Direct Organocatalytic Enantioselective Mannich Reactions of Ketimines: An Approach to Optically Active Quaternary α-Amino Acid Derivatives

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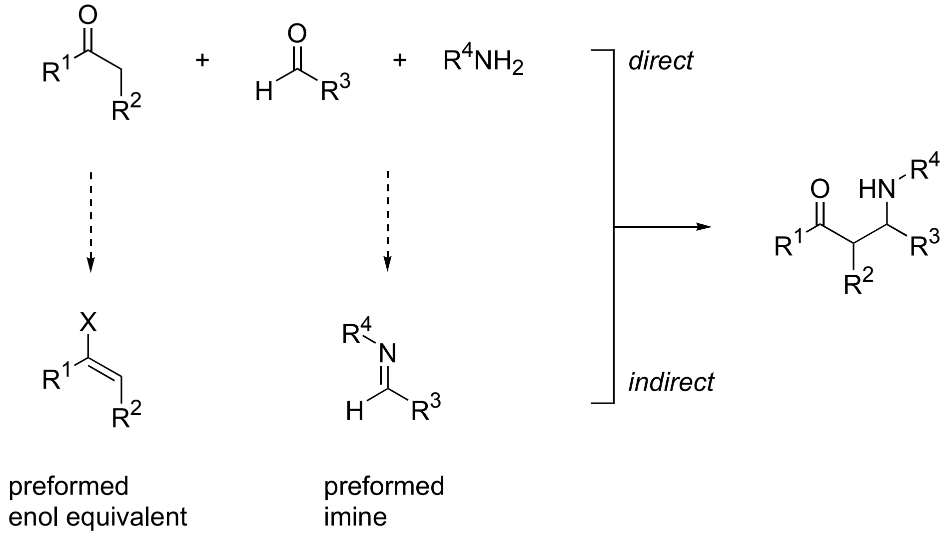
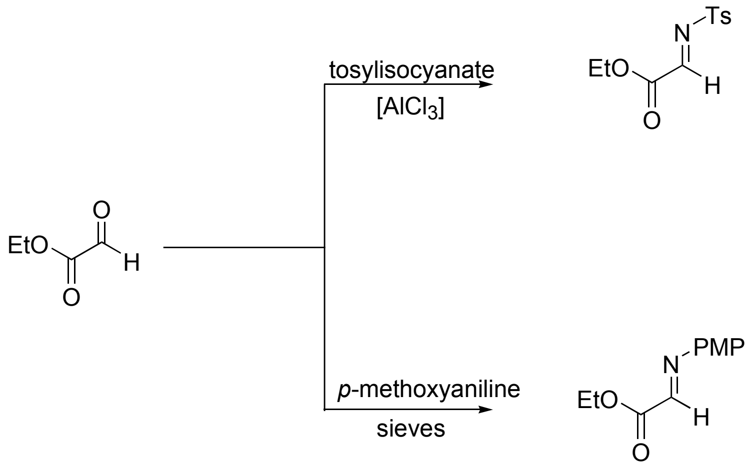
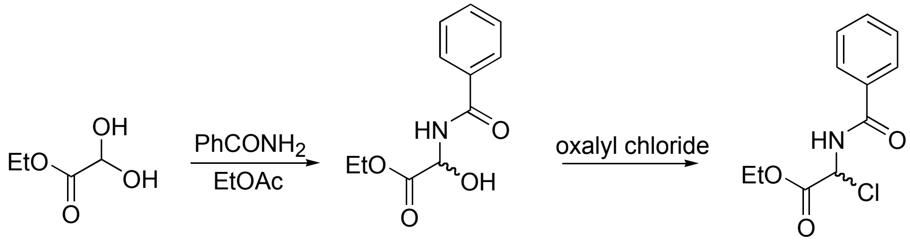
The Mannich Reaction



List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J.; *J. Am. Chem. Soc.* **2002**, *124*, 827-833.

