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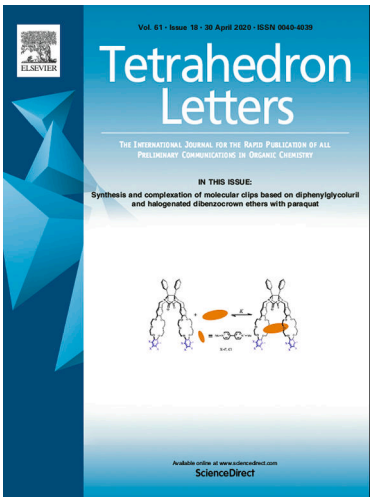

Stereoselective cyclopropanations of amino-acid derived enones

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Stereoselective cyclopropanations of amino-acid derived enones

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Abstract
Stereoselective cyclopropanation of a series of amino acid-derived enones to afford cyclopropyl keto-esters is reported, using a Michael-induced ring closure. The use of quinine and quinidine ether catalysts in the cyclopropanation step afforded the cyclopropyl keto-esters with high stereoselectivity. Results follow a consistent pattern, with the pseudoenantiomeric catalysts leading to opposite stereoselectivity, allowing for synthesis of either the *syn* or *anti* diastereomers.

Keywords: stereoselective cyclopropanation, quinine catalyst, quinidine catalyst, cyclopropyl peptidomimetic

Introduction

Several years ago we reported a novel and efficient synthesis of cyclopropyl peptidomimetics, available in four steps from protected amino acids.[1] Hydroxyethylene peptidomimetics have found great utility as enzyme inhibitors, with examples including the HIV protease inhibitors, HCV NS3 protease inhibitors, and renin inhibitors.[2-5] Adding a cyclopropyl ring to the backbone increases rigidity and has also afforded bioactive compounds.[6,7] The key step in our approach is a Michael-induced ring closure (MIRC) involving addition of the stabilized sulfur ylide EDSA to enones **1a-f** (Figure 1). While this step gave good yields, it lacked stereoselectivity, typically affording a 1:1 mixture of *syn* and *anti* diastereomers. As expected, the cyclopropyl ring is always *trans*, but in all cases, the alkyl group of the amino acid, which is remote from the reacting β-carbon of the enone, has no effect on the stereochemistry of cyclopropanation.

There are a number of reports on the utility of chiral catalysts for cyclopropanations involving MIRC, including Aggarwal's camphor catalysts, Ley's proline catalysts, and Gaunt's use of cinchona catalysts.[8-10] Aggarwal used camphor-derived sulfur ylides, available in four steps from camphor sulfonyl chloride, which afforded high enantioselectivity in cyclopropanations of enones and α, β-unsaturated esters. Ley utilized a commercially available proline-derived tetrazole catalyst in nitro-cyclopropanations of enones, resulting in high stereoselectivity. In particular, Gaunt reported high stereoselectivity using quinine ethers and addition of α-bromo acetates to α, β-unsaturated ketones and esters. Those cyclopropanations proceed *via* formation of transient asymmetric ammonium ylides generated from the chiral amine and the α-bromo acetates.

Results and Discussion

Several of the reported catalysts were investigated in attempts to improve stereoselectivity in our cyclopropanations. The use of ethyl bromoacetate with the cinchona quinine methyl ether catalyst afforded complete stereoselectivity toward the *syn* isomer, but only in cases where the R group is α-branched. The pseudo-enantiomeric quinidine methyl ether afforded no selectivity in any case. However, when using quinine methyl ether with non-α-branched examples such as the leucine and phenylalanine derivatives, no stereoselectivity was observed. Changing the methyl ether for the bulkier quinine benzyl ether catalyst consistently afforded high selectivity for the *syn* isomer in all cases. Conversely, the quinidine benzyl ether afforded high selectivity for the *anti* isomer. These results are summarized in Table 1.

The enones derived from the α-branched amino acids valine, isoleucine and *tert*-leucine (**1a-c**) all afforded very high selectivity. For example, in the original report, the valine enone **1a** afforded a 40:60 ratio of *syn/anti* cyclopropyl ketone with EDSA and no catalyst. However, only the *syn*-isomer is observed when the quinine benzyl ether is present, while reaction with the quinidine benzyl ethyl is highly selective for the *anti* isomer. The results are not as dramatic for non-α-branched amino acid substrates, but there is still an improvement in stereoselectivity in all cases, except for the alanine enone **1f**. For example, the leucine enone **1d** previously afforded a 52:48 ratio of *syn/anti* product **2d** without a catalyst.[1a] With the quinine benzyl ether catalyst, the result is 82:18 *syn/anti* product, and the ratio is reversed (*syn/anti* = 15:85*)* with the quinidine benzyl ether catalyst.

