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Byproduct-Catalyzed Four-Component Reactions of Aldehydes with Hexamethyldisilazane, Chloroformates, and Nucleophiles in Acetonitrile Leading to Protected Primary Amines, β-Amino Esters, and β-Amino Ketones

Bai-Ling Yang, Zhen-Tao Weng, Si-Jie Yang, and Shi-Kai Tian*[a]

Abstract: Multicomponent reactions are a very powerful tool for the construction of complex organic molecules by using readily available starting materials. While most of the multicomponent reactions discovered so far consist of three components, the reactions with four or more components remain sparse. We have successfully developed several four-component reactions using a catalytic amount of water as a hydrolyzing agent to decompose byproduct chlorotrimethylsilane (TMSCl) to yield secondary byproduct HCl that serves as a catalyst. In the presence of 40 mol % of water, the four-component reaction of aldehydes with hexamethyldisilazane (HMDS), chloroformates, and silylated nucleophiles proceeds smoothly at room temperature to give a range of protected primary amines in moderate to excellent yields. Importantly, a wide variety of protic carbon nucleophiles, such as β-keto esters, β-diketones, and ketones, have further been explored as suitable substrates for the synthesis of protected β-amino esters and β-amino ketones that are useful building blocks for various pharmaceuticals and natural products. These four-component reactions proceed through a pathway of tandem nitrogen protection/imine formation/imine addition, and the decomposition of byproduct TMSCl, generated in the first step of nitrogen protection, with water results in the formation of secondary byproduct HCl, a strong Brønsted acid that catalyzes the following imine formation/imine addition. Taking advantage of the fact that alcohols or phenols are also able to decompose byproduct TMSCl to yield secondary byproduct HCl, no catalyst is needed at all for the four-component reactions with aldehydes bearing hydroxy groups.

Keywords: aldehydes · chloroformates · hexamethyldisilazane · multicomponent reactions · water chemistry

Introduction

Multicomponent reactions involve the one-pot transformation of three or more starting materials into a single product that incorporates portions of all the reactants, and are, therefore, very powerful for the construction of complex organic molecules by using readily available starting materials.[1] Owing to their intrinsic step economy, multicomponent reactions, particularly those with more than three components, exhibit much higher efficiency relative to the sequential synthesis of the same targets by conventional bimolecular reactions. In addition, this approach is a greener alternative to multistep bimolecular reactions through the minimization of the amount of solvents and reagents needed for the reactions and purifications. While most of the multicomponent reactions discovered so far consist of three components, the reactions with four or more components remain sparse.

We discovered recently a room temperature, $FeSO_4 \cdot 7H_2O$-catalyzed four-component reaction of aldehydes with hexamethyldisilazane (HMDS), chloroformates, and silylated nucleophiles [Eq. (1)],[2] which was found later by Ramón and Yus to proceed smoothly in the presence of unmodified nanopowder magnetite at 110 °C.[3] The products resulting from these multicomponent reactions are alkoxycarbonyl-protected primary amines (carbamates), which are widely used as synthetic intermediates for biologically important molecules. In addition, the alkoxycarbonyl groups

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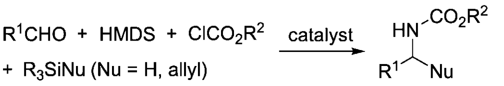
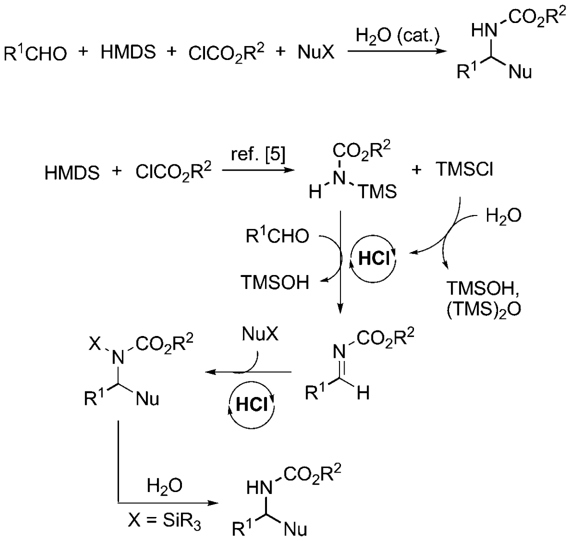
can be readily removed from the nitrogen atoms by using well-established protective-group chemistry.[4]



