Direct-type catalytic Mannich reactions of amides with imines

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Direct-type catalytic Mannich reactions of amides with imines proceeded smoothly using barium phenoxide as a catalyst to afford the desired adducts in high yields with high *anti* selectivities.

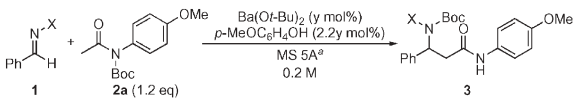
Mannich reactions provide very useful ways for constructing biologically important nitrogen-containing molecules such as β-amino carboxylic acid derivatives.[1] Accordingly, a number of groups have recently developed methods to prepare β-amino carboxylic acid derivatives, some of which have been extended to asymmetric variants.[2] While most of these have focused on the utilization of imines and preformed enolate equivalents such as silyl enol ethers, which are more reactive than their parent carbonyl compounds, such developments, widely known as *indirect-type* Mannich reaction protocols because of their reliance on the use of preformed key intermediates rather than their generation *in situ*, represent an important advance in synthetic utility of Mannich reactions. However, they suffer from the drawback of the necessity of the isolation and purification of enol equivalents. As for the construction of β-amino carboxylic acid derivatives, *direct-type* catalytic Mannich reactions are the most convenient method that proceeds *via* C–C bond formation with a proton transfer pathway. This protocol is superior in terms of atom economy to conventional methods that require stoichiometric amounts of bases and/or silicon sources. Although several metals[3] and organocatalysts[4] have proven to be effective in the direct-type catalytic Mannich reactions, substrates have been mostly limited to aldehydes and ketones. Therefore, direct-type catalytic Mannich reactions using ester equivalents have recently attracted much attention. However, the use of ester equivalents is still very difficult, due to the lower acidity of the α-protons of ester equivalents compared with those of ketones and aldehydes, and only sporadic examples have been reported.[5] We previously reported the use of amides in direct-type aldol reactions in the presence of a catalytic amount of barium phenoxide.[6] Herein we report the direct-type catalytic Mannich reaction of amides with imines. This reaction provides a rapid synthetic method for β-amino carboxylic acid derivatives. The diastereoselective direct-type catalytic Mannich reaction is also described.

In the initial trial, we investigated Mannich-type reactions of (*N*-Boc)acetoanisidide with several kinds of imines bearing different protecting groups. While no Mannich-type adducts were obtained using imines **1a** and **1b**, imines **1c** and **1d** were found to be good substrates for this reaction. After optimization of reaction conditions, it was discovered that the reactions of **1c** and **1d** with amide **2a** proceeded smoothly in polar solvents such as DMF and DMSO to afford the desired Mannich-type adducts in high yields (Table 1). Moreover, the reaction completed within 30 min in the presence of 5 mol% of the catalyst.

We then investigated substrate generality under the optimized reaction conditions. As summarized in Table 2, aryl, heterocyclic, and alkenyl *N*-diphenylphosphinoyl (Dpp) imines reacted with amide **2a** smoothly to afford the desired Mannich-type adducts in high yields. It should be noted that in all examples the reactions proceeded under mild conditions in a short reaction time (30 min).

Next, direct-type catalytic Mannich reactions of (*N*-Boc)propioanisidide **2b** were investigated. In the presence of 10 mol% of $Ba(Ot\text{-}Bu)_2$ and 22 mol% of *p*-methoxyphenol, amide **2b** reacted with imine **1c** to afford the desired Mannich-type adduct in 86% yield with low diastereoselectivity. After screening of several ligands, the use of bulky ones was found to give better diastereoselectivity (Table 3).

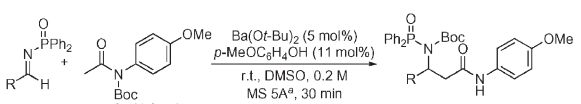
Table 1 Development of direct-type Mannich reaction of amide



Entry	X	*y* mol%	Product	Conditions	Yield (%)
1	Bn (**1a**)	10	**3a**	0 °C to r.t., THF	N.R.
2	Ph (**1b**)	10	**3b**	0 °C to r.t., THF	N.R.
3	$POPh_2$ (**1c**)	10	**3c**	0 °C to r.t., THF, 48 h	19
4	$POPh_2$ (**1c**)	10	**3c**	r.t., DMF, 24 h	46
5	SO_2Ph (**1d**)	10	**3d**	r.t., DMF, 24 h	50
6	$POPh_2$ (**1c**)	10	**3c**	r.t., DMSO, 24 h	75
7	SO_2Ph (**1d**)	10	**3d**	r.t., DMSO, 24 h	65
8	$POPh_2$ (**1c**)	5	**3c**	r.t., DMSO, 30 min	91

[a] 100 mg/0.3 mmol of **1**.