The origin of the stereoselectivity is proposed to be a result of approach of the enone to the presumed ylide intermediate from the convex side of the preferred *anti*-closed conformation of the cinchona alkaloids, as seen in Figure 2. The explanation assumes a Felkin-Anh conformation of the α-substituted enone, where the electronegative C-N bond is perpendicular to the carbonyl. Approach of the enone π system from the less hindered side of the alkaloid, opposite the benzyl ether, results in addition to the *si* face using the quinine ether to give the 1S, 2S (*syn*) product and to the *re* face with the quinidine ether to give the 1R, 2R (*anti*) product.[11,12]

In Gaunt's original examples, enantioselectivity is seen with preferred addition to the *si* face of acrylate esters to give primarily S, S cyclopropanes.[13] Likewise, the same preference is observed here, and with reversal for the quinidine ether. This is logical, given approach opposite the benzyl ether, the size of which has an effect on results, with better selectivity for benzyl than for the methyl ether. What is not clear is the role of the distant R group. Selectivity is better for the bulkier α-branched cases, although the model doesn't explain its effect on the outcome. In fact, approach opposite the R groups would lead to *anti*-selectivity with both catalysts. In support of the model, as predicted, the D-valine derived enone afforded primarily the *anti* (1S, 2S) cyclopropane with quinine benzyl ether, and the *syn* (1R, 2R) derivative with quinidine benzyl ether.[14]

Conclusions

There are numerous examples of stereoselective cyclopropanation reactions.[15] However, outside of Gaunt's original report, there are only a few examples of the use of cinchona catalysts in cyclopropanations using MIRC.[16] The examples presented here are further illustrations of the utility of cinchona catalysts for diastereoselective cyclopropanations to afford useful synthetic intermediates. With access to either the *syn* or *anti* diastereomers, the utility of these peptidomimetics for elaboration to potentially bioactive materials is greatly enhanced.

Acknowledgements

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Appendix A.

Supporting information.

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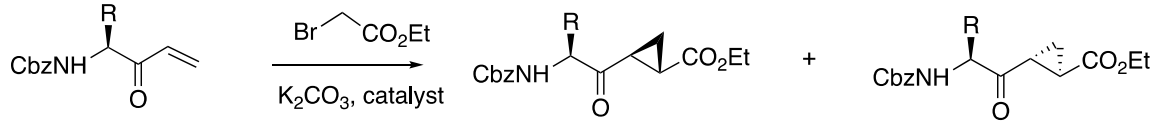
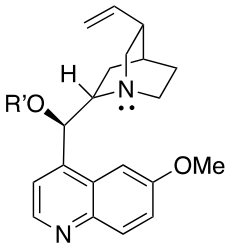
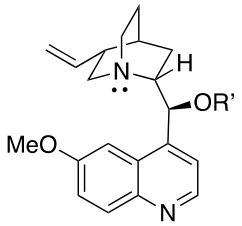
Table 1. Cyclopropanation results with quinine and quinidine ether catalysts.[a]



1a-f **2a-f *syn*** **2a-f *anti***



quinine catalyst (R' = Me or Bn)



quinidine catalyst (R' = Me or Bn)

Entry	R (amino acid)	catalyst	dr (*syn:anti*)	yield (%)
1	**2a** isopropyl (L-val)	quinine OMe	100:0	78
2	**2a** isopropyl (L-val)	quinine OBn	100:0	88
3	**2a** isopropyl (L-val)	quinidine OBn	10:90	65
4	**2a** (4R) isopropyl (D-val)	quinine OBn	0:100	50
5	**2a** (4R) isopropyl (D-val)	quinidine OBn	100:0	56
6	**2b** *sec*-butyl (L-ile)	quinine OMe	100:0	51
7	**2b** *sec*-butyl (L-ile)	quinine OBn	82:8	78
8	**2b** *sec*-butyl (L-ile)	quinidine OBn	7:93	70
9	**2c** N-Boc: *tert*-butyl (L-tle)	quinine OMe	100:0	34
10	**2c** N-Boc: *tert*-butyl (L-tle)	quinine OBn	91:9	59
11	**2c** N-Boc:*tert*-butyl (L-tle)	quinidine OBn	4:96	42
12	**2d** isobutyl (L-leu)	quinine OMe	50:50	86
13	**2d** isobutyl (L-leu)	quinine OBn	82:18	75
14	**2d** isobutyl (L-leu)	quinidine OBn	15:85	67
15	**2e** benzyl (L-phe)	quinine OMe	50:50	74
16	**2e** benzyl (L-phe)	quinine OBn	76:24	76
17	**2e** benzyl (L-phe)	quinidine OBn	31:69	79
18	**2f** methyl (L-ala)	quinine OBn	52:48	22
19	**2f** methyl (L-ala)	quinidine OBn	25:76	82

[a] Ratios determined either by HPLC or integration of the cyclopropyl C1-H signal in the ^{1}H-NMR. All cyclopropanations were carried out in refluxing acetonitrile for 22 hours, using K_2CO_3 as base (12 equiv.), ethyl bromoacetate (3 equiv. added in 3 portions), and 0.3 equiv. of catalyst.

