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Di Wang, Yafei Liu, Wei Zhu, Hong Shen, Haixia Liu,* and Lei Fu*

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Efficient Synthesis of Substituted Morpholine Derivatives via an Indium (III)-Catalyzed Reductive Etherification Reaction

Di Wang, [1,2] Yafei Liu, [2] Wei Zhu, [2] Hong Shen, [2] Haixia Liu, *[2] and Lei Fu*[1]

[1] *School of Pharmacy, Shanghai Jiao Tong University, No. 800 Dongchuan Rd., Shanghai, PR China, 200240*
[2] *Roche Pharmaceutical Research & Early Development, Department of medicinal chemistry, Roche Innovation Center Shanghai, 720 Cailun Road, Building 5, Pudong, Shanghai, P. R. China, 201203*

E-mail: haixia.liu@roche.com; leifu@sjtu.edu.cn

An efficient synthesis of morpholine derivatives has been developed using indium (III)-catalyzed intramolecular reductive etherification reaction. This method allows the construction of various 2-substituted, and 2,3-, 2,5-, 2,6-disubstituted morpholines with good to excellent yields and high diastereoselectivity. In addition, this method demonstrates good compatibility with a broad range of functional groups.

Keywords: Morpholine, Indium Bromide, Reductive Etherification

Morpholine is an important structural motif in various natural products and synthetic bioactive molecules. It is one of the most prevalent structural elements utilized in marketed drugs as well as new pharmaceuticals at discovery and development stages.[1] (Figure 1) Morpholine has attractive physicochemical properties. For example, morpholine is very polar (LogP -0.41).[2] Compared to other nitrogen-containing heterocycles, such as piperidine and piperazine, morpholine has relatively low basicity (pKa 8.51)[2] due to the negative inductive effect of the oxygen atom in the ring. In addition, morpholine can serve as a pharmacophore to interact with biological targets. The lone pair of oxygen atom can function as a weak hydrogen bond acceptor, and the relatively electron deficient morpholine ring can contribute to hydrophobic interaction. Therefore, morpholine-containing building blocks are very popular in the field of medicinal chemistry, and are often employed to modulate compound properties or to fine tune interactions with target proteins. Due to the wide applications of morpholine analogs, significant efforts have been devoted to the development of synthetic methods for diverse morpholine derivatives during the past few years.[3] Many methodologies are based on intramolecular ring closure to form either C-N or C-O bond such as cyclization of amino alcohol and amino diols,[4] reductive etherification of keto alcohols,[5] cyclization of alkynylamines or alkynylalcohols,[6] ring opening of aziridines,[7] direct amination or oxygenation of alkenes or alkynes,[8] and hydroamination of ether amino-alkynes.[9] Furthermore, intermolecular reactions, such as difunctionalization of conjugated dienes,[10] and double allylic substitution,[11] have been described to access substituted morpholines. More recently, novel methodologies using SnAP (stannyl amine protocol) and SLAP (silicon amine protocol) reagents have been developed by Bode and co-workers as versatile methods to access morpholines as well as other aliphatic *N*-heterocycles.[12] Despite these great advances, new methods that could have broader applications, in terms of functional group tolerability and substitution patterns of final morpholine products, remain to be valuable for synthetic and medical chemistry.

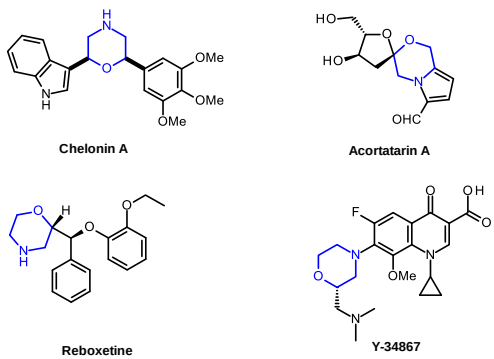


Figure 1. Example of biologically important morpholine derivatives.