(1)

Mechanistic studies indicate that the above four-component reaction proceeds through a pathway of tandem nitrogen protection/imine formation/imine addition.[2,3] While the first step can occur in the absence of catalysts, the last two steps are promoted by acidic species. Importantly, byproduct chlorotrimethylsilane (TMSCl), a silicon Lewis acid generated by the reaction of HMDS with a chloroformate,[5] plays a vital role in combination with an iron species in promoting the imine formation/imine addition. These studies prompted us to use water to promote the four-component reaction by taking advantage of the fact that the decomposition of byproduct TMSCl with water results in the formation of secondary byproduct HCl, a strong Brønsted acid that might catalyze the imine formation/imine addition[2] more efficiently and extend this chemistry to protic carbon nucleophiles (Scheme 1).



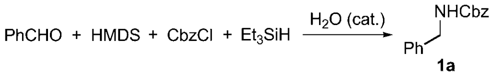
Scheme 1. Proposed four-component reaction of aldehydes with HMDS, chloroformates, and nucleophiles (NuX, X = SiR_3 or H) in the presence of a catalytic amount of water.

Although water has gained widespread focus in recent years as an environmentally benign medium for a broad range of organic transformations,[6] it remains sparse for the use of a catalytic amount of water to accelerate organic reactions.[7] Herein, we describe several four-component reactions that utilize a catalytic amount of water as a hydrolyzing agent to decompose byproduct TMSCl to yield secondary byproduct HCl that serves as a catalyst. The water-promoted four-component reaction of aldehydes with HMDS, chloroformates, and silylated nucleophiles proceeds well at room temperature to give various protected primary amines, and importantly, a wide variety of protic carbon nucleophiles have further been explored as suitable substrates for the synthesis of protected β-amino esters and β-amino ketones that are useful building blocks for various pharmaceuticals and natural products.[8] In addition, no catalyst is needed at all for the four-component reactions with aldehydes bearing hydroxy groups owing to their ability to decompose byproduct TMSCl to yield secondary byproduct HCl.

Results and Discussion

Water-promoted four-component synthesis of protected primary amines: To test our hypothesis, the four-component reaction of benzaldehyde with HMDS, benzyl chloroformate (CbzCl), and triethylsilane was selected as the model reaction performed in acetonitrile at room temperature (Table 1). In the absence of water, this four-component reaction did not occur in 24 h despite the fact that byproduct TMSCl was generated quickly by the reaction of HMDS with CbzCl (Table 1, entry 1).[5] In contrast, 20 mol% of water could promote this four-component reaction to give carbamate **1a** in 41% yield (Table 1, entry 2), and the optimal amount of water was identified to be 40 mol%, which resulted in the formation of carbamate **1a** in 94% yield (Table 1, entry 3). These observations indicate that the imine formation/imine addition is catalyzed by secondary byproduct HCl, a strong Brønsted acid generated through the decomposition of byproduct TMSCl with water (Scheme 1). The role of HCl played in the imine addition is substantially supported by its ability to catalyze the reduction of preformed imine **I-A** with triethylsilane in acetonitrile at room temperature [Eq. (2)].[9,10] It should be noted that this four-component reaction proceeded cleanly without the formation of a secondary carbamate and/or benzyl alcohol. Additional investigations revealed that the yield de-

Table 1. Optimization of reaction conditions.[a]

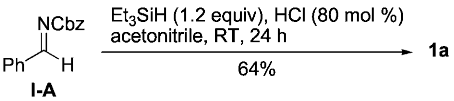


1a

Entry	Water [mol%]	Solvent	Yield [%][b]
1	0	acetonitrile	0
2	20	acetonitrile	41
3	40	acetonitrile	94
4	80	acetonitrile	85
5	40	tetrahydrofuran	24
6	40	dioxane	35
7	40	dichloromethane	0

[a] Reaction conditions: PhCHO (0.50 mmol), HMDS (0.60 mmol), CbzCl (0.60 mmol), Et_3SiH (0.60 mmol), water (0–80 mol%), solvent (0.50 mL), RT, 24 h. [b] Isolated yield.

