Tetrahedron Letters 50 (2009) 3485–3488

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective synthesis of polyketide segments through vinylogous Mukaiyama aldol reactions

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ARTICLE INFO

Article history:
Received 15 January 2009
Revised 28 February 2009
Accepted 3 March 2009
Available online 9 March 2009

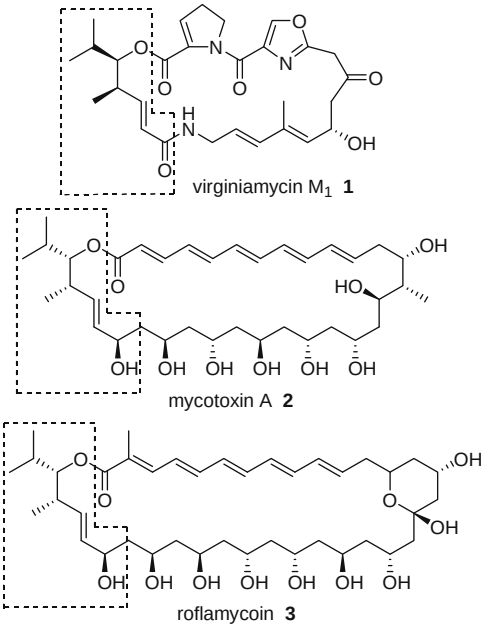
This work is dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday

Keywords:
Vinylogous Mukaiyama aldol
Polyketides
Oxazaborolidines
Natural products
Enantioselective

ABSTRACT

The synthesis of polyketide segments through the vinylogous Mukaiyama aldol reaction is reported. The use of chiral oxazaborolidines allows using terminal substituted ketene acetals and provides access to extended segments and two new chiral centers.

The rapid and efficient assembly of polyketide segments is one of the pivotal requirements for the construction of biologically active compounds. In this context, the vinylogous extension of the Mukaiyama aldol reaction is a strategic concept by which not only larger segments can be constructed rapidly but also it avoids extensive functional group manipulations or protecting group shuffling. This set the background for groundbreaking contributions of various research groups.[1] In order to meet the stereochemical requirements of modern organic chemistry different approaches to provide enantioselective vinylogous aldol reaction have been put forward and in particular enolates or ketene acetals were successfully transformed. Despite the enormous success of such reaction the lack of substitution at the terminal position prevented the general applicability of this concept. The seminal contributions by Denmark[2] and co-workers allowed using terminal substituted ketene acetals in Mukaiyama aldol reactions with aromatic and unsaturated aldehydes leaving aliphatic aldehydes as an unmet challenge. On the other hand a methyl-substituted ketene acetal would allow for the rapid and efficient construction of polyketide segments found in natural products such as virginiamycin (**1**),[3] mycotoxin (**2**)[4] or roflamycoin (**3**)[5] (Scheme 1). In connection with our ongoing program dealing with the synthesis of complex natural products[6] we focused on different Lewis acids for the activation of aldehydes.[7] In this context chiral oxazaborolidinones proved to be superior to other boron centered catalysts and



Scheme 1. Antibiotics virginiamycin, mycotoxin A, roflamycoin.

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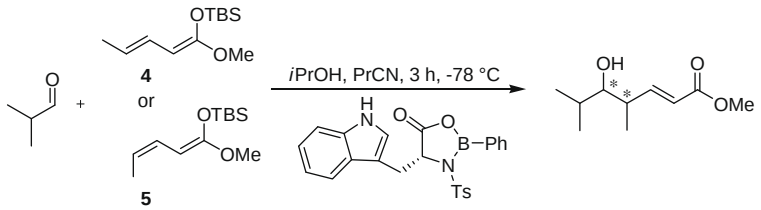
doi:10.1016/j.tetlet.2009.03.013



Scheme 2. Vinylogous Mukaiyama aldol reaction using terminal substituted ketene acetals and *N*-Ts-tryptophan-based oxazaborolidinone.

provided access to highly enantioselective vinylogous Mukaiyama aldol reactions.[8]

In our search for Lewis acids that would allow for the enantioselective addition of substituted ketene acetals, the above-mentioned oxazaborolidinones failed to provide satisfactory selectivities for both the 3,4-*E* (**4**) and the 3,4-*Z* (**5**) configured ketene acetals (Scheme 2, Table 1).

