JOC*Note*

$FeSO_4\cdot 7H_2O$-Catalyzed Four-Component Synthesis of Protected Homoallylic Amines

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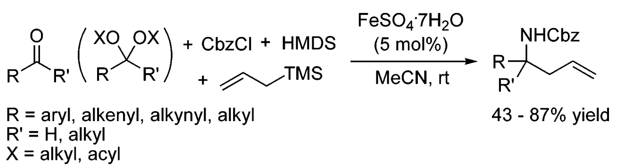
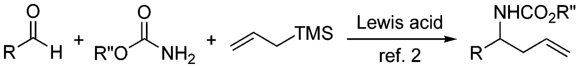


An efficient catalytic four-component reaction of carbonyl compounds (or acetals/ketals), benzyl chloroformate (CbzCl), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and allyltrimethylsilane has been successfully developed to produce Cbz-protected homoallylic amines in the presence of 5 mol % of iron(II) sulfate heptahydrate ($FeSO_4\cdot 7H_2O$), an inexpensive and environmentally friendly catalyst, at room temperature.

One of the most promising approaches to construct complex organic molecules is being pursued by the development of multicomponent reactions (MCRs) that involve the one-pot transformation of three or more starting materials into a single product that incorporates portions of all of the reactants.[1] When compared with the sequential synthesis of the same target by conventional bimolecular reactions, MCRs provide significant advantages such as the atom economical and convergent character, the simplicity of the one-pot procedure, the possible structural variations, and the accessible complexity of the molecules. Recent years have witnessed a number of applications of MCRs in the construction of homoallylic amines,[2−5] useful intermediates in organic synthesis,[6] which are commonly synthesized by the allylation of aldimines, prepared from the corresponding aldehydes and amines in advance using various allylic nucleophiles.[7] Among these MCRs that avoid the prior synthesis of aldimines, the three-component reaction of aldehydes, carbamates, and allyltrimethylsilane to construct the alkoxycarbonyl-protected homoallylic amines (eq 1) is particularly interesting in that the protecting groups are most often employed to handle amines in organic synthesis and can easily undergo further conversions using well-established protective group chemistry without affecting the double bonds.[8]



(1)

The replacement of the carbamate in the above three-component reaction with *N*-silylcarbamate reported by Yokozawa and co-workers not only allowed the reaction to proceed under milder reaction conditions but also extended the chemistry to a couple of simple ketones, though the yields were far from satisfactory.[2h] Given that *N*-silylcarbamate could be easily prepared from the corresponding alkyl chloroformate and 1,1,1,3,3,3-hexamethyldisilazane (HMDS),[9] a four-component

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(1) For reviews, see: (a) Dondoni, A.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (e) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (f) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471. (g) Döemling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (h) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

(2) For the three-component reaction of carbonyl compounds, carbamates, and allyltrialkylsilanes, see: (a) Smitha, G.; Miriyala, B.; Williamson, J. S. *Synlett* **2005**, 839. (b) Ella-Menye, J.-R.; Dobbs, W.; Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2005**, *46*, 1897. (c) Lipomi, D. J.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4701. (d) Kalita, H. R.; Phukan, P. *Synth. Commun.* **2005**, *35*, 475. (e) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005. (f) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003. (g) Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 631. (h) Niimi, L.; Serita, K.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* **2000**, *41*, 7075. (i) Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601. (j) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997.

(3) For the three-component reaction of aldehydes, amines, and allylic organometallics, see: (a) Das, B.; Laxminarayana, K.; Ravikanth, B.; Ramarao, B. *Tetrahedron Lett.* **2006**, *47*, 9103. (b) Das, B.; Ravikanth, B.; Thirupathi, P.; Rao, B. V. *Tetrahedron Lett.* **2006**, *47*, 5041. (c) Li, G.-l.; Zhao, G. *Synthesis* **2006**, 3189. (d) Choudary, B. M.; Jyothi, K.; Madhi, S.; Kantam, M. L. *Synlett* **2004**, 231. (e) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323. (f) Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1157. (g) Akiyama, T.; Iwai, J.; Onuma, Y. Kagoshima, H. *Chem. Commun.* **1999**, 2191.

(4) For the three-component reaction of carbonyl compounds, ammonia, and allyl boron reagents, see: (a) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551. (b) Kobayashi, S.; Hirano, K.; Sugiura, M. *Chem. Commun.* **2005**, 104. (c) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.

