DOI: 10.1002/ejoc.200700627

Iron-Catalyzed Four-Component Reaction for the Synthesis of Protected Primary Amines

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Keywords: Multicomponent reactions / Reductive amination / Carbonyl compounds / Acetals / Primary amines

The first catalytic four-component reaction (4CR) of carbonyl compounds with alkyl chloroformate, HMDS and Et_3SiH has been developed to produce protected primary amines by a novel tandem nitrogen protection/direct reductive amination of carbonyl compounds. In the presence of 5 mol-% of an iron(II) salt, a wide variety of aldehydes and ketones were transformed into their corresponding protected primary amines in good to excellent yields under "pure" multicomponent reaction (MCR) conditions. This chemistry was further extended to masked carbonyl compounds such as acetals, ketals, and vinyl ethers. When compared with previous methods to prepare protected primary amines from a large excess of ammonia or ammonium salts, this 4CR not only saved at least one step of synthetic manipulation, but also utilized nearly stoichiometric nitrogen and hydrogen sources and avoided the formation of (protected) secondary amines. Additional advantages of this protocol include broader substrate scope, the use of an inexpensive and environmentally friendly catalyst, and mild reaction conditions.

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Introduction

Multicomponent reactions (MCRs), which involve the one-pot transformation of three or more starting materials into a single product that incorporates portions of all the reactants,[1] are powerful for the construction of complex organic molecules. When compared with the sequential synthesis of the same target by conventional bimolecular reactions (2CRs), MCRs, especially those with more than three components, exhibit much higher efficiency because they need fewer synthetic manipulations. While most of the MCRs discovered so far consist of three components, the reactions with four or more components are quite rare.

Primary amines exist in many biologically important molecules, and are also widely used as intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals. Although an amino functionality can be directly introduced into a molecule by the displacement of a halide or sulfonate with ammonia, overalkylation of ammonia is a common side reaction. A superior method is the direct reductive amination of carbonyl compounds, a three-component reaction (3CR) wherein the carbonyl groups react with ammonia or ammonium salts in the presence of mild reducing agents.[2,3] However, such a 3CR is also complicated by the formation of secondary and tertiary amines and by the reduction of carbonyl compounds to alcohols, and often requires a large excess of nitrogen and hydrogen sources to achieve good yields. Furthermore, high pressure and/or precious metals are used in many of these 3CRs. Due to their high reactivity, primary amines often need an additional step of protection prior to their further application in organic synthesis [Scheme 1 a)]. The most widely employed protecting groups for amines are alkoxycarbonyl groups since they can easily undergo further conversions using well-established protective-group chemistry.[4] Alternatively, ammonia can be protected prior to the direct reductive amination of carbonyl compounds [Scheme 1 b)].[2,5] The incorporation of direct reductive amination of carbonyl compounds and nitrogen-protection into a single four-component reaction (4CR) would greatly facilitate the manipulation to synthesize protected primary amines [Scheme 1 c)] since it can save one step when compared with a sequential 3CR and 2CR, and save two steps when compared with three sequential 2CRs. Herein, we report the first four-component synthesis of alkoxycarbonyl-protected primary amines by tandem nitrogen protection/direct reductive amination of carbonyl compounds (acetals, ketals, or vinyl ethers) in the presence of 5 mol-% of an iron(II) salt at room temperature. When compared with previous methods to prepare protected primary amines from ammonia or ammonium salts, this four-component synthesis under "pure" MCR conditions[1h] not only saved at least one step of synthetic manipulation, but also utilized nearly stoichiometric nitrogen and hydrogen sources and avoided the formation of (protected) secondary amines.