Table 2 Substrate generality of direct-type Mannich reaction



Entry	R	Product	Yield (%)
1	Ph	**3c**	91
2	*p*-MeC_6H_4	**3d**	89
3	*p*-$CH_3OC_6H_4$	**3e**	63[b]
4	*p*-ClC_6H_4	**3f**	81
5	1-naphthyl	**3g**	95
6	2-furyl	**3h**	78
7	3-furyl	**3i**	86
8	2-thienyl	**3j**	83
9	(*E*)-PhCH=CH	**3k**	76

[a] 100 mg/0.3 mmol of **1**. [b] 4 h.

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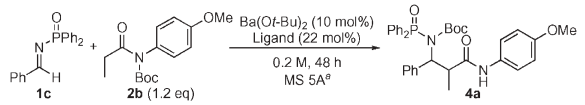
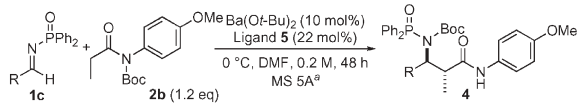
Table 3 Development of diastereoselective direct-type Mannich reaction of amide



	Entry	Ligand	Conditions	Yield (%)	*syn*/*anti*[b]
	1	*p*-$MeOC_6H_4OH$	r.t., DMSO	86	47/53
	2	*p*-$MeOC_6H_4OH$	r.t., THF	84	65/35
OMe	3	**5**	0 °C, THF	78	65/35
OH	4	**5**	0 °C, DMF	86	14/86
5					

[a] 100 mg/0.3 mmol of **1**. [b] Determined by ^{1}H NMR analysis.

Table 4 Substrate generality of diastereoselective direct-type Mannich reaction of amide



Entry	R	Product	Yield (%)	*syn*/*anti*[b]
1	Ph	**4a**	86	14/86
2	1-naphthyl	**4b**	76	8/92
3	2-furyl	**4c**	81	9/91
4	3-furyl	**4d**	89	16/84
5	2-thienyl	**4e**	81	15/85

[a] 100 mg/0.3 mmol of **1c**. [b] Determined by ^{1}H NMR analysis.

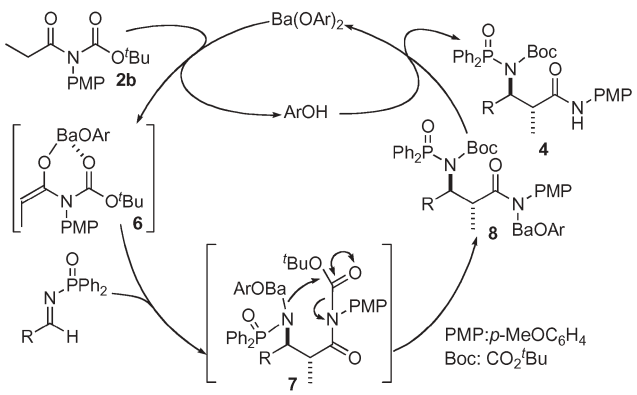


Fig. 1 Assumed catalytic cycle.

Several imines including aryl, heterocyclic, and alkenyl *N*-Dpp imines[7] were tested under the optimized reaction conditions, and in all cases catalytic diastereoselective Mannich reactions proceeded smoothly to afford the desired *anti*-Mannich adducts[8] in high yields with high diastereoselectivities (Table 4).

The proposed catalytic cycle is outlined in Fig. 1. Initially, barium alkoxide deprotonates the α-proton of acylamide **2b** to give barium enolate **6** *in situ*. This barium enolate then reacts with an imine to afford the initial Mannich-type adduct **7**. Subsequent intramolecular Boc-transfer then occurs spontaneously with concomitant release of steric strain, followed by a protonation reaction to afford the desired adduct **4** along with regeneration of the catalyst.

In summary, we have developed a highly diastereoselective direct-type catalytic Mannich reaction of amides with imines. The reaction proceeds smoothly in the presence of a catalytic amount of barium phenoxide under mild conditions. The use of (*N*-Boc)acylanisidides and *N*-Dpp imines is key, and a wide range of aromatic, heterocyclic, α,β-unsaturated aldehydes derived *N*-Dpp imines are applicable to afford the desired adducts in high yields with high diastereoselectivities. Further investigations to clarify the precise mechanism of this reaction and of asymmetric catalysis are now in progress.

Notes and references

† CCDC 633141. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b618490a

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7 An aliphatic imine did not give the desired adduct under the conditions.

8 Relative stereochemical assignment was made by X-ray crystal structure analysis of **4a**†.