(5) For the three-component reaction of aldehydes, tosylamide, and α-methylstyrene, see: Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, *68*, 3112.

(6) For some of the recent applications of homoallylic amines in organic synthesis, see: (a) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046. (b) Friestad, G. K.; Korapala, C. S.; Ding, H. *J. Org. Chem.* **2006**, *71*, 281. (c) Pandey, M. K.; Bisai, A.; Pandey, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 5039. (d) Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669. (e) Ramachandran, P. V.; Burghardt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911. (f) Varlamov, A. V.; Zubkov, F. I.; Boltukhina, E. V.; Sidorenko, N. V.; Borisov, R. S. *Tetrahedron Lett.* **2003**, *44*, 3641. (g) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932. (h) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879. (h) Kim, G.; Jung, S.; Lee, E.; Kim, N. *J. Org. Chem.* **2003**, *68*, 5395. (i) Jain, R. P.; Williams, R. M. *J. Org. Chem.* **2002**, *67*, 6361. (j) Expósito, A.; Fernández-Suárez, M.; Iglesias, T.; Muñoz, L.; Riguera, R. *J. Org. Chem.* **2001**, *66*, 4206. (k) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (l) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771.

(7) For reviews, see: (a) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. For the allylation of acylhydrazones, see: (e) Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176. (f) Kobayashi, S.; Sugiura, M.; Ogawa, C. *Adv. Synth. Catal.* **2004**, *346*, 1023.

(8) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(9) Pump, J.; Wannagat, U. *Monatsh. Chem.* **1962**, *93*, 352.

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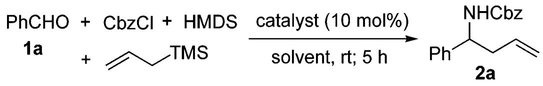
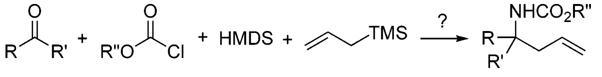
TABLE 1. Survey of Lewis Acid Catalysts and Solvents[a]



entry	catalyst	solvent	conversion (%)[b]
1	None	MeCN	*c*
2	$BiCl_3$	MeCN	74
3	$CeCl_3 \cdot 7H_2O$	MeCN	80
4	$H_3PMo_{12}O_{40}$	MeCN	86
5	$FeCl_3$	MeCN	91
6	$FeCl_3 \cdot 6H_2O$	MeCN	72
7	$FeCl_2 \cdot 4H_2O$	MeCN	50
8	$Fe_2(SO_4)_3 \cdot 5H_2O$	MeCN	*c*
9	$FeSO_4 \cdot 7H_2O$	MeCN	**98**
10	$FeSO_4 \cdot 7H_2O$	THF	40
11	$FeSO_4 \cdot 7H_2O$	CH_2Cl_2	65
12	$FeSO_4 \cdot 7H_2O$	$CHCl_3$	32

[a] The reaction was performed by the treatment of **1a** (0.20 mmol) in solvent (1.0 mL) at room temperature with CbzCl (1.2 equiv), HMDS (1.2 equiv), allyltrimethylsilane (1.2 equiv), and catalyst (10 mol %). [b] Determined by proton NMR analysis. [c] No or trace amount of **2a** was detected by TLC.

reaction of carbonyl compounds, alkyl chloroformate, HMDS, and allyltrimethylsilane was envisioned to facilitate the synthesis of the alkoxycarbonyl-protected homoallylic amines by avoiding the prior synthesis of *N*-silylcarbamate (eq 2). However, to our knowledge, there was no four-component synthesis of homoallylic amines reported previously, and the presence of both two electrophiles (carbonyl compound and alkyl chloroformate) and two nucleophiles (HMDS and allyltrimethylsilane) in a one-pot reaction offers a formidable challenge to drive this reaction, as compared to the corresponding three-component reaction where there is only one electrophile (carbonyl compound) present, to give the desired homoallylic amine as the predominant product. Besides the possible allylation of the carbonyl compound, one more obvious side reaction may result from electrophilic alkyl chloroformate and nucleophilic allyltrimethylsilane.[10] Herein we wish to report an efficient four-component reaction of carbonyl compounds (or acetals/ketals), benzyl chloroformate (CbzCl), HMDS, and allyltrimethylsilane to produce Cbz-protected homoallylic amines in the presence of 5 mol % of iron(II) sulfate heptahydrate ($FeSO_4 \cdot 7H_2O$), an inexpensive and environmentally friendly catalyst, at room temperature.