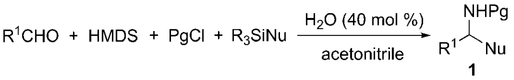
creased dramatically when acetonitrile was replaced with another common organic solvent such as tetrahydrofuran, dioxane, or dichloromethane (Table 1, entries 5–7).[11]

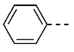
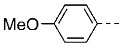
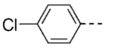
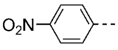
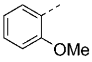
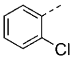
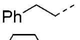
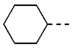
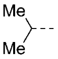
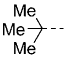
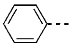
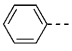
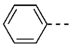
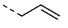
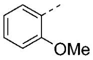
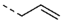


(2)

In the presence of 40 mol % of water, a range of aromatic and aliphatic aldehydes, including the sterically demanding ones, underwent smoothly tandem nitrogen protection/direct reductive amination of aldehydes at room temperature to give the corresponding carbamates in good to excellent yields that are comparable to those obtained from the corresponding iron-catalyzed four-component reaction reported recently (Table 2, entries 1–10).[2b] Furthermore, this four-component reaction avoids the employment of a large excess of nitrogen source, reducing agent, and acidic catalyst when compared to the three-component reaction of aldehydes, primary carbamates, and triethylsilane for the synthesis of the same targets.[12] The replacement of CbzCl with another chloroformate, such as PhOCOCl, or an acyl chloride, such as PhCOCl, could lead to the formation of the corresponding carbamate or amide, another form of protected primary amine (Table 2, entries 11 and 12). In addition, allyltrimethylsilane could serve as a silylated carbon nucleophile and the corresponding four-component reaction provided a convenient access to protected homoallylic amines in moderate yields (Table 2, entries 13 and 14).

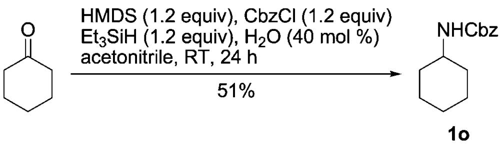
Table 2. Water promoted four-component reaction of aldehydes with HMDS, PgCl, and silylated nucleophiles.[a]



Entry	R^1	Pg	R	Nu	Product	t [h]	Yield [%][b]
1		Cbz	Et	H	**1a**	24	94
2		Cbz	Et	H	**1b**	36	89
3		Cbz	Et	H	**1c**	18	93
4		Cbz	Et	H	**1d**	24	78
5		Cbz	Et	H	**1e**	24	98
6		Cbz	Et	H	**1f**	20	94
7		Cbz	Et	H	**1g**	30	68
8		Cbz	Et	H	**1h**	24	76
9		Cbz	Et	H	**1i**	20	68
10		Cbz	Et	H	**1j**	32	71
11		CO_2Ph	Et	H	**1k**	4	97
12		COPh	Et	H	**1l**	20	81
13		Cbz	Me		**1m**	72	43
14		Cbz	Me		**1n**	72	58

[a] Reaction conditions: aldehyde (0.50 mmol), HMDS (0.60 mmol), PgCl (0.60 mmol), R_3SiNu (0.60 mmol), water (40 mol %), acetonitrile (0.50 mL), RT. [b] Isolated yield.

