 127.2, 126.3, 61.9, 54.6, 26.0, 24.3; IR ($CH_2Cl_2$) 3035, 2927, 2855, 1799, 1499, 1447 cm$^{-1}$; LRMS (EI) 201 ($M^+$, 100), 200 (77), 117 (46); HRMS (EI) calcd for $C_{14}H_{19}N$ ($M^+$) 201.1518, found 201.1504.

**4-Cinnamylmorpholine (3c):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.54; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.36 (m, 2H), 7.32−7.28 (m, 2H), 7.26−7.22 (m, 1H), 6.53 (d, $J$ = 15.9 Hz, 1H), 6.25, (dt, $J$ = 15.9, 6.8 Hz, 1H), 3.73 (t, $J$ = 4.7 Hz, 4H), 3.15 (dd, $J$ = 6.8, 1.3 Hz, 2H), 2.50 (br s, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.1, 133.7, 128.9, 127.9, 126.6, 126.3, 67.3, 61.8, 54.0; IR ($CH_2Cl_2$) 3035, 2921, 2853, 1495, 1447 cm$^{-1}$; LRMS (EI) 203 ($M^+$, 81), 117 (65), 112 (100); HRMS (EI) calcd for $C_{13}H_{17}NO$ ($M^+$) 203.1310, found 203.1304.

**1-Cinnamylpiperidin-4-one (3d):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.17; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40−7.37 (m, 2H), 7.34−7.29 (m, 2H), 7.27−7.21 (m, 1H), 6.63 (d, $J$ = 15.9 Hz, 1H), 6.30 (dt, $J$ = 15.9, 6.7 Hz, 1H), 3.26 (d, $J$ = 6.7 Hz, 2H), 2.80 (t, $J$ = 6.0 Hz, 4H), 2.48 (t, $J$ = 6.0 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.9, 136.6, 133.3, 128.5, 127.6, 126.3, 126.2, 59.9, 52.9, 41.2; IR ($CH_2Cl_2$) 3035, 1911, 2811, 1705, 1588, 1482 cm$^{-1}$; LRMS (EI) 215 ($M^+$, 65), 124 (99), 117 (100); HRMS (EI) calcd for $C_{14}H_{17}NO$ ($M^+$) 215.1310, found 215.1302.

**1-Cinnamylpiperidin-3-ol (3e):** analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f$ 0.25; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.39−7.20 (m, 5H), 6.50 (d, $J$ = 15.9 Hz, 1H), 6.24 (dt, $J$ = 15.9, 6.7 Hz, 1H), 3.84−3.81 (br m, 1H), 3.18 (d, $J$ = 6.7 Hz, 2H), 2.64

(br s, 2H), 2.41 (br s, 3H), 1.82−1.68 (br m, 2H), 1.57−1.52 (br m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 136.8, 132.9, 128.5, 127.4, 126.6, 126.3, 66.4, 61.0, 60.4, 53.5, 32.0, 21.9; IR ($CH_2Cl_2$) 3432, 2936, 2803, 1643 cm$^{-1}$; LRMS (EI) 217 ($M^+$, 43), 126 (100), 117 (59), 114 (58); HRMS (EI) calcd for $C_{14}H_{19}NO$ ($M^+$) 217.1467, found 217.1468.

**(*S*)-(1-Cinnamylpyrrolidin-2-yl)methanol (3f):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.24; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.37 (m, 2H), 7.33−7.29 (m, 2H), 7.25−7.21 (m, 1H), 6.53 (d, $J$ = 15.9 Hz, 1H), 6.28 (ddd, $J$ = 15.9, 7.6, 7.6 Hz, 1H), 3.68 (dd, $J$ = 10.8, 3.7 Hz, 1H), 3.57 (ddd, $J$ = 13.6, 5.8, 1.5 Hz, 1H), 3.44 (dd, $J$ = 10.8, 2.7 Hz, 1H), 3.19−3.14 (m, 1H), 3.11 (ddd, $J$ = 13.6, 7.6, 1.0 Hz, 1H), 2.74−2.68 (m, 1H), 2.45−2.36 (m, 1H), 1.95−1.88 (m, 1H), 1.82−1.80 (m, 2H), 1.76−1.71 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.0, 132.1, 128.6, 127.5, 127.4, 126.3, 64.0, 62.1, 56.5, 54.4, 27.9, 22.7; IR ($CH_2Cl_2$) 3690, 2929, 2856, 2362, 1609 cm$^{-1}$; LRMS (EI) 186 ($M^+ - CH_2OH$, 52), 117 (100); HRMS (EI) calcd for $C_{13}H_{16}N$ ($M^+ - CH_2OH$) 186.1282, found 186.1285.