(2)

The search for proper catalytic conditions for the four-component reaction of carbonyl compounds, alkyl chloroformate, HMDS, and allyltrimethylsilane was launched with the evaluation of a wide variety of commercially available solid Lewis acids (Table 1). This catalytic four-component reaction was performed under a "pure" MCR condition[1h] by adding successively CbzCl, HMDS, allyltrimethylsilane, and Lewis acid (10 mol %) to a stirred solution of benzaldehyde (**1a**) in acetonitrile at room temperature, and the conversion of benzaldehyde (**1a**) was determined by proton NMR analysis.[11] To our delight, inexpensive and environmentally friendly $FeSO_4 \cdot 7H_2O$ was identified as a highly effective catalyst,[12] with which the reaction proceeded in 98% conversion (entry 9, Table 1). Interestingly, $FeSO_4 \cdot 7H_2O$ was found to be ineffective in catalyzing the corresponding three-component reaction of benzaldehyde (**1a**), $CbzNH_2$, and allyltrimethylsilane. Further survey of the reaction conditions revealed that acetonitrile was the solvent of choice (Table 1), and the catalyst loading could be lowered down without sacrificing the yield. In the presence of 5 mol % of $FeSO_4 \cdot 7H_2O$, the reaction gave product **2a** in 87% yield (vide infra). The reaction proceeded well with other alkyl chloroformates such as PhOCOCl (74% yield) and EtOCOCl (78% yield). However, the replacement of CbzCl with PhCOCl, Boc_2O, or TsCl led to less than 40% yield or no desired product at all.[13] In addition, using $BnNH_2$ instead of HMDS in this four-component reaction failed to give the desired homoallylic amine.

The substrate scope for the four-component reaction of carbonyl compounds, CbzCl, HMDS, and allyltrimethylsilane was found to be very general (Table 2). In the presence of 5 mol % of $FeSO_4 \cdot 7H_2O$, a variety of conjugated and unconjugated aldehydes were successfully transformed to their corresponding homoallylic amines at room temperature (entries 1–12, Table 2) in good yields. Importantly, acid-sensitive TBS ether was allowed (entry 5, Table 2), and cyclic ketones (entries 13 and 14, Table 2) could also serve as suitable substrates for this four-component reaction.[14] Furthermore, this chemistry was successfully extended to various masked carbonyl compounds (entries 15–23, Table 2) that, stable in the air and inert to many nucleophiles, provide significant advantages over the corresponding aldehydes or ketones in synthetic manipulations. It is notable that varied yields for the synthesis of the same Cbz-protected homoallylic amine could be obtained from different acetal derivatives of the aldehyde (entries 15–18, Table 2). In addition, the use of the acetal derivative of an aldehyde with low boiling point (e.g., acetaldehyde) could greatly facilitate the synthesis of the corresponding Cbz-protected homoallylic amine at room temperature (entry 22, Table 2).[15]

Because CbzCl could quickly react with HMDS in the absence of catalyst to generate *N*-silylcarbamate CbzNH(TMS) and chlorotrimethylsilane (TMSCl),[9,16] $FeSO_4 \cdot 7H_2O$ itself or in combination with TMSCl should promote the subsequent three-component reaction of carbonyl compounds (or acetals/ketals), CbzNH(TMS), and allyltrimethylsilane. Thus, on the basis of the studies reported in the literature,[2] we propose a reaction pathway in which imine **4** should be generated as a key intermediate for the formation of homoallylic amine **5**, which can be hydrolyzed to give **2**, in the four-component reaction of carbonyl compounds (or acetals/ketals), CbzCl, HMDS, and allyltrimethylsilane (Scheme 1). In order to gain more insights into the role played by $FeSO_4 \cdot 7H_2O$, imine **4a** was prepared in

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[10] Alkyl chloroformate was reported to react with allyltrimethylsilane in the presence of Lewis acids. See: (a) Olah, G. A.; VanVliet, D. S.; Wang, Q.; Prakash, G. K. S. *Synthesis* **1995**, 159. (b) Mayr, H.; Gabriel, A. O.; Schumacher, R. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 1583.

[11] The proton NMR analysis was carried out only when a significant amount of product **2a** was detected by TLC. For all entries of Table 1, the only detectable byproduct, if any, was benzoic acid, which was taken into account when calculating the conversion of benzaldehyde (**1a**).