Only a few reactive ketones could serve as acceptable substrates for this water-promoted four-component reaction to furnish the corresponding carbamates in moderate yields. For example, the four-component reaction of cyclohexanone with HMDS, CbzCl, and triethylsilane proceeded smoothly in acetonitrile in the presence of 40 mol % of water at room temperature for 20 h to give Cbz-protected cyclohexyl amine **1o** in 51 % yield [Eq. (3)].



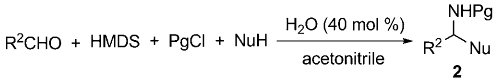
(3)

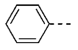
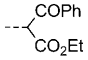
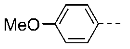
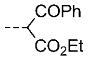
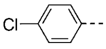
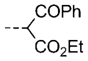
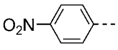
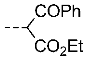
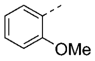
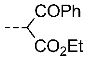
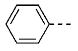
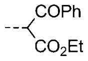
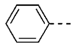
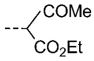
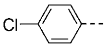
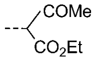
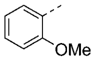
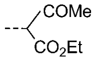
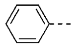
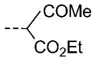
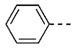
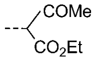
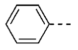
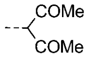
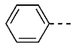
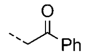
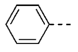
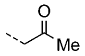
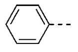
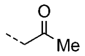
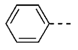
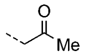
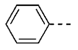
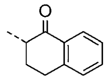
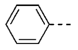
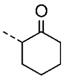
Water-promoted four-component synthesis of protected β-amino esters and β-amino ketones: The water-promoted four-component reaction has been successfully extended to a wide variety of protic carbon nucleophiles, and for the first time, several four-component Mannich-type reactions have been developed for the synthesis of alkoxycarbonyl-protected β-amino esters and β- amino ketones, which are useful building blocks for various pharmaceuticals and natural products.[8] In the presence of 40 mol % of water, the four-component reaction of aldehydes with HMDS, chloroformates, and β-keto esters proceeded smoothly at 40 °C to afford structurally diversified protected α-acyl β-amino esters in moderate to good yields (Table 3, entries 1–11).[13] Other active methylene compounds, such as 1,3-diketones, could also serves as useful protic carbon nucleophiles under the same reaction conditions. For example, the water-promoted four-component reaction of benzaldehyde with HMDS, CbzCl, and 2,4-pentadione furnished Cbz-protected α-acyl β-amino ketone **2l** in 64 % yield (Table 3, entry 12). Further investigations revealed that the four-component reaction proceeded well with enolizable ketones, such as acetophenone, acetone, 1-tetralone, and cyclohexanone, to give the corresponding protected β-amino ketones in moderate yields (Table 3, entries 13–18).

It should be noted that a competitive pathway for the consumption of an aldehyde in the four-component reaction is the Knoevenagel or aldol condensation reaction of the aldehyde with an enolizable carbon nucleophile, which was found to be more competitive relative to the four-component reaction when the reaction proceeded in the presence of a metal Lewis acid. For example, the replacement of water with $FeSO_4{\cdot}7H_2O$ (5 mol%) to catalyze the four-component reaction of benzaldehyde with HMDS, CbzCl, and ethyl benzoylacetate decreased the yield for the desired product from 84 to 67% when benzaldehyde was completely consumed.

In contrast to the four-component reaction of aldehydes with HMDS, chloroformates, and silylated nucleophiles, these four-component Mannich-type reactions could occur in the absence of water in acetonitrile, but they proceeded much slower relative to those promoted by water. For example, the four-component reaction of benzaldehyde with HMDS, CbzCl, and ethyl benzoylacetate proceeded in the absence of water in acetonitrile at 40°C for 8 h to afford protected α-acyl β-amino ester **2a** in only 12% yield, which is much lower than that for the corresponding reaction in the presence of 40 mol% of water (84% yield, Table 3, entry 1).