**(*S*)-Methyl 1-cinnamylpyrrolidine-2-carboxylate (3g):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.22; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.37−7.35 (m, 2H), 7.32−7.27 (m, 2H), 7.24−7.19 (m, 1H), 6.51 (d, $J$ = 15.9 Hz, 1H), 6.32 (dt, $J$ = 15.9, 6.8 Hz, 1H), 3.64 (s, 3H), 3.43 (dd, $J$ = 13.1, 6.8 Hz, 1H), 3.31 (dd, $J$ = 13.1, 6.9 Hz, 1H), 3.25−3.16 (m, 2H), 2.40 (q, $J$ = 8.4 Hz, 1H), 2.22−2.11 (m, 1H), 1.98−1.89 (m, 2H), 1.86−1.79 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.6, 136.8, 132.4, 128.4, 127.4, 126.8, 126.2, 65.4, 57.0, 53.7, 51.8, 29.5, 23.0; IR ($CH_2Cl_2$) 3031, 2948, 1731, 1632, 1486, 1433 cm$^{-1}$; LRMS (EI) 245 ($M^+$, 13), 186 (56), 117 (100); HRMS (EI) calcd for $C_{15}H_{19}NO_2$ ($M^+$) 245.1416, found 245.1423.

**1-Cinnamylindoline-2-carboxylic acid (3h):** analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f$ 0.32; $^1$H NMR (400 MHz, $CD_3OD + D_2O$) $\delta$ 7.36−7.22 (m, 5H), 7.19−7.09 (m, 2H), 6.78 (t, $J$ = 7.4 Hz, 1H), 6.70−6.60 (m, 2H), 6.22 (dt, $J$ = 15.8, 6.5 Hz, 1H), 4.18 (t, $J$ = 9.6 Hz, 1H), 4.16−4.05 (m, 1H), 3.94 (dd, $J$ = 15.6, 7.3 Hz, 1H), 3.31 (dd, $J$ = 16.3, 10.6 Hz, 1H), 3.02 (dd, $J$ = 16.0, 8.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$) $\delta$ 181.2, 153.3, 138.4, 134.1, 129.7, 129.5, 128.4 (2C), 127.4, 126.3, 125.0, 118.7, 108.5, 69.3, 50.8, 35.4; IR ($CH_2Cl_2$) 3472, 3019, 2925, 1713, 1603 cm$^{-1}$; LRMS (EI) 233 ($M^+ - COOH$, 44), 117 (100); HRMS (EI) calcd for $C_{17}H_{15}N$ ($M^+ - COOH$) 233.1204, found 233.1208.

**(*E*)-*N*,*N*-Dibenzyl-3-phenylprop-2-en-1-amine (3i):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.60; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.38 (m, 4H), 7.36−7.26 (m, 8H), 7.24−7.19 (m, 3H), 6.52 (d, $J$ = 15.9 Hz, 1H), 6.29 (dt, $J$ = 15.9, 6.5 Hz, 1H), 3.62 (br s, 4H), 3.21 (dd, $J$ = 6.5, 1.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.6, 137.2, 132.4, 128.8, 128.5, 128.2, 127.7, 127.3, 126.8, 126.2, 57.9, 55.7; IR ($CH_2Cl_2$) 3025, 2925, 2797, 1491, 1439 cm$^{-1}$; LRMS (EI) 313 ($M^+$, 27), 222 (100), 117 (58); HRMS (EI) calcd for $C_{23}H_{23}N$ ($M^+$) 313.1831, found 313.1832.

***N*-Methyl-*N*-(2-methylallyl)benzenamine (3j):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.65; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.25−7.18 (m, 2H), 6.70−6.65 (m, 3H), 4.84 (br s, 1H), 4.80 (br s, 1H), 3.79 (s, 2H), 2.94 (s, 3 H), 1.53 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.0, 141.8, 129.4, 116.3, 112.4, 111.0, 59.1, 38.6, 20.4; IR ($CH_2Cl_2$) 2968, 2875, 1606, 1467, 1417 cm$^{-1}$; LRMS (EI) 161 ($M^+$, 16); HRMS (EI) calcd for $C_{11}H_{15}N$ ($M^+$) 161.1204, found 161.1212.

