Ti-mediated direct and highly stereoselective Mannich reactions between esters and oxime ethers†

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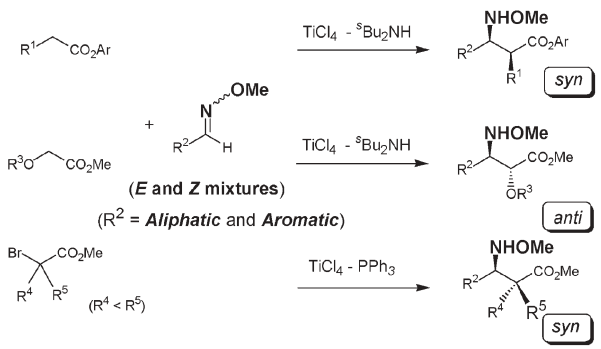
The first general method of direct and highly stereoselective Ti-mediated Mannich reaction between three types of simple esters and *E* and *Z* mixtures of oxime ethers (aliphatic and aromatic) is accomplished.

The Mannich reaction is well recognized as a fundamental C–C bond forming reaction for the preparation of useful β-amino carbonyl compounds and β-lactams.[1] Direct methods using simple esters as nucleophiles are considerably limited compared with those of ketones because of their lower enolization ability, and in addition the Mannich reaction generally utilizes relatively unstable *imines* for the counter electrophiles.[2] Oxime ethers are well-known superior isosters to imines due to easier preparation and inherently higher stability, especially for reliable *aliphatic* aldoximes derived from enolizable aldehydes. The reaction using oxime ethers, therefore, has a clear advantage over that of imines, because of its wide variation. As part of our continuing studies of Ti-Claisen condensation[3] and related reactions,[4] we disclose here direct and stereoselective (*syn* or *anti*) Ti-mediated Mannich-type reactions between three types of esters and methyl *oxime ethers* (aldoximes and aryloximes, *E* and *Z* mixtures) (Scheme 1). To the best of our knowledge, this is the first reported general method of a Mannich reaction between simple esters and oxime ethers.

The initial attempt was guided by the reaction of phenyl and 4-nitrophenyl hexanoates with the *O*-methyloxime of 1-octanal utilizing a $TiCl_4$–$^sBu_2NH$ reagent,[3i] because aryl esters have an advantage over alkyl esters in smoother Ti-enolate formation[4e] (Table 1).‡ The desired phenyl and 4-nitrophenyl 2-butyl-3-methoxyamino esters **1** and **2** were successfully obtained in 63 and 90% yield, respectively, with high *syn*-selectivity[5] (entries 1, 2). The stereochemistry (*E* and *Z*) of the oxime ethers is speculated to be of primary importance in this reaction. Surprisingly, the reaction using $PhCH_2CH_2CHN{=}OMe$ with three different *E* : *Z*-ratios produced almost the same results in yield and *syn*/*anti* selectivity (entries 3–5).



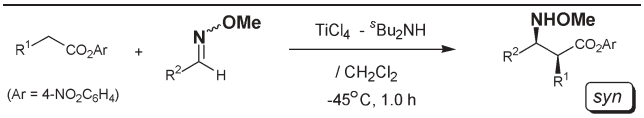
Scheme 1

Thus, *O*-methyloximes with inherent *E* : *Z*-ratios (unnecessary for any specific separation) can be used for the present method. Reactions using several *O*-methyloximes successfully produced the corresponding β-amino esters **4**, **6–11** with high *syn*-selectivity (*syn* : *anti* = >90 : 10) (entries 6–13), except for cyclohexyl analogue **5** (*syn* : *anti* = 74 : 26) (entry 7). Functionalities such as a terminal double bond, a furan, and ω-chloro groups were tolerated (entries 6, 9, 11, 13).

With these results in hand, we next investigated the reaction of several methyl α-alkoxy esters with *O*-methyloximes because of the utility of α-hydroxy-β-aminoacids.[2a,d] Table 2‡ lists the successful results of *anti*-selective reactions (but not *syn*) under optimized conditions.