Table 3. Water-promoted four-component reaction of aldehydes with HMDS, chloroformates, and protic carbon nucleophiles.[a]



Entry	R^2	Pg	Nu	Product	*t* [h]	Yield [%][b]
1		Cbz		**2a**	8	84
2		Cbz		**2b**	15	62
3		Cbz		**2c**	15	65
4		Cbz		**2d**	15	82
5		Cbz		**2e**	2	85
6		CO_2Ph		**2f**	20	68
7		Cbz		**2g**	10	65
8		Cbz		**2h**	24	67
9		Cbz		**2i**	10	55
10		CO_2Et		**2j**	16	65
11		CO_2Ph		**2k**	20	67
12		Cbz		**2l**	20	64
13		Cbz		**2m**	9	53
14[c]		Cbz		**2n**	15	68
15[c]		CO_2Et		**2o**	40	59
16[c]		CO_2Ph		**2p**	24	58
17		CO_2Et		**2q**	21	60
18		Cbz		**2r**	4	53

[a] Reaction conditions: aldehyde (0.50 mmol), HMDS (0.60 mmol), PgCl (0.60 mmol), NuH (0.75 mmol), water (40 mol%), acetonitrile (0.50 mL), 40°C. [b] Isolated yield. [c] Acetone (0.50 mL) was used as the solvent and the reaction was performed at 15°C.

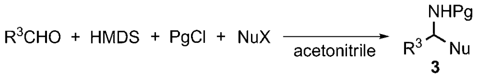
Catalyst-free four-component reactions with aldehydes bearing hydroxy groups: Since alcohols or phenols are also able to decompose byproduct TMSCl to yield secondary byproduct HCl,[14] they are expected to serve as alternative effective catalysts for the above four-component reactions. To our delight, either ethanol or phenol could promote the four-component reaction of benzaldehyde with HMDS, CbzCl, and triethylsilane to give carbamate **1a** in an excellent yield [Eq. (4)]. These observations prompted us to develop several catalyst-free four-component reactions of hydroxy-containing aldehydes with HMDS, chloroformates, and various nucleophiles.

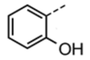
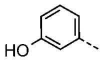
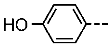
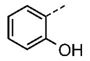
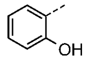
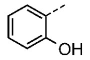
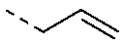
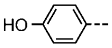
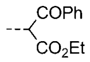
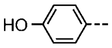
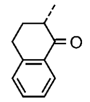
$$\mathrm{PhCHO} \xrightarrow[\substack{\text{R = Et, 91\%} \\ \text{R = Ph, 91\%}}]{\substack{\text{HMDS (1.2 equiv), CbzCl (1.2 equiv)} \\ \text{Et}_3\text{SiH (1.2 equiv), ROH (100 mol\%)} \\ \text{acetonitrile, RT, 24 h}}} \mathbf{1a} \qquad (4)$$

In the absence of external catalysts and additives, the four-component reactions of hydroxy-substituted benzaldehydes with HMDS, chloroformates, and triethylsilane proceeded smoothly at room temperature to give the corresponding carbamates in good yields (Table 4, entries 1–5). Allyltrimethylsilane, β-keto esters, and ketones could also serve as useful carbon nucleophiles for the catalyst-free four-component reactions (Table 4, entries 6–8). Interestingly, a much lower yield was obtained for the corresponding four-component reaction in the presence of a metal Lewis acid. For example, the $FeSO_4{\cdot}7H_2O$ (5 mol%)-catalyzed four-component reaction of 4-hydroxybenzaldehyde with HMDS, CbzCl, and triethylsilane furnished carbamate **3c** in only 12% yield, which is much lower than that for the present catalyst-free one (73% yield, Table 4, entry 3).

The use of molecular sieves (4 Å) to sequester secondary byproduct HCl in the four-component reaction of 2-hydroxybenzaldehyde with HMDS, CbzCl, and triethylsilane could completely shutdown the formation of carbamate **3a**.[15] This result suggests that secondary byproduct HCl, generated through the decomposition of byproduct TMSCl with the hydroxy group, plays a vital role for the catalyst-free four-component reactions of hydroxy-containing aldehydes with HMDS, chloroformates, and nucleophiles to produce various amine derivatives.