**(*E*)-*N*-Methyl-*N*-(2-methylbut-2-enyl)benzenamine (3k):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.64; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.23−7.17 (m, 2H), 6.74−6.64 (m, 3H), 5.34−5.28 (br m, 1H), 3.75 (s, 2H), 2.88 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.0, 131.8, 129.0, 119.3, 115.9, 112.0, 60.1, 37.8, 14.0, 13.1; IR ($CH_2Cl_2$) 3035, 2927, 1603, 1495, 1374 cm$^{-1}$; LRMS (EI) 175 ($M^+$, 61), 120 (100), 107 (52); HRMS (EI) calcd for $C_{12}H_{17}N$ ($M^+$) 175.1361, found 175.1363.

***N*-Methyl-*N*-(3-methylbut-2-enyl)benzenamine (3*l*):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.65; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24−7.20 (m, 2H), 6.74−6.67 (m, 3H), 5.20 (qt, $J$ = 6.4, 1.4 Hz, 1H), 3.88 (d, $J$ = 6.4 Hz, 2H), 2.88 (s, 3H), 1.71 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.1, 134.9, 129.4, 121.2, 116.7, 113.3, 50.8, 38.2, 26.0, 18.2; IR ($CH_2Cl_2$) 2954, 2907, 2867, 1599, 1506 cm$^{-1}$; LRMS (EI) 175 ($M^+$, 100), 153 (42), 145 (11); HRMS (EI) calcd for $C_{12}H_{17}N$ ($M^+$) 175.1361, found 175.1356.

***N*-(3,7-Dimethylocta-2,6-dienyl)-*N*-methylbenzenamine (3m):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.65; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.24−7.19 (m, 2H), 6.75−6.67 (m, 3H), 5.20 (t, $J$ = 6.3 Hz, 1H), 5.05 (t, $J$ = 5.6 Hz, 1H), 3.88 (d, $J$ = 6.3 Hz, 2H), 2.87 (s, 3H), 2.12−1.99 (m, 4H), 1.71−1.58 (m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.2, 138.5, 131.8, 129.4, 124.4, 122.1, 121.3, 116.8, 113.3, 50.8, 39.9, 38.2, 26.8, 26.1, 18.0, 16.6; IR ($CH_2Cl_2$) 2979, 2923, 2850, 1599, 1499, 1443, 1376 cm$^{-1}$; LRMS (EI) 243 ($M^+$, 78), 186 (23), 107 (100); HRMS (EI) calcd for $C_{17}H_{25}N$ ($M^+$) 243.1987, found 243.1988.

**(*Z*)-*N*-(Dec-4-enyl)-*N*-methylbenzenamine (3n):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.62; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.25−7.19 (m, 2H), 6.70−6.64 (m, 3H), 5.41−5.36 (m, 2H), 3.30 (t, $J$ = 7.6 Hz, 2H), 2.92 (s, 3H), 2.10−1.98 (m, 4H), 1.63 (quintet, $J$ = 7.4 Hz, 2H), 1.29−1.37 (m, 6H), 0.89 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.4, 130.8, 129.1, 128.8, 115.9, 112.2, 52.3, 38.2, 31.5, 29.4, 27.2, 26.6, 24.7, 22.6, 14.1; IR ($CH_2Cl_2$) 2933, 2868, 1606, 1505, 1382 cm$^{-1}$; LRMS (EI) 245 ($M^+$, 20), 120 (100); HRMS (EI) calcd for $C_{17}H_{27}N$ ($M^+$) 245.2144, found 245.2141.

**(*E*)-1-(Dec-4-enyl)piperidin-4-one (3o):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.66; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.49−5.34 (m, 2H), 2.74 (t, $J$ = 6.1 Hz, 4H), 2.47−2.42 (m, 6H), 2.11−1.94 (br m, 4H), 1.59 (quintet, $J$ = 7.5 Hz, 2H), 1.39−1.25 (br m, 6H), 0.88 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 209.3, 131.2, 129.4, 56.9, 53.2, 41.3, 32.5, 31.4, 30.4, 29.3, 27.3, 22.5, 14.1; IR ($CH_2Cl_2$) 2979, 2929, 2861, 1705, 1449, 1353 cm$^{-1}$; LRMS (EI) 237 ($M^+$, 1), 138 (12), 112 (100); HRMS (EI) calcd for $C_{15}H_{27}NO$ ($M^+$) 237.2093, found 237.2087.