The initial attempted reaction of methyl methoxyacetate with $CH_3(CH_2)_6CH{=}NOMe$ proceeded smoothly to give the desired

Table 1 Ti-mediated direct *syn*-selective Mannich reaction between aryl esters and *O*-methyloximes[a]



Entry	R^1	R^2	*E* : *Z*[b]	Product	Yield (%)	*syn* : *anti*[c]
1	*n*-Bu	*n*-Oct	61 : 39	**1**	63[d]	90 : 10
2	*n*-Bu	*n*-Oct	61 : 39	**2**	90	94 : 6
3	*n*-Bu	$PhCH_2CH_2$	>99 : 1	**3**	81	95 : 5
4	*n*-Bu	$PhCH_2CH_2$	1 : >99	**3**	80	94 : 5
5	*n*-Bu	$PhCH_2CH_2$	57 : 43	**3**	80	95 : 5
6	*n*-Bu	$CH_2{=}CH(CH_2)_8$	60 : 40	**4**	85	96 : 4
7	*n*-Bu	*c*-Hex	78 : 22	**5**	86	74 : 26
8	*n*-Bu	Ph	>99 : 1	**6**	84	>99 : 1
9	*n*-Bu	2-Furyl	78 : 22	**7**	61	>99 : 1
10	Me	*n*-Oct	61 : 39	**8**	57	90 : 10
11	$CH_2{=}CHCH_2$	*n*-Oct	61 : 39	**9**	82	95 : 5
12	$PhCH_2$	*n*-Oct	61 : 39	**10**	69	90 : 10
13	$Cl(CH_2)_3$	*n*-Oct	61 : 39	**11**	74	97 : 3

[a] Ester : oxime ether : $TiCl_4$: $^sBu_2NH$ = 1.0 : 1.4 : 3.0 : 2.5. [b] *E* : *Z* ratio of *O*-methyloxime. [c] Determined by ^1H NMR of the crude product. [d] Ar = Ph.

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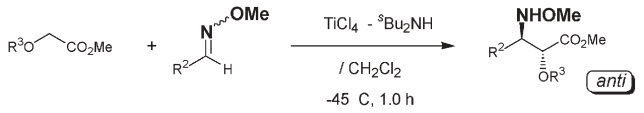
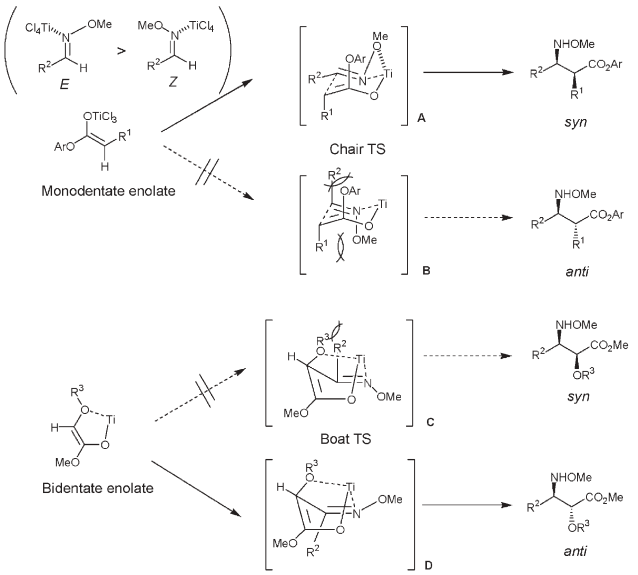
Table 2 Ti-mediated direct *anti*-selective Mannich reaction between methyl 2-alkoxy esters and *O*-methyloximes[a]



Entry	R^3	R^2	$E : Z^b$	Product	Yield (%)	*syn* : *anti*[c]
1	Me	*n*-Oct	61 : 39	**12**	85	2 : 98 (1 : >99)
				(**13**)[d]	(51)	
2	Bn	*n*-Oct	61 : 39	**14**	83	4 : 96
3	Ts	*n*-Oct	61 : 39	**15**	83	9 : 91
4	Allyl	$PhCH_2CH_2$	>99 : 1	**16**	81	1 : >99
5	Allyl	$PhCH_2CH_2$	1 : >99	**16**	81	1 : >99
6	Allyl	$PhCH_2CH_2$	57 : 43	**16**	81	1 : >99
7	Allyl	$CH_2{=}CH(CH_2)_8$	60 : 40	**17**	78	1 : >99
8	Allyl	*n*-Oct	61 : 39	**18**	80	1 : >99
9	Allyl	*c*-Hex	61 : 39	**19**	81	1 : >99

[a] Ester : Oxime ether : $TiCl_4$: $^sBu_2NH$ = 1.0 : 1.4 : 2.0 : 2.5. [b] *E* : *Z* ratio of *O*-methyloxime. [c] Determined by ^1H NMR of the crude product. [d] Use of *O*-benzyloxime ether.