In order to extend the diversity of the catalysts employed we examined Lewis acids that proved to be successful in other vinylogous aldol reactions. Among these catalysts are the titanium-based complexes **6** and **7** developed by Carreira,[9] Evan's copper pybox complex **8**,[10] Yamamoto's[11] acyloxyboranes **9**–**11** for which Sato et al.[12] could show that they provide significantly higher selectivities compared to oxazaborolidinones as well as the Keck catalyst **12**[13] which was successfully employed in vinylogous Mukaiyama aldol reaction of terminally unsubstituted ketene acetals by Paterson et al. (Fig. 1).[14] Despite their structural diversity, none of these catalysts exceeded 76% enantiomeric excess in reactions with 4-methylated silyl ketene acetals.

We therefore changed our focus to the phenylalanine and valine derived oxazaborolidines that were employed either with no additive or with additional Lewis acid ($SnCl_4$) or Brønsted acid (TfOH), respectively.[15] Even though all catalysts provided acceptable yields in the order of 50% and with diastereomeric excess greater than 95%, the ee values never exceeded 80% (Fig. 2).

Finally, the contributions of Boeckman et al.[16] prompted us to examine proline-derived oxazaborolidines. In the first attempt

Table 1
Vinylogous Mukaiyama aldol reaction using *N*-Ts-tryptophan-based oxazaborolidinone

Entry	Ketene acetal	Yield (%)	de (%)	ee (%)
1	**4**	24	58	24
2	**5**	31	77	52

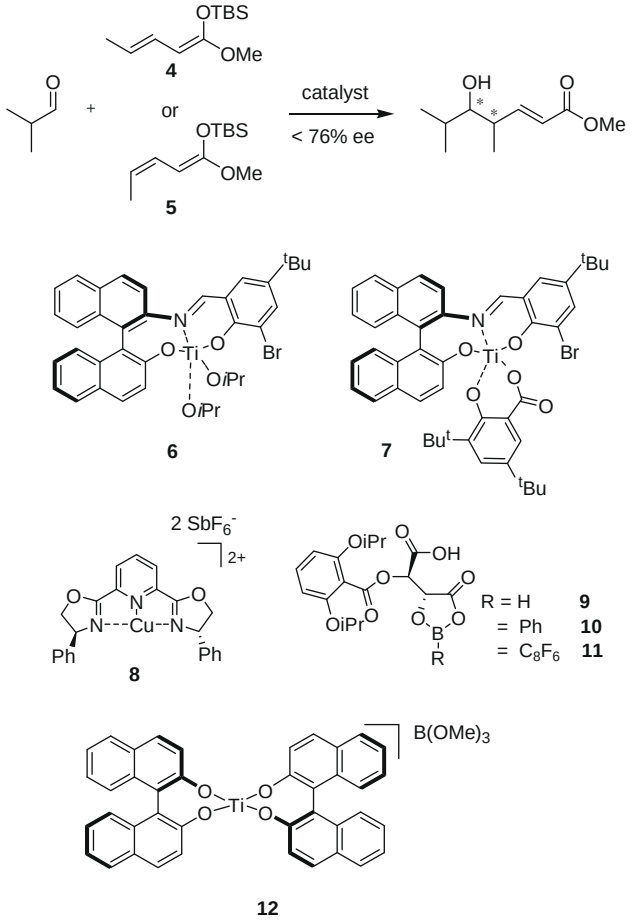


Figure 1. Lewis acids used in vinylogous Mukaiyama aldol reactions with terminal substituted silyl ketene acetals.