Gharpur and co-worker reported an reductive esterification condition to convert ketoalcohol **3** to morpholine derivatives, however the method requires stoichiometric amount of strong Lewis acid TMOTf, and tosyl group is the only reported *N*-protecting group.[5] Inspired by this work, to further expand substrate scope and functional group tolerability, we describe herein an efficient indium (III)-promoted intramolecular reductive etherification reaction to access substituted morpholine derivatives. (Figure 2) We started our study with readily available keto alcohols **3**, which can be synthesized from the corresponding amino alcohols **1** and *a*-bromoketones **2** via a two-step sequence with easily removable carbamate protecting groups (PG = Cbz-, Boc-, Fmoc-).

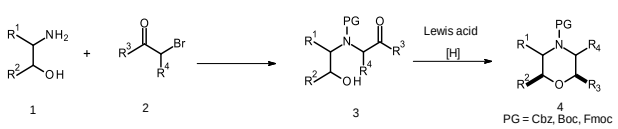
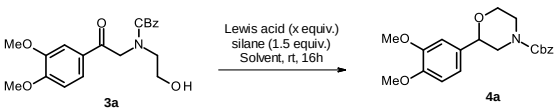


Figure 2. Our approach to construct morpholine scaffold.

In our initial attempt, **3a** was employed as a model substrate to evaluate the reductive etherification reaction in the presence of various commonly used Lewis acids, and the results are listed in Table 1. To our delight, the use of indium (III) salts such as $InBr_3$ and $In(OTf)_3$ provided the desired products with good yields (Table 1, entries 1-2). Other Lewis acids such as $FeCl_3$, $Mg(OTf)_2$, $Cu(OTf)_2$ and $CuBr_2$ gave modest results (Table 1, entries 3-5). $Ga(OTf)_3$ and $Bi(OTf)_3$ only afforded a trace amount of the desirable product (Table 1, entries 8 and 9), and $Zn(OTf)_2$ and $Hf(OTf)_4$ did not lead

to the desirable morpholine product (Table 1, entries 6 and 10). In addition, catalyst loading was evaluated (Table 1, entries 11-13), and we got nearly quantitative yield in the presence of 0.2 equivalent of $InBr_3$ over 24 h (Table 1, entry 12). Further decreasing the catalyst loading to 0.1 equivalent could give a similar yield, however prolonged reaction time was necessary to achieve full conversion (Table 1, entry 13). Moreover, various silanes were investigated. Et_3SiH and $PhSiH_3$ were identified as the most efficient reducing reagents. Lastly, the solvent impact on the reductive etherification is profound. Dichloromethane was found to be the best medium. Other solvents such as THF, CH_3CN and toluene were less effective, and only 10-65% yield of **4a** was obtained (Table 1, entries 20-22). The reaction did not occur in DMF (Table 1, entry 19).

Table 1. Optimization of the reaction condition[a]



Entry	Catalyst	X	Silane	Solvent	Yield[b]
1	$InBr_3$	1.1	Et_3SiH	CH_2Cl_2	86%
2	$In(OTf)_3$	1.1	Et_3SiH	CH_2Cl_2	53%
3	$FeCl_3$	1.1	Et_3SiH	CH_2Cl_2	41%
4	$Cu(OTf)_2$	1.1	Et_3SiH	CH_2Cl_2	52%
5	$CuBr_2$	1.1	Et_3SiH	CH_2Cl_2	54%
6	$Zn(OTf)_2$	1.1	Et_3SiH	CH_2Cl_2	NR
7	$Mg(OTf)_2$	1.1	Et_3SiH	CH_2Cl_2	15%
8	$Ga(OTf)_3$	1.1	Et_3SiH	CH_2Cl_2	trace
9	$Bi(OTf)_3$	1.1	Et_3SiH	CH_2Cl_2	trace
10	$Hf(OTf)_4$	1.1	Et_3SiH	CH_2Cl_2	NR
11	$InBr_3$	0.5	Et_3SiH	CH_2Cl_2	89%
12[c]	$InBr_3$	0.2	Et_3SiH	CH_2Cl_2	99%
13[d]	$InBr_3$	0.1	Et_3SiH	CH_2Cl_2	99%
14[c]	$InBr_3$	0.2	Me_2PhSiH	CH_2Cl_2	90%
15[c]	$InBr_3$	0.2	TMDS	CH_2Cl_2	71%
16[c]	$InBr_3$	0.2	PMHS	CH_2Cl_2	31%
17[c]	$InBr_3$	0.2	$PhSiH_3$	CH_2Cl_2	99%
18[c]	$InBr_3$	0.2	Ph_2SiH_2	CH_2Cl_2	91%
19[c]	$InBr_3$	0.2	Et_3SiH	DMF	NR
20[c]	$InBr_3$	0.2	Et_3SiH	CH_3CN	86%
21[c]	$InBr_3$	0.2	Et_3SiH	Toluene	29%
22[c]	$InBr_3$	0.2	Et_3SiH	THF	44%