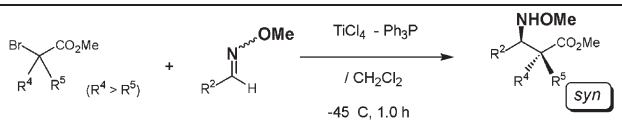
Scheme 2

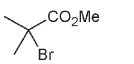
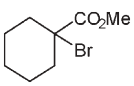
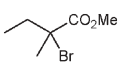
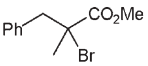
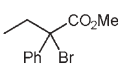
product **12** in 85% yield with excellent *anti*-selectivity[5] (*syn* : *anti* = 2 : 98) (entry 1).

Three stereoisomeric substrates of $PhCH_2CH_2CH{=}NOMe$ (*E*-, *Z*- and *E*,*Z*-mixtures) also produced results similar to that described in Table 1, entries 4–6. Our attention was focused on the reaction using methyl allyloxyacetate (R^3 = allyl), taking the possibility of deprotection into account. Thus, the desired α-allyloxy-β-methoxyesters **14–19** were produced with almost complete *anti*-selectivity (entries 4–9).

Scheme 2 illustrates a couple of proposed mechanisms for the present switching mode of *syn*- and *anti*-selectivities. A basic working hypothesis is that the $TiCl_4$-coordinated *E*-oxime ether

Table 3 Reductive Mannich-type addition between methyl 2-bromo-2,2-dialkyl esters and *O*-methyloximes.[a]



Entry	α-Bromoester	R^2	*E* : *Z*[b]	Product	Yield (%)	*syn* : *anti*[c]
1		*n*-Oct	61 : 39	**20**	87	—
2		$CH_2{=}CH(CH_2)_8$	60 : 40	**21**	72	—
3		$PhCH_2CH_2$	57 : 43	**22**	71	—
4		$(CH_3)_2CHCH_2$	57 : 43	**23**	75	—
5		$Ph(CH_3)CHCH_2$	53 : 47	**24**	81	—
6		$BnO(CH_2)_4$	64 : 36	**25**	91	—
7		Ph	>99 : 1	**26**	92	—
8		2-Naph	98 : 2	**27**	70	—
9		*m*-ClC_6H_4	96 : 4	**28**	80	—
10		*p*-$CF_3C_6H_4$	97 : 3	**29**	76	—
11		2-thiophenyl	—	**30**	79	—
12		*n*-Oct	61 : 39	**31**	59	—
13		*n*-Oct	61 : 39	**32**	91	54 : 46[d]
14		*n*-Oct	61 : 39	**33**	96	57 : 43[d]
15		*n*-Oct	61 : 39	**34**	60	96 : 4
16		*n*-Oct	61 : 39	**35**	79	85 : 15
17		$BnO(CH_2)_4$	64 : 36	**36**	73	85 : 15
18		Ph	>99 : 1	**37**	90	96 : 4

[a] Ester : oxime ether : $TiCl_4$: Ph_3P = 1.0 : 1.0 : 2.4 : 1.6. [b] *E* : *Z* ratio of *O*-methyloxime. [c] Determined by ^1H NMR of the crude product. [d] *Syn*/*anti* was not assigned.

has higher content and/or reactivity than the *Z*-oxime ether *in situ*. For a simple aryl ester, Ti-monodendate enolate reacts with an *E*-isomer to form the chair transition state (TS) **A** or **B**. Due to double 1,3-diaxial repulsions between R^2 and OAr, R^1 and OMe in TS-**B**, TS-**A** is preferentially formed to give the *syn*-adduct. For a methyl alkoxyacetate, Ti-bidentate enolate forms the boat TS-**C** or TS-**D**. Due to repulsion between R^3O and R^2, TS-**D** is preferentially formed to give the *anti*-adduct.

As a notable extension, we focused our attention on an alternative reductive Ti-Mannich reaction utilizing a $TiCl_4$–PPh_3 reagent.[6] Table 3‡ lists the successful results using a couple of substrates, α,α-dialkyl-α-bromoesters and *O*-methylaldoximes or aryloximes. A striking feature is the application to the preparation of various α,α-*dialkylated* β-(methoxyamino)esters **20–37**, because these products could not be obtained (no reaction) for the reaction by the aforementioned $TiCl_4$–$^s Bu_2NH$ method. Note that the use of α-methyl-γ-butyrolactone and α-ethyl-α-phenyl ester analogues provided good to excellent *syn*-selectivity (entries 15–18).