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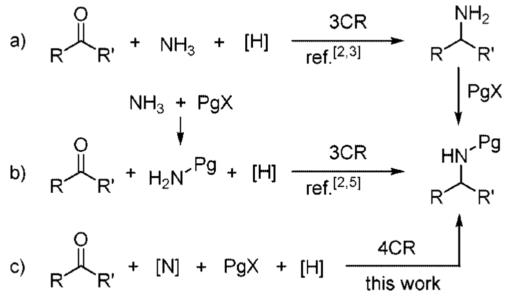


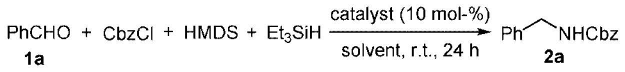
Scheme 1. Multicomponent synthesis of (protected) primary amines. [H] = reducing agent, Pg = protecting group, [N] = nitrogen source.

Results and Discussion

The employment of carbamates as the nitrogen sources in the three-component synthesis of protected primary amines, reported by Dubé and Scholte in 1999,[5] is particularly interesting in that the corresponding alkoxycarbonyl groups serve as the protecting groups for primary amines, despite the fact that in this 3CR excessive carbamates (3.0 equiv.), triethylsilane (Et_3SiH, 3.0 equiv.), and trifluoroacetic acid (2.9 equiv.) were used. Realizing that *N*-silylcarbamate could be easily generated from alkyl chloroformate and hexamethyldisilazane (HMDS),[6] we envisioned a 4CR of carbonyl compounds, alkyl chloroformate, HMDS and Et_3SiH to synthesize alkoxycarbonyl-protected primary amines by tandem nitrogen protection/direct reductive amination of carbonyl compounds. However, the presence of both two electrophiles (carbonyl compound and alkyl chloroformate) and two nucleophiles (HMDS and Et_3SiH) in a one-pot reaction offers a formidable challenge for this reaction to give predominantly the desired product.

The selectivity for the reactions of electrophiles with nucleophiles in a multicomponent system was expected to be attained by the choice of Lewis acids. Thus, a large number of inexpensive solid Lewis acids were evaluated for their ability to catalyze the 4CR of carbonyl compounds, alkyl chloroformate, HMDS and Et_3SiH (Table 1). Using benzaldehyde (**1a**) as the model substrate, this reaction was performed under "pure" MCR conditions[1h] by adding successively benzyl chloroformate (CbzCl, 1.2 equiv.), HMDS (1.2 equiv.), Et_3SiH (1.2 equiv.), and solid Lewis acid (10 mol-%) to a stirred solution of benzaldehyde (**1a**) in acetonitrile at room temperature. A number of common solid Lewis acids, especially iron salts,[7] showed high catalytic activities in this 4CR (Table 1). Importantly, the best yield (91%) was achieved with iron(II) sulfate heptahydrate ($FeSO_4·7H_2O$), which is inexpensive and environmentally friendly (Table 1, Entry 10). Furthermore, this iron(II) salt is insoluble in acetonitrile and can be removed simply by filtration. Interestingly, $FeSO_4·7H_2O$ was found to be totally ineffective in catalyzing the corresponding 3CR of benzaldehyde (**1a**), $CbzNH_2$, and Et_3SiH.

Table 1. Survey of solid Lewis acid catalysts and solvents.[a]

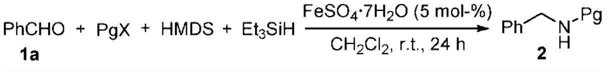


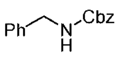
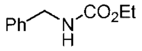
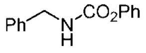
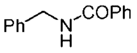
Entry	Catalyst	Solvent	Isolated yield [%]
1	none	MeCN	[b]
2	$ZnCl_2$	MeCN	87
3	$CuCl_2·2H_2O$	MeCN	55
4	$CeCl_3·7H_2O$	MeCN	72
5	$BiCl_3$	MeCN	88
6	$FeCl_3$	MeCN	80
7	$FeCl_3·6H_2O$	MeCN	67
8	$FeCl_2·4H_2O$	MeCN	83
9	$Fe_2(SO_4)_3·5H_2O$	MeCN	85
10	$FeSO_4·7H_2O$	MeCN	91
11	$FeSO_4·7H_2O$	THF	63
12	$FeSO_4·7H_2O$	dioxane	83
13	$FeSO_4·7H_2O$	EtOAc	90
14	$FeSO_4·7H_2O$	CH_2Cl_2	93
15	$FeSO_4·7H_2O$	$CHCl_3$	80
16	$FeSO_4·7H_2O$	$ClCH_2CH_2Cl$	90
17	$FeSO_4·7H_2O$	PhMe	66