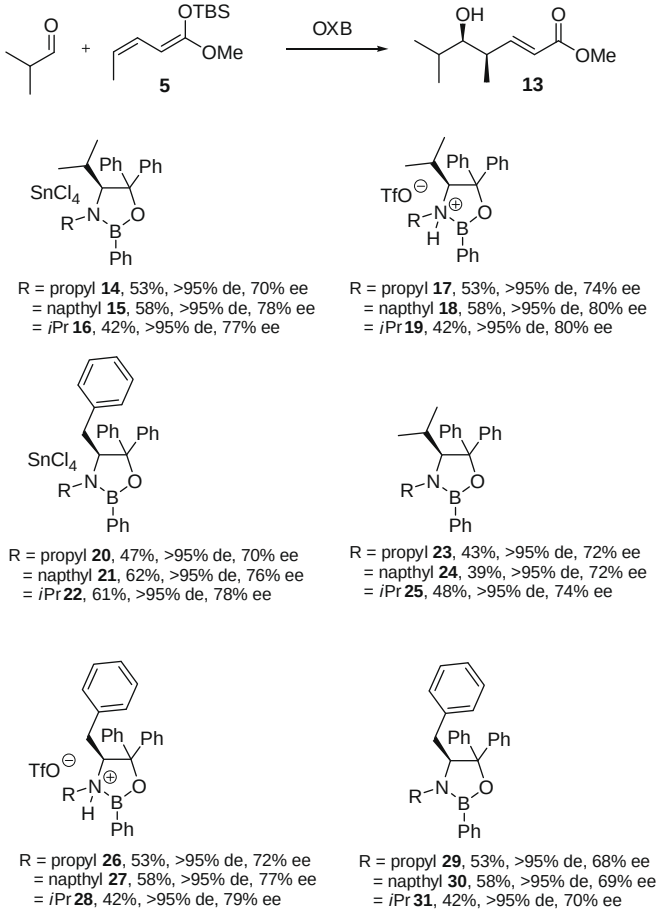
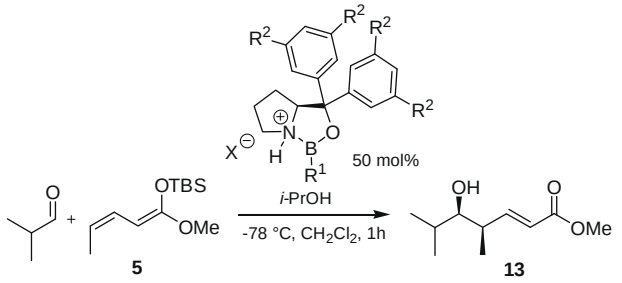


Figure 2. Oxazaborolidines (OXBs) used in vinylogous Mukaiyama aldol reactions.



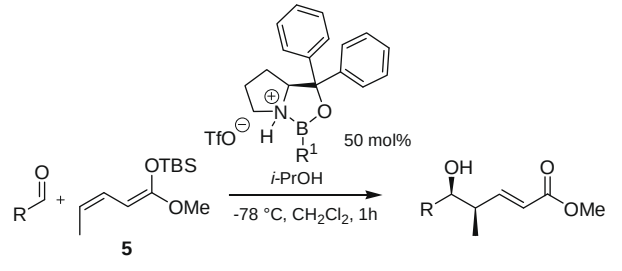
Scheme 3. Vinylogous Mukaiyama aldol reactions using proline-based oxazaborolidines.