Table 4. Catalyst-free four-component reactions of hydroxy-containing aldehydes with HMDS, chloroformates, and nucleophiles.[a]



Entry	R^3	Pg	Nu	X	Product	t [h]	Yield [%][b]
1		Cbz	H	$SiEt_3$	**3a**	48	84
2		Cbz	H	$SiEt_3$	**3b**	44	64
3		Cbz	H	$SiEt_3$	**3c**	32	73
4		CO_2Et	H	$SiEt_3$	**3d**	30	72
5		CO_2Ph	H	$SiEt_3$	**3e**	30	79
6		Cbz		$SiMe_3$	**3f**	24	52
7		Cbz		H	**3g**	35	61
8		Cbz		H	**3h**	35	67

[a] Reaction conditions: aldehyde (0.50 mmol), HMDS (0.60 mmol), PgCl (0.60 mmol), NuX (0.60 mmol), acetonitrile (0.50 mL), RT. [b] Isolated yield.

Conclusion

We have developed, for the first time, an efficient byproduct-catalyzed four-component reaction of aldehydes with HMDS, chloroformates, and nucleophiles to produce a wide variety of protected primary amines, β-amino esters, and β-amino ketones, which are useful building blocks for various pharmaceuticals and natural products. In the presence of 40 mol% of water, the four-component reaction of aldehydes with HMDS, chloroformates, and silylated nucleophiles proceeds smoothly at room temperature to give a range of protected primary amines in moderate to excellent yields. Importantly, the water promoted four-component reaction has been successfully extended to a wide variety of protic carbon nucleophiles, such as β-keto esters, β-diketones, and ketones, and several four-component Mannich-type reactions have been developed for the synthesis of protected β-amino esters and β-amino ketones in moderate to good yields. These four-component reactions proceed through a pathway of tandem nitrogen protection/imine formation/imine addition, and the decomposition of byproduct TMSCl, generated in the first step of nitrogen protection, with water results in the formation of secondary byproduct HCl, a strong Brønsted acid that promotes the following imine formation/imine addition. Taking advantage of the fact that alcohols or phenols are also able to decompose byproduct TMSCl to yield secondary byproduct HCl, no catalyst is needed at all for the four-component reactions with aldehydes bearing hydroxy groups.

Experimental Section

General information: Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for the products are given in the Supporting Information.

General procedure for the water-promoted four-component reactions of aldehydes with HMDS, PgCl, and silylated nucleophiles (Table 2): HMDS (96.8 mg, 0.125 mL, 0.60 mmol), PgCl (0.60 mmol), and silylated nucleophiles (0.60 mmol) were added successively to a stirred solution of an aldehyde (0.50 mmol) in dry acetonitrile (0.25 mL) at room temperature. The mixture was stirred at room temperature for 5 h and was then added to a solution of water (3.6 mg, 0.20 mmol, 40 mol%) in acetonitrile (0.25 mL). The resulting mixture was stirred at room temperature until no further transformation was observed by TLC and was then purified directly by preparative TLC, developing with petroleum ether/ethyl acetate 10:1, to afford carbamates **1**.

General procedure for the water-promoted four-component reaction of aldehydes with HMDS, chloroformates, and protic carbon nucleophiles (Table 3, entries 1–13 and 17 and 18): HMDS (96.8 mg, 0.125 mL, 0.60 mmol), a chloroformate (0.60 mmol), and a protic carbon nucleophile (0.75 mmol) were added successively to a stirred solution of an aldehyde (0.50 mmol) in dry acetonitrile (0.25 mL) at room temperature. The mixture was stirred at 40 °C for 2 h and was then added to a solution of water (3.6 mg, 0.20 mmol) in acetonitrile (0.25 mL). The resulting mixture was stirred at 40 °C until no further transformation was observed by TLC, and was then purified directly by preparative TLC, developing with petroleum ether/ethyl acetate 10:1, to afford protected β-amino carbonyl compounds **2**.