[a] The reaction was performed by treatment of **1a** (0.25 mmol) in solvent (0.25 mL) at room temp. with CbzCl (0.30 mmol), HMDS (0.30 mmol), Et_3SiH (0.30 mmol), and catalyst (10 mol-%). [b] No desired product was detected by TLC.

A further survey of the reaction conditions revealed that dichloromethane was the solvent of choice (Table 1, Entry 14), and the catalyst loading could be lowered without sacrificing the yield. In the presence of 5 mol-% of $FeSO_4·7H_2O$, this 4CR proceeded cleanly without the formation of protected secondary amine and/or benzyl alcohol, and gave Cbz-protected primary amine **2a** in 95% yield (Table 2, Entry 1). The employment of polymethylhydrosiloxane (PMSH) as the hydride source in this 4CR was also examined and found to give a much lower yield (Table 2, Entry 2). In addition, lower yields were obtained with many other alkyl chloroformates such as EtOCOCl and PhOCOCl, and with acyl chloride such as PhCOCl (Table 2, Entries 3–5).

Table 2. Survey of protecting groups for primary amines.[a]



Entry	PgX	Product	Isolated yield [%]
1	CbzCl	 **2a**	95
2	CbzCl	**2a**	66[b]
3	EtOCOCl	 **2ab**	60
4	PhOCOCl	 **2ac**	76
5	PhCOCl	 **2ad**	80

[a] The reaction was performed by treatment of **1a** (0.25 mmol) in CH_2Cl_2 (0.25 mL) at room temp. with PgX (0.30 mmol), HMDS (0.30 mmol), Et_3SiH (0.30 mmol), and $FeSO_4·7H_2O$ (5 mol-%). [b] PMSH was used.

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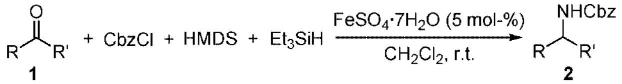
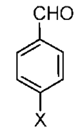
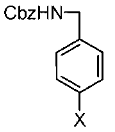
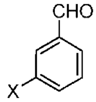
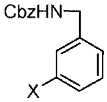
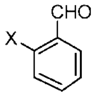
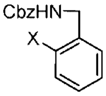
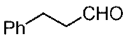
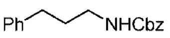
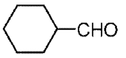
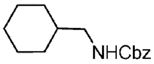
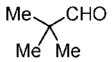
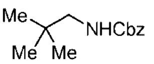
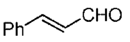
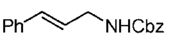
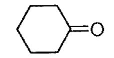
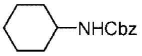
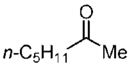
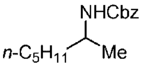
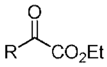
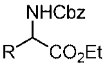
Next, we investigated the substrate scope for the 4CR of carbonyl compounds, CbzCl, HMDS, and Et_3SiH since this reaction gave the best yield with CbzCl and Cbz is more often employed as a protecting group for a reactive amine. In the presence of 5 mol-% of $FeSO_4{\cdot}7H_2O$, a variety of aromatic and aliphatic aldehydes, including sterically hindered ones, were transformed into their corresponding protected primary amines at room temperature in good to excellent yields (Table 3, Entries 1–13). Importantly, the reducible nitro group and carbon–carbon double bonds, as well as acid-labile TBS ether and Boc groups were all allowed in this 4CR (Table 3, Entries 3, 5–7 and 9). The reaction of an α,β-unsaturated aldehyde was complicated by the reduction of the carbon–carbon double bond (Table 3, Entry 14). Cyclic and acyclic ketones could also serve as suitable substrates for this 4CR (Table 3, Entries 15–18), and the reaction of α-keto esters are particularly interesting since they can be utilized to synthesize protected α-amino esters.