[a]Reaction conditions: (0.1 M in solvent).
[b]Yields were determined by ^1H NMR.
[c]The reaction time was 24 h.
[d]The reation time was 90 h.

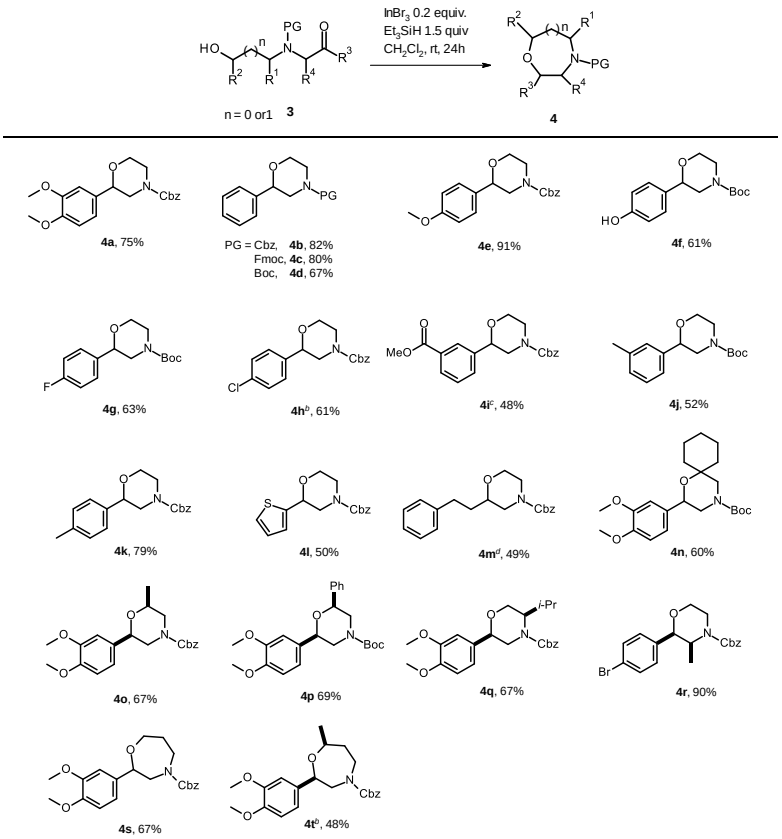
Having obtained the optimal reaction conditions, the generality of this transformation was investigated, and the results were listed in Scheme 1. The reaction was compatible with various widely used *N*-protecting groups such as Boc, Cbz and Fmoc with good to excellent yields. With regards to the aromatic ketones, different substitution patterns and electronic properties such as electron-donating (e.g. methoxy, hydroxyl, methyl) and electron-withdrawing (e.g. halogens and carboxylate) groups were well tolerated. Notably, a high percentage of catalyst loading was necessary to ensure full conversion for electron deficient substitutions such as *p*-Cl and *m*-CO_2Me. Furthermore, hetero-aromatic and aliphatic ketones were viable substrates. Various morpholines (2,3-, 2,5- and 2,6-disubstituted) could be synthesized conveniently under this mild reaction condition to afford the *cis*-disubstituted morpholines as the major products with high diastereoselectivity.[13] Moreover, a spiro-morpholine (**4n**) was obtained by using such protocol. Notably, the reaction can be easily scaled-up, and compound **4k** was synthesized with 79% yield on a 10 g scale. Interestingly, this strategy was further extended to the synthesis of 1,4-oxazepanes with good yield, and 2,7-disubstituted 1,4-oxazepane **4t** with high diastereoselectivity.[13]