The obtained various β-*O*-methyloxime ester products were readily converted to the corresponding β-amino esters using Zn–AcOH reagent under mild conditions with retentive *syn* or *anti* stereochemistry.[7]

In conclusion, we developed the first general method for highly stereoselective Ti-mediated Mannich-type reactions between readily available esters and oxime ethers to give a variety of 3-(methoxyamino)-2-substituted esters (all new compounds). The present method provides a new avenue for the synthesis of various new stereocontrolled β-amino ester derivatives.

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Notes and references

‡ *General procedure* of Table 1: $TiCl_4$ (142 mg, 0.75 mmol) and $^s Bu_2NH$ (100 mg, 0.75 mmol) were successively added to a stirred solution of an *O*-methyloxime (0.70 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C under an Ar atmosphere. After stirring at the same temperature for 10 min, an ester (0.50 mmol) in CH_2Cl_2 (0.5 mL) and $TiCl_4$ (47 mg, 0.25 mmol) was added to the mixture, followed by being stirred at −50 to −40 °C for 0.5 h. Additional $TiCl_4$ (95 mg, 0.50 mmol) and $^s Bu_2NH$ (65 mg, 0.50 mmol) were successively added to the mixture. After stirring at the same temperature for 1.0 h, water was added to the mixture, with stirring, which was extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography to give the desired aryl *syn*-3-(methoxyamino)-2-alkylester as a major product.

General procedure of Table 2: $TiCl_4$ (190 mg, 1.00 mmol) and $^s Bu_2NH$ (162 mg, 1.25 mmol) were successively added to a stirred solution of an *O*-methyloxime (0.70 mmol) and an methyl alkoxyacetate (0.70 mmol) in CH_2Cl_2 (1.5 mL) at −50 to −40 °C under an Ar atmosphere. A similar work up of Table 1 gave the desired methyl *anti*-3-(methoxyamino)-2-alkoxy ester as a major product. (Note: sat. $NaHCO_3$ aqueous solution was used instead of water to ensure the basicity of the aqueous phase).

General procedure of Table 3: PPh_3 (210 mg, 0.80 mmol) in CH_2Cl_2 (0.5 mL) and $TiCl_4$ (228 mg, 1.2 mmol) were successively added to a solution of an *O*-methyloxime (0.50 mmol) and an α,α-dialkyl-α-bromoester (0.50 mmol) in CH_2Cl_2 (1.0 mL) at −50 to 40 °C under Ar atmosphere. A similar work up of Table 1 gave the desired *syn*-3-(methoxyamino)-2,2-dialkyl ester as a major product.

1 For examples: (*a*) F. F. Blicke, *Org. React.*, 1942, **1**, 303; (*b*) E. F. Kleinman, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, Oxford, 1991, vol. 2, p. 893; (*c*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1045; (*d*) L. Kürti and B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, 2005, p. 274; (*e*) M. B. Smith and J. March, *March's Advanced Organic Chemistry*, Wiley, New York, 6th edn, 2007, p. 1292.

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4 (*a*) Y. Tanabe, K. Mitarai, T. Higashi, T. Misaki and Y. Nishii, *Chem. Commun.*, 2002, 2542; (*b*) Y. Tanabe, N. Matsumoto, T. Higashi, T. Misaki, T. Itoh, M. Yamamoto, K. Mitarai and Y. Nishii, *Tetrahedron*, 2002, **58**, 8269 (Symposium); (*c*) A. Iida, K. Takai, T. Okabayashi, T. Misaki and Y. Tanabe, *Chem. Commun.*, 2005, 3171; (*d*) M. Katayama, R. Nagase, K. Mitarai, T. Misaki and Y. Tanabe, *Synlett*, 2006, 129; (*e*) R. Nagase, N. Matsumoto, K. Hosomi, T. Higashi, S. Funakoshi, T. Misaki and Y. Tanabe, *Org. Biomol. Chem.*, 2007, **7**, 151.

5 The *syn* or *anti* configuration was unambiguously determined on the basis of vicinal J_H coupling values of β-lactams, which were derived from the obtained β-hydroxymethyl esters (ESI†).

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7 Yields of the β-amino esters from **2**, **18** and **28** were 85, 55, and 87%, respectively. Experimental details are described in ESI.† For other methods, see: *Comprehensive Organic Transformations*, Wiley, New York, 2nd edn, 1999, p. 843.