[12] For a review on the catalysis with iron, see: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

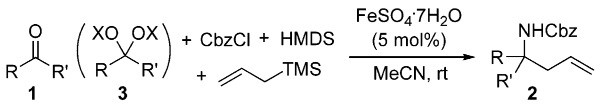
[13] For the reaction with TsCl, PhCH=NTs was the major product.

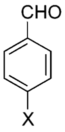
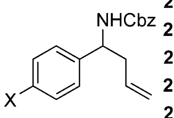
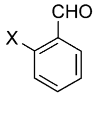
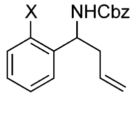
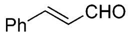
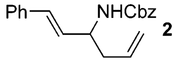
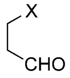
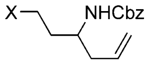
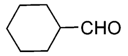
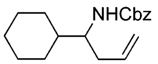
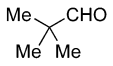
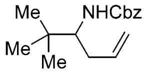
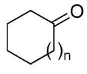
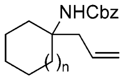
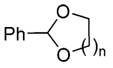
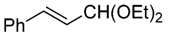
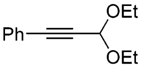
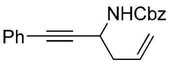
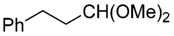
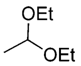
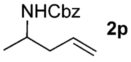
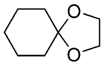
[14] The four-component reaction involving either cyclopentanone or acyclic 2-heptanone proceeded in less than 30% yield.

[15] The boiling point of acetaldehyde is 21°C, and that of acetaldehyde diethyl acetal (**3h**) is 103 °C.

[16] We observed that CbzNH(TMS) was generated quickly, and its amount was shown by TLC to decrease gradually in this four-component reaction. CbzNH(TMS) decomposed to $CbzNH_2$ on a TLC plate because of its sensitivity to moisture.

TABLE 2. Iron-Catalyzed Four-Component Synthesis of Protected Homoallylic Amines[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **1a:** X = H	 **2a**	18	87
2	**1b:** X = OMe	**2b**	18	71
3	**1c:** X = Cl	**2c**	20	80
4	**1d:** X = NO_2	**2d**	34	53
5	**1e:** X = OTBS	**2e**	24	63
6	 **1f:** X = OMe	 **2f**	3	86
7	**1g:** X = Cl	**2g**	24	78
8	 **1h**	 **2h**	3	79
9	 **1i:** X = Ph	 **2i**	20	70
10	**1j:** X = CH_2OBn	**2j**	21	59
11	 **1k**	 **2k**	24	86
12	 **1l**	 **2l**	51	43
13	 **1m:** n = 1	 **2m**	48	70
14	**1n:** n = 2	**2n**	48	56
15	$PhCH(OEt)_2$ **3a**	**2a**	4	80
16	 **3b:** n = 1	**2a**	24	73
17	**3c:** n = 2	**2a**	96	49
18	$PhCH(OAc)_2$ **3d**	**2a**	24	61
19	 **3e**	**2h**	3	61
20	 **3f**	 **2o**	24	48
21	 **3g**	**2i**	4	74
22	 **3h**	 **2p**	2	61
23	 **3i**	**2m**	47	56

[a] The reaction was performed by the treatment of substrate **1** or **3** (0.50 mmol) in dry MeCN (0.50 mL) at room temperature with CbzCl (1.2 equiv), HMDS (1.2 equiv), allyltrimethylsilane (1.2 equiv), and $FeSO_4·7H_2O$ (5 mol %). [b] Isolated yield.

SCHEME 1 . Proposed Major Reaction Pathway

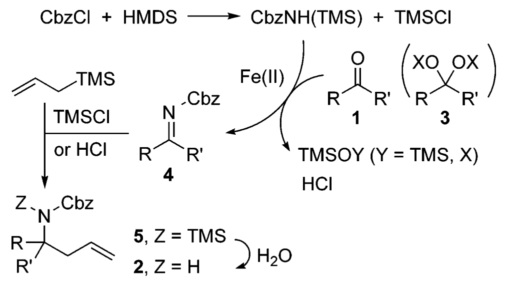
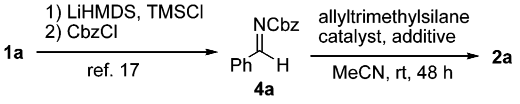