**(*S*,*E*)-Methyl 1-(dec-4-enyl)pyrrolidine-2-carboxylate (3p):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.66; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.43−5.33 (m, 2H), 3.72 (s, 3H), 3.21−3.16 (m, 1H), 3.13 (dd, $J$ = 8.9, 6.0 Hz, 1H), 2.68−2.61 (m, 1H), 2.41−2.29 (m, 2H), 2.17−2.05 (m, 1H), 2.03−1.86 (m, 6H), 1.81−1.76 (m, 1H), 1.55 (quintet, $J$ = 7.6 Hz, 2H), 1.35−1.23 (m, 6H), 0.88 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.2, 131.2, 129.8, 66.5, 55.1, 53.9, 52.1, 32.8, 31.7, 30.8, 29.7, 29.6, 28.8, 23.5, 22.8, 14.4; IR ($CH_2Cl_2$) 2933, 2860, 1745, 1470 cm$^{-1}$; LRMS (EI) 209 ($M^+ - C_2H_2O_2$, 20), 208 ($M^+ -$ COOMe, 100); HRMS (EI) calcd for $C_{14}H_{26}N$ ($M^+ -$ COOMe) 208.2065, found 208.2062.

***N*-Hexyl-*N*-methylbenzenamine (3q):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.66; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24−7.19 (m, 2H), 6.70−6.64 (m, 3H), 3.29 (t, $J$ = 7.5 Hz, 2H), 2.91 (s, 3H), 1.65−1.54 (m, 2H), 1.30 (br s, 6H), 0.89 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.7, 129.5, 116.1, 112.4, 53.2, 38.6, 32.1, 27.2, 27.0, 23.0, 14.4; IR ($CH_2Cl_2$) 2967, 2921, 2853, 1599, 1507, 1459, 1370 cm$^{-1}$; LRMS (EI) 191 ($M^+$, 15), 153 (13), 120 (100); HRMS (EI) calcd for $C_{13}H_{21}N$ ($M^+$) 191.1674, found 191.1673.

***N*-(4-Methoxybenzyl)-*N*-methylbenzenamine (3r):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.34; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.23−7.17 (m, 2H), 7.13 (d, $J$ = 8.7 Hz, 2H), 6.82 (d, $J$ = 8.7 Hz, 2H), 6.75−6.67 (m, 3H), 4.43 (s, 2H), 3.74 (s, 3H), 2.95 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 158.5, 149.8, 130.8, 129.1, 127.9, 116.5, 113.9, 112.4, 56.0, 55.2, 38.2; IR ($CH_2Cl_2$) 3049, 2933, 2837, 1601, 1510, 1467 cm$^{-1}$; LRMS (EI) 227 ($M^+$, 35), 121 (100); HRMS (EI) calcd for $C_{15}H_{17}NO$ ($M^+$) 227.1310, found 227.1306 ($M^+$).

**4-(4-Methoxybenzyl)morpholine (3s):** analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f$ 0.30; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 3.78 (s, 3H), 3.69 (t, $J$ = 4.6 Hz, 4H), 3.43 (s, 2H), 2.41 (t, $J$ = 4.6 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.1, 130.6, 130.0, 113.9, 67.3, 63.1, 55.5, 53.8; IR ($CH_2Cl_2$) 3017, 1961, 2867, 2805, 1611, 1511, 1455 cm$^{-1}$; LRMS (EI) 207 ($M^+$, 31), 121 (100); HRMS (EI) calcd for $C_{12}H_{17}NO_2$ ($M^+$) 207.1259, found 207.1248.

**(*S*)-Methyl 1-(4-methoxybenzyl)pyrrolidine-2-carboxylate (3t):** analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f$ 0.44; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24−7.21 (m, 2H), 6.86−6.82 (m, 2H), 3.80 (d, $J$ = 12.7 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.52 (d, $J$ = 12.7 Hz, 1H), 3.21 (dd, $J$ = 9.0, 6.5 Hz, 1H), 3.06−3.01 (m, 1H), 2.37 (q, $J$ = 8.7 Hz, 1H), 2.17−2.09 (m, 1H), 1.98−1.87 (m, 1H), 1.84−1.72 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.9, 159.0, 130.7, 130.6, 113.8, 65.4, 58.3, 55.5, 53.5, 52.0, 29.7, 23.2; IR ($CH_2Cl_2$) 3046, 2956, 2834, 1734, 1605, 1511, 1443 cm$^{-1}$; LRMS (EI) 249 ($M^+$, 2), 190 (100); HRMS (EI) calcd for $C_{14}H_{19}NO_3$ ($M^+$) 249.1365, found 249.1376.