Table 2
Different oxazaborolidines used in the vinylogous Mukaiyama aldol reaction

Entry	R^1	X	R^2	γ:α	γ Yield (%)	γ de (%)	γ ee (%)
1	Ph	—	H	99:1	67	95	83
2	*o*-Tol	—	H	99:1	60	95	83
3	Ph	—	Me	99:1	67	95	83
4	Ph	OTf	H	99:1	85	>95	90
5	Ph	NTf_2	H	99:1	68	>95	86
6	Ph	$AlBr_3$	H	99:1	54	>95	83
7	Ph	$SnCl_4$	H	99:1	73	>95	82
8	Ph	OTf	Me	99:1	52	>95	90
9	*o*-Tol	OTf	H	99:1	52	95	90
10	*o*-Tol	OTf	Me	99:1	52	95	90
11	Ph	OTF	H	63:37	12	54	85

we investigated the addition of 3,4-*Z* configured ketene acetal **5** to isobutyraldehyde and introduced variations by changing the R^1-substituent at boron and the substitution pattern of the phenyl R^2-substituents (Scheme 3). Additionally, activation through the addition of Lewis or Brønsted acids was examined. In all cases the yields reached satisfactory levels between 52% and 85% when 50 mol % of the catalyst was employed. The ratio of γ versus α alkylation was also excellent and at least 99:1 with diastereomeric excess higher than 95%. Finally, the highest enantioselectivities were obtained when an additional activation through trifluoroacetic acid was employed. In these cases the aryl groups employed as well as variations of the substituent R^1 did not change the selectivities (Table 2). However, the best yields (85%) were observed when R^1 is phenyl and R^2 is hydrogen (entry 4).[17]

Table 3
Vinylogous Mukaiyama aldol reactions using proline-based oxazaborolidines on different aldehydes



Entry	Aldehyde	γ:α	γ yield (%)	γ de (%)	γ ee (%)
1	Cyclohexane carbaldehyde	99:1	84	95	85
2	Pivalaldehyde	99:1	37	95	90
3	Valeralaldehyde	95:5	76	92	92
4	Benzaldehyde	64:26	53	54	82
5	2-Furaldehyde	78:22	51	71	80
6	*E*-Cinnamaldehyde	58:42	38	51	71

Initially, we had expected to selectively generate *anti* products by employing *E*-configured silyl ketene acetal **4**. Nevertheless, even applying the most efficient reaction conditions only produced the *syn* product **13** in poor yields and selectivities (entry 11).

In order to evaluate the substrate range different aldehydes were employed under the conditions summarized in entry 4 (Table 3). It can be seen from Table 3 that in particular aliphatic aldehydes provide very good selectivities. In contrast aromatic or unsaturated aldehydes provide only moderate results with ee values between 71% and 82% ee.

Even though the rational for this different selectivity remains obscure, the protocol presented here complements the work by Denmark and the investigations by Kobayashi and co-workers[18] which allows also access to the corresponding *anti* products. Taken these protocols together the enantioselective addition of terminal substituted aldehydes can now be performed in a convenient manner for virtually all possible aldehydes and thus extends our repertoire of the vinylogous extension of the aldol reaction significantly.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.013.

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17. *General method of the oxazaborolidine promoted VMAR*: To a solution of α,α-diphenyl-L-prolinol (69.7 mg, 0.275 mmol) in CH_2Cl_2 (2.5 mL) dichlorophenylborane (35.8 μL, 0.275 mmol) was added and stirred at room temperature under argon for 1 h. The mixture was concentrated under reduced pressure and CH_2Cl_2 (2 mL) was added. The solution was cooled to −78 °C and trifluoromethanesulfonic acid (22 μL, 0.247 mmol) in CH_2Cl_2 (0.1 mL) was

added dropwise. The solution was stirred for 15 min and then a mixture of ketene acetal (151 mg, 0.66 mmol), aldehyde (0.55 mmol) and isopropanol (50.5 μL, 0.66 mmol) in CH_2Cl_2 (0.5 mL) was added via syringe pump over 10 min. The mixture was stirred at −78 °C for 1 h and quenched with 2 M $NaHCO_3$ solution (10 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography to afford the corresponding γ-hydroxy-α,β-unsaturated ester. The enantiomeric excess as well as the absolute configuration was determined using the Mosher method.

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