Iminoesters as Useful Electrophiles in Mannich Reactions

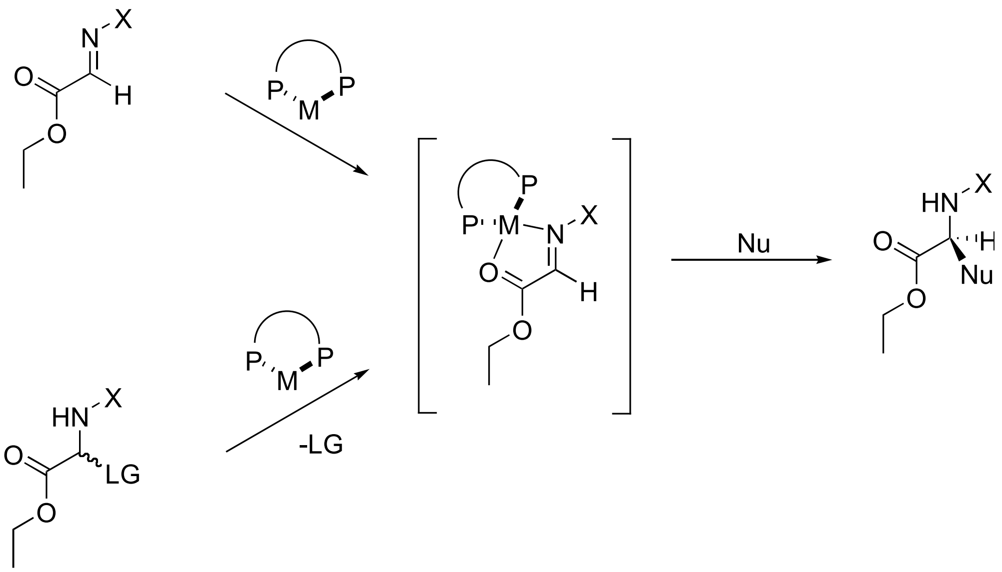




α-haloglycine

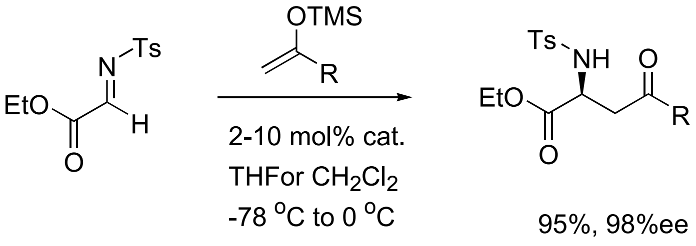
Taggi, A. E.; Hafez, A. M.; Leckta, T. *Acc. Chem. Res.* **2003**, *36*, 10-19.

Lewis Acid Catalyzed Mannich Reactions of α-Imino Esters

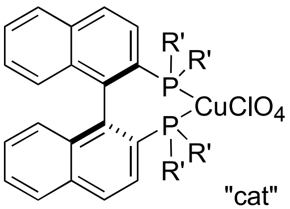


Taggi, A. E.; Hafez, A. M.; Leckta, T. *Acc. Chem. Res.* **2003**, *36*, 10-19.

Chiral Lewis Acid Catalyzed Mannich Reactions - 1



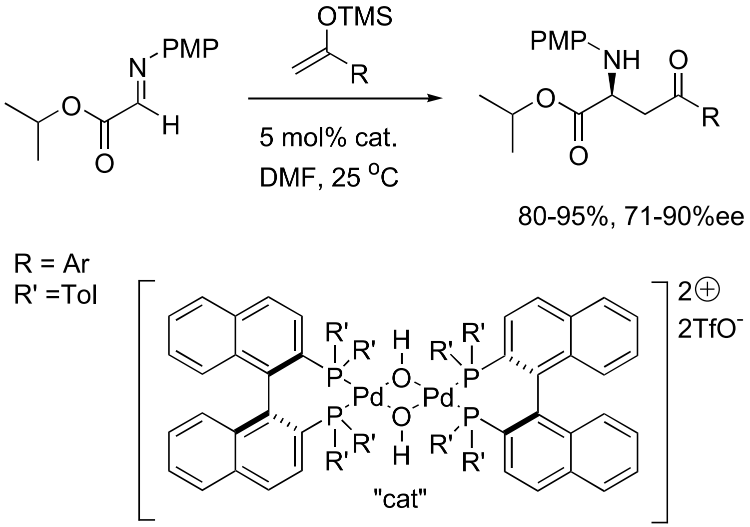
R = Ar, Alk
R' =*p*-Me-Ph



"cat"

(a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548-4549. (b) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J.; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168-2169. (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, Lev.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67-77.