Table 3. Iron-catalyzed 4CR of carbonyl compounds, CbzCl, HMDS, and Et_3SiH.[a]

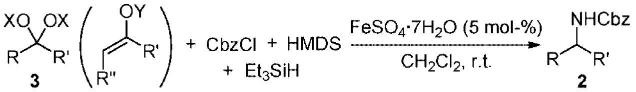


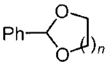
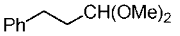
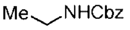
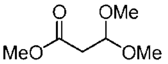
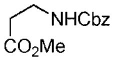
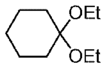
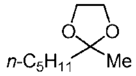
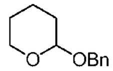
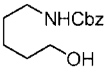
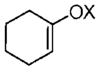
Entry	Substrate	Product	Time [h]	Yield [%][b]
1	 **1a**: X = H	 **2a**	24	95
2	**1b**: X = OMe	**2b**	26	93
3	**1c**: X = OTBS	**2c**	14	73
4	**1d**: X = Cl	**2d**	64	92
5	**1e**: X = NO_2	**2e**	23	77
6	 **1f**: X = NHBoc	 **2f**	40	62
7	**1g**: X = NO_2	**2g**	48	93
8	 **1h**: X = OMe	 **2h**	6	84
9	**1i**: X = $OCH_2CH{=}CH_2$	**2i**	24	85
10	**1j**: X = Cl	**2j**	24	84
11	 **1k**	 **2k**	16	61
12	 **1l**	 **2l**	48	80
13	 **1m**	 **2m**	48	80
14	 **1n**	 **2n**	18	57[c]
15	 **1o**	 **2o**	48	84
16	 **1p**	 **2p**	60	87
17	 **1q**: R = Me	 **2q**	48	42
18	**1r**: R = Ph	**2r**	96	54

[a] The reaction was performed by treatment of **1** (0.50 mmol) in CH_2Cl_2 (0.50 mL) at room temp. with CbzCl (0.60 mmol), HMDS (0.60 mmol), Et_3SiH (0.60 mmol), and $FeSO_4{\cdot}7H_2O$ (5 mol-%). [b] Isolated yield. [c] A 90:10 mixture of **2n**/**2k** (determined by ^1H NMR analysis).

This 4CR was further extended to various masked carbonyl compounds (Table 4) that, stable in air and inert to many nucleophiles, offer significant advantages over the corresponding aldehydes or ketones in many synthetic manipulations. It is notable that good yields could be obtained using this 4CR to synthesize the same protected primary amine from several different acetal derivatives of the same aldehyde (Table 4, Entries 1–4). In addition, the use of the acetal derivative of an aldehyde with a low boiling point (e.g., acetaldehyde) could greatly facilitate the synthesis of the corresponding protected primary amine at room temperature (Table 4, Entry 6).[8] Interestingly, vinyl ethers could also serve as surrogates of carbonyl compounds in this 4CR (Table 4, Entries 11–12), though the yields were lower than those for the corresponding carbonyl compounds (Table 3, Entry 15).