Figure 1. Cyclopropanation of amino-acid derived enones.

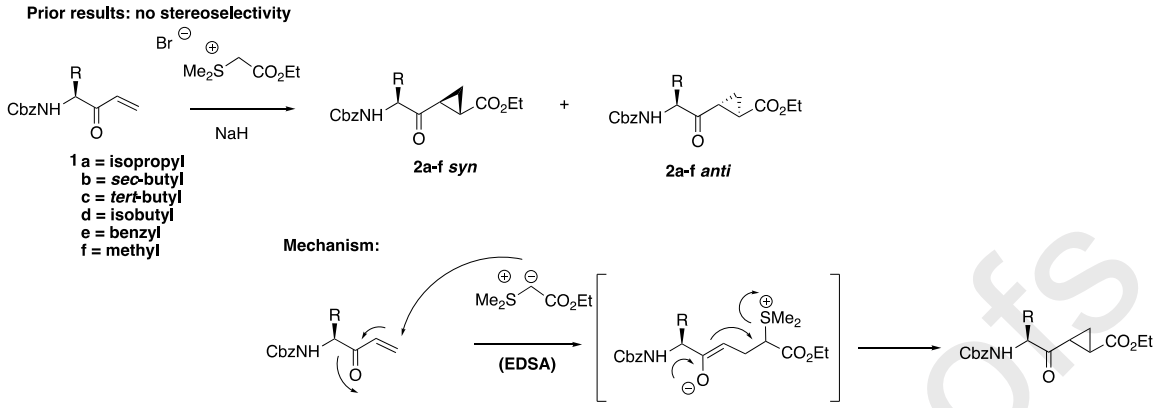
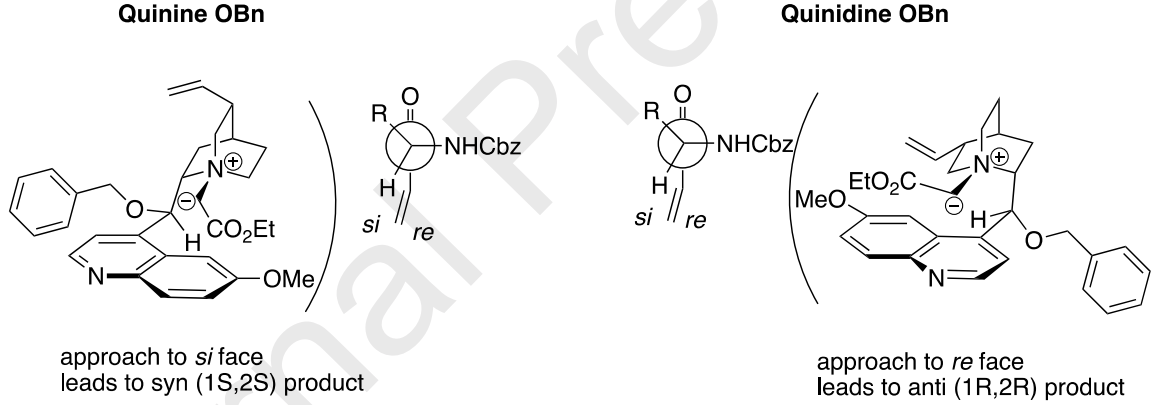


Figure 2. Proposed model for the observed stereoselectivity in cyclopropanation.[a]



approach to *si* face
leads to syn (1S,2S) product

approach to *re* face
leads to anti (1R,2R) product

[a] Ylide intermediates of the quinine and quinidine ethers are drawn in the preferred anti-closed configuration where: anti refers to the orientation of the benzyl ether relative to the quinuclidine C-N bond and closed refers to the orientation of the quinuclidine ring over the bicyclic aryl system.[11,12]

Declaration of interests

x The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights:

- stereoselective synthesis of cyclopropyl peptidomimetics
- quinine and quinidine ether catalyze diastereoselective cyclopropanation with opposite selectivity
- efficient three step approach to core structures suitable for elaboration to bioactive peptidomimetics