Chiral Lewis Acid Catalyzed Mannich Reactions - 2

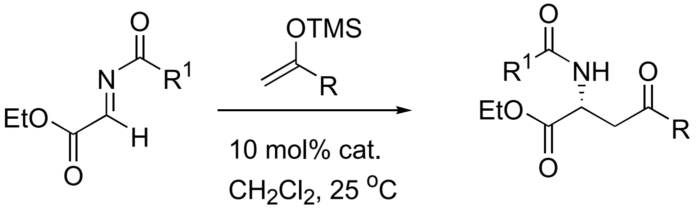


80-95%, 71-90%ee

R = Ar
R' =Tol

(a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474-2475. (b) Fujii, A.; Sodeoka, M.; **1999**, *40*, 8011-8014.

Chiral Lewis Acid Catalyzed Mannich Reactions - 3

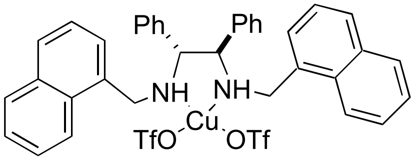


10 mol% cat.

CH_2Cl_2, 25 °C

77-97%, 90-97%%ee

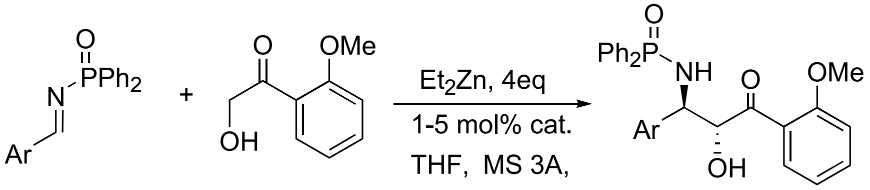
R = Ar, OMe, SEt
R' = Ar, Alk



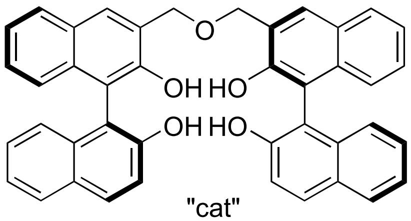
"cat"

(a) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143-145. (b) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640-5641.

Chiral Lewis Acid Catalyzed Mannich Reactions - 4



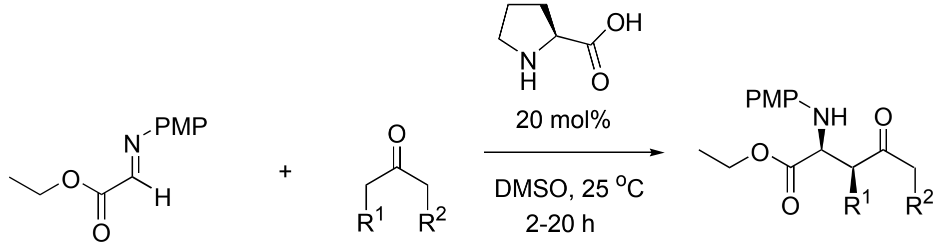
93-98%, 88/12-96/4 de,
95-98% ee



"cat"

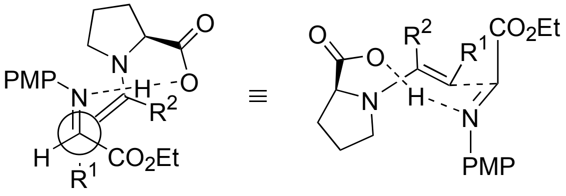
Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712-4713.