The reaction mechanism is proposed in Figure 3. The reaction path involves three steps. First, $InBr_3$ promotes the cyclization and dehydration to afford oxocarbenium ion **III**. Second, the reaction between In (III) and Et_3SiH generates reducing species $HInBr_2$.[14] Third, the hydride reduction of the oxocarbenium provides the final product. The *cis*-diastereoselectivity for 2,3- and 2,5-disubstituted morpholines could be interpreted by invoking the axial hydride reduction of the oxocarbenium **IIIa** through a half-chair conformation, where the R^1 or R^4 substitutions are at the axial position in order to minimize the steric hindrance with the carbamate group on nitrogen. (Figure 4) Similarly, for the 2,6-disubstituted morpholine and 2,7-disubstituted 1,4-oxazepane, the R^2 substitution is at an equatorial position of the oxocarbenium **IIIa** and **IIIb**, respectively, and hydride approaches the oxocarbenium from the axial position to generate the *cis*-product. In many cases of the reductive etherification reactions, we observed an intermediate with a mass of targeted MW minus 2 from LC/MS, indicating the possible formation of a dihydrooxazine.[16] By treating substrate **3a** with 0.2 eq $InBr_3$ without adding a silane, we successfully isolated the dihydraoxazine **3aa** with a good yield.

In summary, we have developed an InBr3-promoted intramolecular reductive etherification reaction for the synthesis of morpholine derivatives with good function group tolerability. A broad range of 2-substituted, *cis*-2,3-disubstituted, *cis*-2,5-disubstituted, *cis*-2,6-disubstituted and spirocyclic morpholines were prepared with good yields and high diastereoselectivity. This chemistry features mild catalytic reaction conditions with high functional group compatibility. For example, readily removable *N*-protecting groups such as Boc-, Cbz-, and Fmoc- are well tolerated. In addition, this method can be further extended to the synthesis of 2-substituted and 2,7-disubstituted 1,4-oxazepanes with

moderate yields. Its application in drug discovery project is in progress, and will be reported in due course.

Scheme 1. $InBr_3$-promoted intramolecular cyclization of keto alcohols **3**



[a]Isolated yield.
[b]with 0.5 equiv of $InBr_3$
[c]with 1.0 equiv. of $InBr_3$.
[d]with 4.0 equiv. of Et_3SiH.
[e]dr was determined on the crude reaction mixtures by ^1H NMR, and was found to be > 19:1.

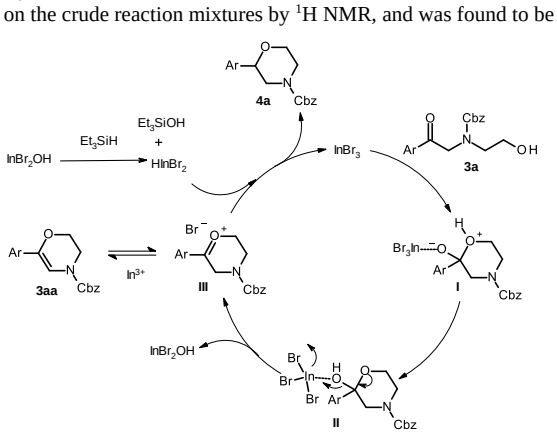


Figure 3. Plausible reaction mechanism

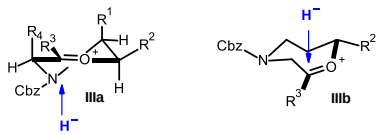


Figure 4. conformations of oxacarbeniums and hydride approaching direction [15]

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Full experimental detail, copies of ^{1}H and ^{13}C NMR spectra of compound **3**, **4** and **3aa** are provided. Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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15. A detailed diastereoselectivity analysis is depicted in the supporting information.
16. For the synthesis of **3q**, we obtained the dihydrooxazine **3q'** in the purification on silica gel chromatography. For the synthesis **3r**, we obtained a mixture of **3r** and **3r'** under the reaction conditions.