***N*-Cyclopentyl-*N*-methylbenzenamine (3u):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.48; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.25−7.19 (m, 2H), 6.83−6.80 (d, $J$ = 8.0 Hz, 2H), 6.70 (t, $J$ = 7.2 Hz, 1H), 4.14 (quintet, $J$ = 7.9 Hz, 1H), 2.77 (s, 3H), 1.88−1.83 (m, 2H), 1.71−1.67 (m, 2H), 1.63−1.54 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.4, 129.3, 117.1, 114.4, 60.6, 32.9, 29.0, 24.7; IR ($CH_2Cl_2$) 2946, 2861, 1597, 1504 cm$^{-1}$; LRMS (EI) 175 ($M^+$, 36), 146 (100); HRMS (EI) calcd for $C_{12}H_{17}N$ ($M^+$) 175.1361, found 175.1359.

***N*-Cyclohexyl-*N*-methylbenzenamine (3v):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.47; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25−7.19 (m, 2H), 6.78 (d, $J$ = 8.1 Hz, 2H), 6.68 (t, $J$ = 7.2 Hz, 1H), 3.56 (tt, $J$ = 14.8, 3.4 Hz, 1H), 2.77 (s, 3H), 1.85−1.77 (m, 4H), 1.70−1.67 (m, 1H), 1.50−1.33 (m, 4H), 1.18−1.10 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.3, 129.2, 116.4, 113.3, 58.2, 31.3, 30.2, 26.4, 26.1; IR ($CH_2Cl_2$) 2946, 2861, 1597, 1504 cm$^{-1}$; LRMS (EI) 189 ($M^+$, 26), 146 (100), 132 (20); HRMS (EI) calcd for $C_{13}H_{19}N$ ($M^+$) 189.1518, found 189.1517.

***N*-Methyl-*N*-phenylcycloheptanamine (3w):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.48; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24−7.19 (m, 2H), 6.75 (d, $J$ = 8.1 Hz, 2H), 6.67 (t, $J$ = 7.2 Hz, 1H), 3.77 (tt, $J$ = 9.9, 3.6 Hz,1H), 2.75 (s, 3H), 1.93−1.79 (m, 2H), 1.78−1.69 (m, 2H), 1.67−1.59 (m, 4H), 1.58−1.43 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.4, 129.5, 116.5, 113.4, 60.1, 32.4, 31.7, 28.1, 26.0; IR ($CH_2Cl_2$) 3023, 2929, 2873, 1588, 1499 cm$^{-1}$; LRMS (EI) 203 ($M^+$, 31), 146 (100); HRMS (EI) calcd for $C_{14}H_{21}N$ ($M^+$) 203.1674, found 203.1668.

***N*-Methyl-*N*-phenyl-2,3-dihydro-1*H*-inden-2-amine (3x):** analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f$ 0.30; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25−7.18 (m, 4H), 7.16−7.13 (m, 2H), 6.86 (d, $J$ = 8.0 Hz, 2H), 6.74 (t, $J$ = 7.3 Hz, 1H), 4.74 (quintet, $J$ = 7.4 Hz, 1H), 3.15 (dd, $J$ = 16.2, 8.1 Hz, 2H), 3.02 (dd, $J$ = 16.2, 6.8 Hz, 2H), 2.72 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.8, 142.0, 129.5, 126.8, 124.8, 117.8, 114.8, 59.7, 36.3, 33.2; IR ($CH_2Cl_2$) 3073, 3029, 2950, 2906, 1599, 1504 cm$^{-1}$; LRMS (EI) 223 ($M^+$, 100), 208 (12), 116 (15); HRMS (EI) calcd for $C_{16}H_{17}N$ ($M^+$) 223.1361, found 223.1359.

**1-Cyclopentyl-1,2,3,4-tetrahydroquinoline (3y):** analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f$ 0.38; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.03 (t, $J$ = 7.7 Hz, 1H), 6.91 (d, $J$ = 7.2 Hz, 1H), 6.70 (d, $J$ = 8.3 Hz, 1H), 6.53 (t, $J$ = 7.2 Hz, 1H), 4.17 (quintet, $J$ = 7.7 Hz, 1H), 3.16 (t, $J$ = 5.8 Hz, 2H), 2.71 (t, $J$ = 6.4 Hz, 2H), 1.92−1.84 (m, 4H), 1.70−1.59 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 146.2, 128.9, 127.0, 123.2, 115.2, 111.0, 58.5, 42.0, 28.4, 28.0, 24.1, 22.6; IR ($CH_2Cl_2$) 2956, 1605, 1501 cm$^{-1}$; LRMS (EI) 201 ($M^+$, 59), 172 (100); HRMS (EI) calcd for $C_{14}H_{19}N$ ($M^+$) 201.1518, found 201.1517.

**Acknowledgment.** This work was supported by The University of Hong Kong and Hong Kong Research Grants Council.

**Supporting Information Available:** Spectral characterization data for compounds **3a**−**y**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8016082