Mannich Reactions by Organocatalysis

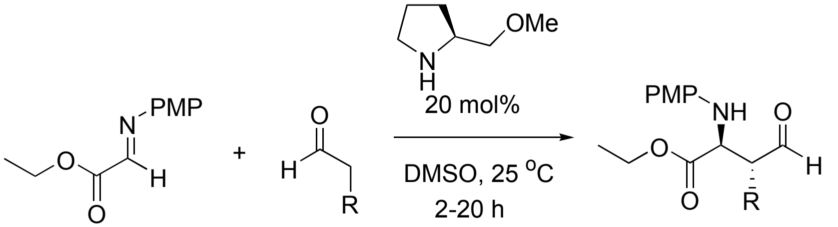


47-86%, 11-99%ee, 19:1 dr

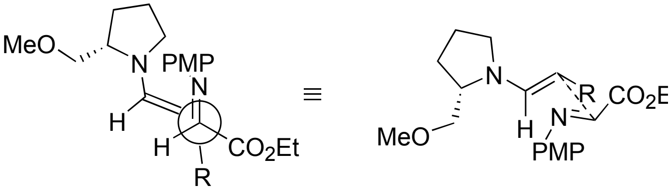
Proposed Transition States



(a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337. (b) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002,** *124*, 1842-1842.

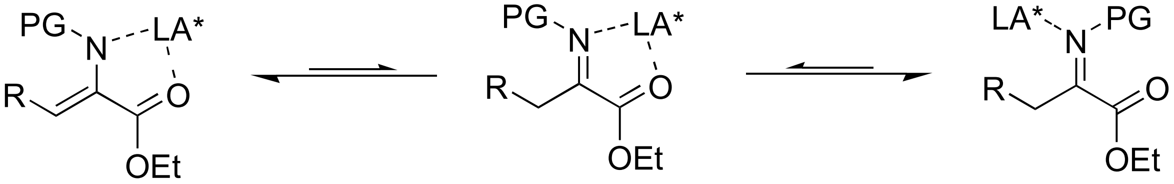


44-78%, 74-92%ee, 5:1-19:1 dr



(a) Cordova, A.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749-7752. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580-591.

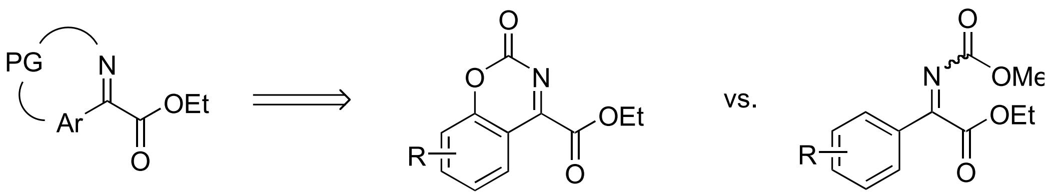
The Scoop: Mannich Reactions Largely Restricted to Imines Derived From Aldehydes



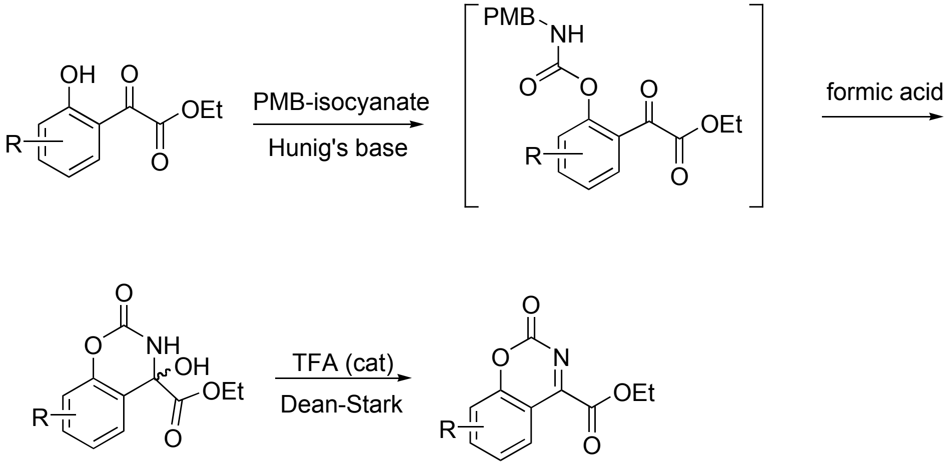
Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 6145-6154.

- Imines bearing α-protons are susceptible to form enamines in the presence of Bronstead or Lewis acids.
- The equilibrium of the flexible imine double bond is often shifted towards the *Z* isomer and thereby render difficult a constrained and rigid bidentate coordination to a Lewis acid complex
- A characteristic and fundamental problem related to the use of ketimine substrates is steric hindrance.
- The disubstituted carbon atom of a prochiral ketimine double bond is much less reactive than the analagous monosubstituted prochiral aldimine, owing to unfavorable steric interactions during the C—C bond forming step.