General procedure for the four-component synthesis of protected β-amino ketones 2n, 2o, and 2p (Table 3, entries 14–16): A mixture of an aldehyde (0.50 mmol), HMDS (96.8 mg, 0.125 mL, 0.60 mmol), a chloroformate (0.60 mmol), and acetone (0.25 mL) was stirred at 15 °C for 4 h, and was then added to a solution of water (3.6 mg, 0.20 mmol) in acetone (0.25 mL). The resulting mixture was stirred at 15 °C until no further transformation was observed by TLC, and was then purified directly by preparative TLC, developing with petroleum ether/ethyl acetate 10:1, to afford protected β-amino ketones **2n**, **2o**, or **2p**.

General procedure for the catalyst-free four-component reaction of hydroxy-containing aldehydes with HMDS, chloroformates, and nucleophiles (Table 4): HMDS (96.8 mg, 0.125 mL, 0.60 mmol), a chloroformate (0.60 mmol), and a nucleophile (0.60 mmol) were added successively to a stirred solution of an aldehyde (0.50 mmol) in dry acetonitrile (0.50 mL) at room temperature. The resulting mixture was stirred at room temperature until no further transformation was observed by TLC, and was then purified directly by preparative TLC, developing with petroleum ether/ethyl acetate 5:1, to afford protected primary amines **3**.

Acknowledgements

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[2] a) Q.-Y. Song, B.-L. Yang, S.-K. Tian, *J. Org. Chem.* **2007**, *72*, 5407–5410; b) B.-L. Yang, S.-K. Tian, *Eur. J. Org. Chem.* **2007**, 4646–4650.

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[6] For recent reviews, see: a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; b) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82; c) C. I. Herrerías, X. Yao, Z. Li, C.-J. Li, *Chem. Rev.* **2007**, *107*, 2546–2562; d) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591; e) H. C. Hailes, *Org. Process Res. Dev.* **2007**, *11*, 114–120; f) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725–748.

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[8] For reviews, see: a) E. F. Kleinmann in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M.Trost, I. Flemming), Pergamon Press, New York, **1991**, pp. 893–951; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094.

[9] Imine **I-A** was prepared in situ from benzaldehyde, HMDS, and CbzCl, and used directly without purification. HCl was prepared in acetonitrile by treatment of TMSCl with water (0.50 equiv) at room temperature. For details, see the Supporting Information.

[10] The reaction did not occur in the absence of a catalyst under the same reaction conditions. See reference [2b].

[11] In contrast, dichloromethane is the solvent of choice for the corresponding $FeSO_4{\cdot}7H_2O$ catalyzed four-component reaction we reported recently. See reference [2b].

[12] $CbzNH_2$ (3 equiv), triethylsilane (3 equiv), and trifluoroacetic acid (catalyst, 2.9 equiv) were used for the three-component reaction. See: D. Dubé, A. A. Scholte, *Tetrahedron Lett.* **1999**, *40*, 2295–2298. Owing to the lack of byproduct TMSCl, water was found to be totally ineffective in promoting the three-component reaction of benzaldehyde with $CbzNH_2$ and triethylsilane.

[13] As determined by integrating the RR′C*H*N signals in the ^{1}H NMR spectra, the diastereoselectivity ranges from 63:37 to 50:50. In addition, the same level of diastereoselectivity, ranging from 30:70 to 50:50 (vide infra), was also obtained from the four-component reactions with ketones, which were shown in Table 3 (entries 17 and 18) and Table 4 (entries 7 and 8). For details, see the Supporting Information.

[14] For a relevant study, see: H.-H. Li, D.-J. Dong, S.-K. Tian, *Eur. J. Org. Chem.* **2008**, 3623–3626.

[15] For examples of using molecular sieves to scavenge HCl, see: a) L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, M. Sletzinger, *Tetrahedron Lett.* **1975**, *16*, 3979–3982; b) Reference [14].

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