TABLE 3. Allylation of Imine 4a



entry	catalyst (mol %)	additive (equiv)	yield (%)[a]
1			*b*
2	$FeSO_4·7H_2O$ (10)		*b*
3	Fe(II) (10)[c]		*b*
4	$FeSO_4·7H_2O$ (10)	TMSCl (1.2)	58
5	$FeSO_4·7H_2O$ (10)	TMSCl (0.30)	9.7
6		TMSCl (1.2)	58
7		TMSCl (0.30)	8.3
8		TMSCl (0.30) + H_2O (0.15)	11

[a] Isolated yield. [b] No or trace amount of **2a** was detected by TLC. [c] Prepared from $FeSO_4·7H_2O$ and TMSCl (10 equiv) at room temperature.

situ from benzaldehyde (**1a**)[17] and subjected to the allylation with allyltrimethylsilane (Table 3). Surprisingly, neither $FeSO_4·7H_2O$ nor the iron(II) species prepared from $FeSO_4·7H_2O$ and TMSCl[18] could catalyze the allylation of imine **4a** (entries 2 and 3, Table 3), which instead could be promoted by either TMSCl (entries 6 and 7, Table 3) or HCl (generated in situ from TMSCl and water, entry 8, Table 3). Nevertheless, $FeSO_4·7H_2O$ (10 mol %) itself was found to be able to catalyze the corresponding three-component reaction of benzaldehyde (**1a**), CbzNH(TMS), and allyltrimethylsilane to give product **2a** in 14% yield in 48 h, and the replacement of $FeSO_4·7H_2O$ with either TMSCl (1.2 equiv) or water (0.10−0.70 equiv to generate HCl in situ) in the four-component reaction only gave product **2a** in less than 5% yield. Taken together, $FeSO_4·7H_2O$ should play a major role for the generation of imine **4**, and TMSCl and/or HCl generated previously should be the major promoter(s) for the allylation of imine **4** to generate product(s) **5** and/or **2**, respectively.

In summary, we have developed, for the first time, an efficient catalytic four-component reaction of carbonyl compounds (or acetals/ketals), CbzCl, HMDS and allyltrimethylsilane. In the presence of a catalytic amount of inexpensive and environmentally friendly $FeSO_4·7H_2O$, a wide variety of aldehydes, ketones, acetals and ketals were successfully transformed to their corresponding Cbz-protected homoallylic amines by performing the four-component reactions under mild reaction conditions. This protocol not only presents a novel four-component synthesis of Cbz-protected homoallylic amines, but also adds a synthetically useful entry into the catalysis with iron(II) salts. Further extension of this chemistry to other catalytic MCRs is ongoing.

Experimental Section

General Procedure for the Four-Component Reaction. To a stirred solution of carbonyl compound **1** (or acetal/ketal **3**, 0.50 mmol) in dry acetonitrile (0.50 mL) at room temperature were added CbzCl (102 mg, 0.086 mL, 0.60 mmol), HMDS (96.8 mg, 0.125

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[17] (a) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15. (b) Kupfer, R.; Meier, S.; Wurtwein, E.-U. *Synthesis* **1984**, 688. (c) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.

[18] The iron(II) species was prepared by the treatment of $FeSO_4·7H_2O$ with TMSCl (10 equiv) at room temperature for 24 h and the subsequent evaporation under reduced pressure.

mL, 0.60 mmol), allyltrimethylsiliane (68.6 mg, 0.095 mL, 0.60 mmol), and $FeSO_4 \cdot 7H_2O$ (7.0 mg, 5 mol %). When the reaction did not proceed further as indicated by TLC, the reaction mixture was concentrated and purified by flash column chromatography on silica gel (eluting with 40:1 petroleum ether/EtOAc) to give homoallylic amine **2**.

General Procedure for the Allylation of Imine 4a. Imine **4a** was prepared in situ from benzaldehyde (**1a**) according to the known procedures.[17] To a stirred solution of crude imine **4a** (0.25 mmol) in dry acetonitrile (0.25 mL) at room temperature were added allyltrimethylsilane (34.3 mg, 0.048 mL, 0.30 mmol) and catalyst (if any, 10 mol %). The reaction mixture was stirred for 48 h and purified by flash column chromatography on silica gel to give product **2a** (if any).

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Supporting Information Available: General information, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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