Intrinsic Protecting Groups: Their Role in Modulating Ketimine Reactivity

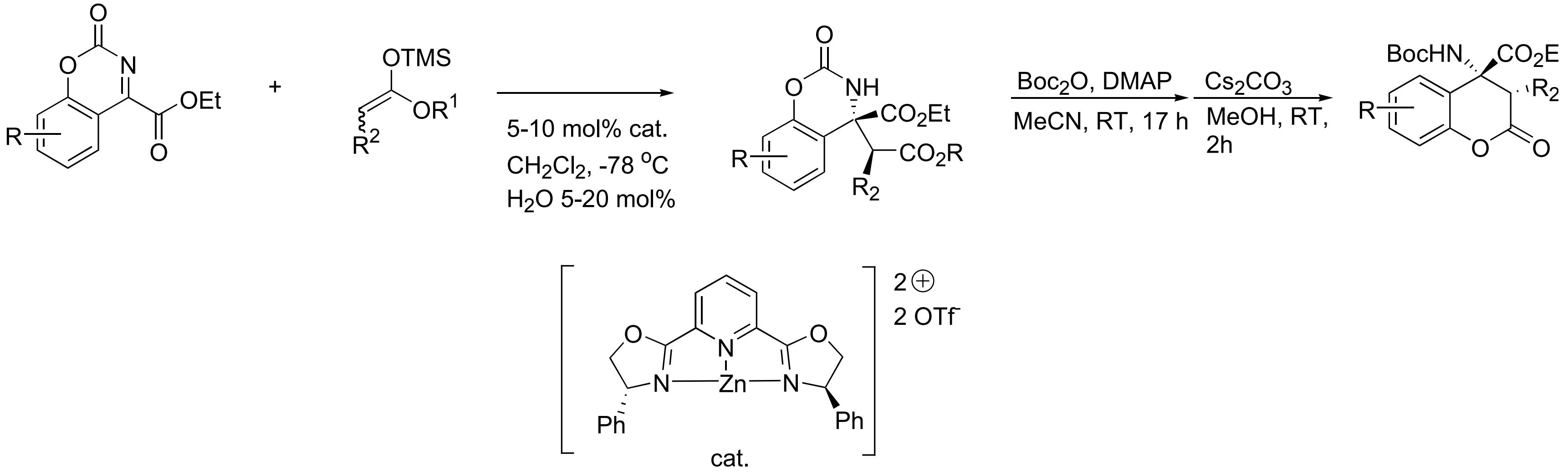


> "…By anchoring the nitrogen protecting group by means of an aryl substituent, the degree of rotational freedom, as well as possible imine double bond isomerization, is minimized, rendering a beneficial preorganized structure for bidentate Lewis acid activation. Moreover, the problem of enamine formation is also circumvented…"

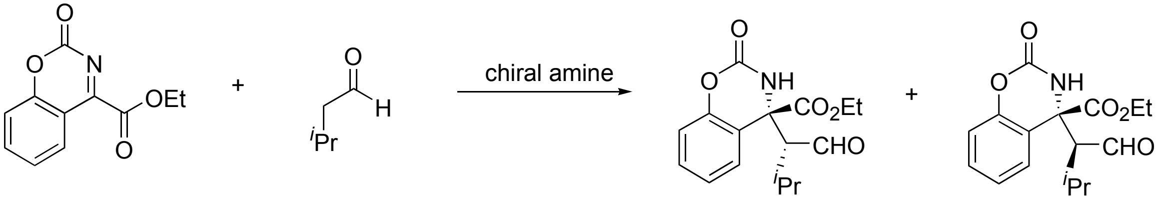


Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 6145-6154.

Lewis Acid Catalyzed Ketimine Alkylation



Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 6145-6154.

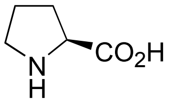


1a **2a** **3a** **4a**

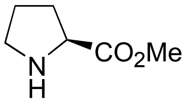
Table 1: Direct organocatalytic asymetric Mannich reaction of ketimine **1a** with **2a**.