Table 4. Iron-catalyzed four-component synthesis of protected primary amines from ketals, acetals, or vinyl ethers.[a]



Entry	Substrate	Product	Time [h]	Yield [%][b]
1	$PhCH(OEt)_2$ **3a**	**2a**	42	73
2	 **3b**: *n* = 1	**2a**	36	73
3	**3c**: *n* = 2	**2a**	36	78
4	$PhCH(OAc)_2$ **3d**	**2a**	42	71
5	 **3e**	**2k**	15	65
6	$MeCH(OEt)_2$ **3f**	 **2s**	48	53
7	 **3g**	 **2t**	48	70
8	 **3h**	**2o**	60	72
9	 **3i**	**2p**	60	81
10	 **3j**	 **2u**	24	40
11	 **3k**: X = TMS	**2o**	48	65
12	**3l**: X = Et	**2o**	48	37

[a] The reaction was performed by treatment of **3** (0.50 mmol) in CH_2Cl_2 (0.50 mL) at room temp. with CbzCl (0.60 mmol), HMDS (0.60 mmol), Et_3SiH (0.60 mmol), and $FeSO_4{\cdot}7H_2O$ (5 mol-%). [b] Isolated yield.

During the 4CR of carbonyl compounds (acetals, ketals, or vinyl ethers), CbzCl, HMDS, and Et_3SiH, we observed that the reaction of CbzCl with HMDS proceeded quickly to generate *N*-silylcarbamate CbzNH(TMS),[6] the amount of which was indicated by TLC to decrease gradually.[9] Thus, it is reasonable to conclude that $FeSO_4{\cdot}7H_2O$ itself or in combination with chlorotrimethylsilane (TMSCl), which is generated in situ along with CbzNH(TMS) from CbzCl and HMDS, should promote the subsequent direct

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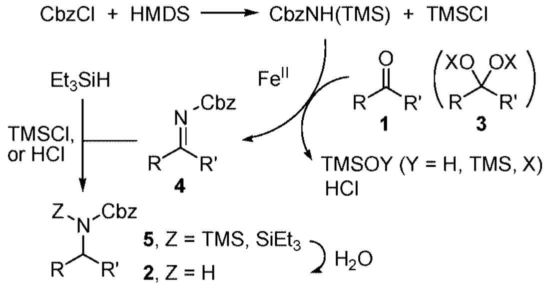
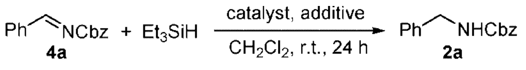
reductive amination of carbonyl compounds (acetals, ketals, or vinyl ethers). On the basis of the mechanistic studies on the direct reductive amination of carbonyl compounds,[2] we propose for this 4CR a reaction pathway in which imine **4** should be generated as the key intermediate for the formation of **5**, which can be hydrolyzed to give product **2** (Scheme 2).



Scheme 2. Proposed major reaction pathway.

To gain more insight into the role played by $FeSO_4{\cdot}7H_2O$, imine **4a** was prepared in situ from benzaldehyde (**1a**)[10] and subjected to reduction with Et_3SiH (Table 5). Surprisingly, neither $FeSO_4{\cdot}7H_2O$ nor the iron(II) species prepared from $FeSO_4{\cdot}7H_2O$ and TMSCl (10 equiv.)[11] could catalyze the reduction of imine **4a** (Table 5, Entries 2–3), which, instead, could be promoted by either TMSCl (Table 5, Entries 6–7) or HCl (generated in situ from TMSCl and water; Table 4, Entries 8–9). Nevertheless, the replacement of $FeSO_4{\cdot}7H_2O$ in this 4CR with water (0.10 or 0.70 equiv., to generate HCl), as indicated by TLC, did not give product **2a**. In addition, 10 mol-% of $FeSO_4{\cdot}7H_2O$ was found to be able to catalyze the corresponding three-component reaction of benzaldehyde (**1a**), CbzNH(TMS), and Et_3SiH to give product **2a** in 40% yield, which is significantly lower than that in the presence of TMSCl (93% yield; Table 1, Entry 14). Taken together, the iron(II) salt should play a major role in the generation of imine **4** (Scheme 2), the reduction of which can be promoted mainly by TMSCl and/or HCl, both of which are generated in situ during the reaction.[12]

Table 5. Reduction of imine **4a** with Et_3SiH.