Entry	Catalyst (mol%)	T [°C]	**2a** [equiv]	Solvent	Yield[a] [%]	**3a/4a**[b]	*ee*[c] [%]
1	**5a** (30)	0	5	CH_2Cl_2	84	1:8	82
2	**5b** (30)	0	5	CH_2Cl_2	11	>20:1	7
3	**5c** (30)	0	5	CH_2Cl_2	trace	>20:1	–
4	**5d** (30)	0	5	CH_2Cl_2	39	>20:1	80
5	**5e** (5)	0	5	CH_2Cl_2	56	15:1	86
6	**5e** (5)	0	5	CH_2Cl_2	73	2:1	88
7	**5e** (5)	0	5	Et_2O	74	19:1	90
8	**5e** (5)	0	2	Et_2O	99	>20:1	91
9	**5e** (5)	-24	2	Et_2O	51	17:1	92
10	**5e** (2)	0	2	Et_2O	93	18:1	91

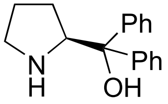
[a] Combined yield of the two isolated diastereomeric products. [b] The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude product mixture. [c] The *ee* of the major product was determined by HPLC on a Daicel Chiralpak AS column.



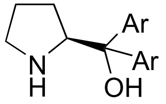
5a



5b

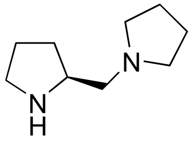


5c



Ar = 3,5 xylyl

5d



5e

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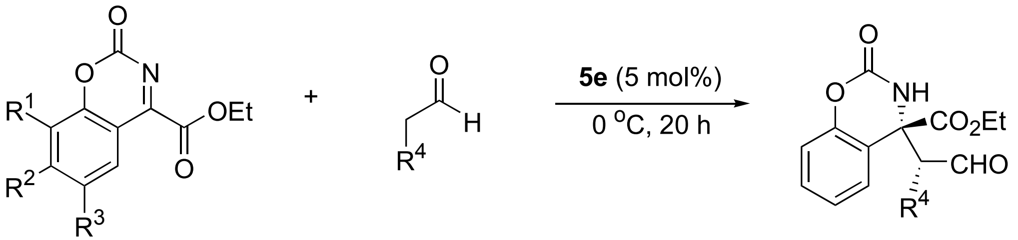

1a-f

2a R^4 = *i*Pr
2b R^4 = Me
2c R^4 = allyl

3a-h

Table 2. Reaction of ketimines **1a-f** with aldehydes **2a-c** under the optimized reaction conditions

Entry	Imine	Solvent	R^1	R^2	R^3	R^4	Product	Yield [%][a]	**3/4**[b]	*ee*[%][c]
1	**1a**	Et_2O	H	H	H	*i*Pr	**3a**	99	>20:1	91
2	**1b**	Et_2O	H	H	Me	*i*Pr	**3b**	98	6:1	89
3	**1c**	Et_2O	H	H	OMe	*i*Pr	**3c**	95	9:1	86
4	**1d**	Et_2O	H	H	F	*i*Pr	**3d**	97	19:1	83
5	**1e**	Et_2O	H	OMe	H	*i*Pr	**3e**	90	>20:1	87
6	**1f**	Et_2O	$–C_4H_4–$		H	*i*Pr	**3f**	93	>20:1	84
7	**1a**	CH_2Cl_2	H	H	H	Me	**3g**	72	5:1	95
8	**1a**	CH_2Cl_2	H	H	H	allyl	**3h**	82	4:1	98

[a] Combined yield of the two isolated diastereomeric products. [b] The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude product. [c] The *ee* value of the major product (with *R* configuration at the quaternary center) was determined by HPLC on a Chiral stationary phase (see Supporting Information for details).

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Conclusions

- The first organocatalytic, enantioselective Mannich reaction of ketimines and unmodified aldehydes based on the concept of intrinsic protecting group anchoring has been reported.
- Catalysis is achieved by the addition of simple chiral amines (2-5 mol%) providing optically active quaternary α-amino acid derivatives in high yields (72-99%) and good optical purities (83-98% *ee*).
- Through careful selection of the amine catalyst, the diastereoselectivity of the reaction can be controlled.