Entry	Catalyst [mol-%]	Additive [equiv.]	Yield [%][a]
1	none	none	[b]
2	$FeSO_4{\cdot}7H_2O$ (10)	none	[b]
3	Fe^{II} (10)[c]	none	[b]
4	$FeSO_4{\cdot}7H_2O$ (10)	TMSCl (1.2)	95
5	$FeSO_4{\cdot}7H_2O$ (10)	TMSCl (0.30)	45
6	none	TMSCl (1.2)	94
7	none	TMSCl (0.30)	42
8	none	TMSCl (1.2) + H_2O (0.60)	85
9	none	TMSCl (0.30) + H_2O (0.15)	45

[a] Isolated yield. [b] No or a trace amount of **2a** was detected by TLC. [c] Prepared from $FeSO_4{\cdot}7H_2O$ and TMSCl at room temp.

Conclusions

We have developed the first catalytic 4CR of carbonyl compounds with alkyl chloroformate, HMDS, and Et_3SiH to produce protected primary amines by a novel tandem nitrogen protection/direct reductive amination of carbonyl compounds. In the presence of 5 mol-% of $FeSO_4{\cdot}7H_2O$, a wide variety of aldehydes and ketones were transformed into their corresponding alkoxycarbonyl-protected primary amines in good to excellent yields by performing the 4CRs under mild "pure" MCR conditions. This chemistry was further extended to masked carbonyl compounds such as acetals, ketals, and vinyl ethers. When compared with previous methods to prepare protected primary amines from a large excess of ammonia or ammonium salts, this 4CR not only saved at least one step of synthetic manipulation, but also utilized nearly stoichiometric nitrogen and hydrogen sources and avoided the formation of (protected) secondary amines. Additional advantages of this protocol include broader substrate scope, the employment of a catalytic amount of inexpensive and environmentally friendly catalyst, and mild reaction conditions. Furthermore, this study adds a synthetically useful entry into MCRs and iron catalysis.

Experimental Section

General Procedure for the Four-Component Synthesis of Protected Primary Amines: To a stirred solution of carbonyl compound **1** (acetal, ketal, or vinyl ether **3**, 0.50 mmol) in dry dichloromethane (0.50 mL) at room temperature were added successively CbzCl (102 mg, 0.086 mL, 0.60 mmol), HMDS (96.8 mg, 0.125 mL, 0.60 mmol), Et_3SiH (69.8 mg, 0.096 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 purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (40:1 to 10:1), to give protected primary amine **2** (Tables 3 and 4).

General Procedure for the Reduction of Imine 4a: Imine **4a** was prepared in situ from benzaldehyde (**1a**) according to known procedures.[10] To a stirred solution of crude imine **4a** (0.25 mmol) in dry dichloromethane (0.25 mL) at room temperature were added successively Et_3SiH (34.9 mg, 0.048 mL, 0.30 mmol), catalyst (if any, 10 mol-%), and additive (if any). The reaction mixture was stirred for 24 h and purified by flash column chromatography on silica gel to give product **2a** (if any, Table 5).

Supporting Information (see footnote on the first page of this article): Additional experimental procedures and characterization of the products.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (no. 20672105) and the University of Science and Technology of China.

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[11] The iron(II) species was prepared by treatment of $FeSO_4{\cdot}7H_2O$ with TMSCl (10 equiv.) at room temperature for 24 h and subsequent concentration under reduced pressure (15–0.1 Torr).

[12] When HCl serves as the promoter for the reduction of imine **4**, product **2** should be generated directly. HCl can be generated by the reaction of TMSCl, which was generated in situ along with CbzNH(TMS) from CbzCl and HMDS, with the water from $FeSO_4{\cdot}7H_2O$ or with TMSOH, which was generated in situ during the formation of imine **4**.

Received: July 9, 2007
Published Online: August 3, 2007

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