Asymmetric Synthesis of Di- and Trisubstituted Cyclopropanes through an Intramolecular Ring Closure

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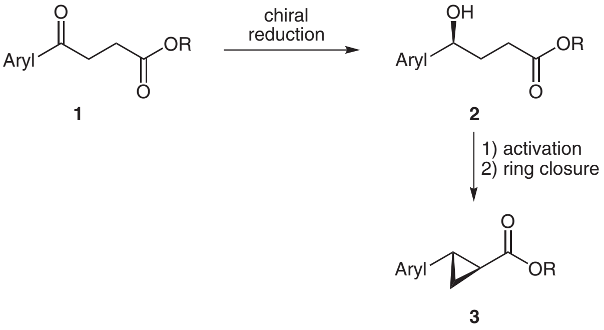
Abstract: An asymmetric synthesis of di- and trisubstituted cyclopropanes proceeding through an intramolecular ring closure of activated chiral benzyl alcohols has been developed. The chiral alcohol intermediates are obtained from asymmetric reduction of readily available 1,4-keto esters and undergo a one-pot activation and ring closure to provide the ester-functionalized cyclopropanes in high enantio- and diastereomeric purity. This methodology avoids the use of hazardous diazo and alkyl zinc reagents commonly employed in cyclopropanation reactions.

Key words: cyclopropane, ring closure, asymmetric synthesis, asymmetric reduction, stereoselectivity

Chiral cyclopropanes are prevalent in a wide array of natural products and pharmaceuticals.[1] A number of methodologies have been developed to rigorously control the enantio- and diastereoselective formation of the cyclopropane ring from simple starting materials.[2,3] Some of the best developed enantioselective cyclopropanation methods are limited for the formation of ester-substituted cyclopropanes. For example, cyclopropanation of alkenes using diazoesters[4,5] suffer from low diastereoselectivities, with the exception of recently developed Co-porphyrin catalysts,[6,7] whereas cyclopropanation of allylic alcohols with Simmons-Smith reagents[8] require subsequent oxidation of the primary alcohol to the ester. The formation of ester-substituted cyclopropanes by 1,4-additions using chiral sulfur ylides do provide high stereoselectivities when stoichiometric chiral reagents are used[9,10] while catalytic versions of this reaction have a limited scope.[11,12]

An alternative approach to the asymmetric cyclopropanation of alkenes is to form the ester-substituted cyclopropane ring through an intramolecular ring closure.[2] Until recent work by Taylor and coworkers on displacement of benzylic mesylates by intramolecular allylation to form alkenyl-substituted cyclopropanes,[13] no extensive study on the electronic and steric factors that influence the diastereo- and enantioselectivity of the ring closure has been reported.[14] Feringa and coworkers have recently demonstrated the synthesis of disubstituted cyclopropanes through a conjugate addition enolate-trapping ring closure, however, this method suffers from low enantioselectivity for the formation of aryl-substituted cyclopropanes.[15]

We desired a direct formation of the synthetically useful aryl-ester cyclopropanes and envisioned that 4-aryl-4-oxy butanonic esters **1**, which are readily available by Friedel–Crafts acylation of arenes with succinic anhydride,[16] could be asymmetrically reduced to the alcohol, **2**.[17] Activation of the alcohol and ring closure through the ester enolate would afford the chiral cyclopropane **3** (Scheme 1). This approach would be amenable to large-scale reactions by avoiding the use of hazardous diazo or alkylzinc reagents commonly employed in cyclopropanantion reactions. Several key questions would need to be answered during the method development, firstly the level of the enantiospecificity observed during the ring closure where S_N1 and S_N2 pathways may be competitive in the displacement of the benzylic leaving group. Additionally, the factors that influence the diastereoselectivity of the ring closure to afford *trans*- or *cis*-substituted products would need to be understood.



Scheme 1

To investigate the feasibility of the stereoselective cyclopropane formation through an intramolecular ring closure, methyl (**1a**), isopropyl (**1b**), and *tert*-butyl (**1c**) esters were prepared from the commercially available 4-(4′-bromophenyl)-4-oxobutanoic acid. The reduction of the aromatic ketone catalyzed by 10 mol% of (*R*)-Me-CBS afforded the chiral alcohols in high yields and enantiopurities (Table 1).[17] The lower yield in the reduction of **1a** was due to formation of the γ-lactone **4**. Only a minor amount of **4** was observed during reduction of **1b** and none with **1c**.

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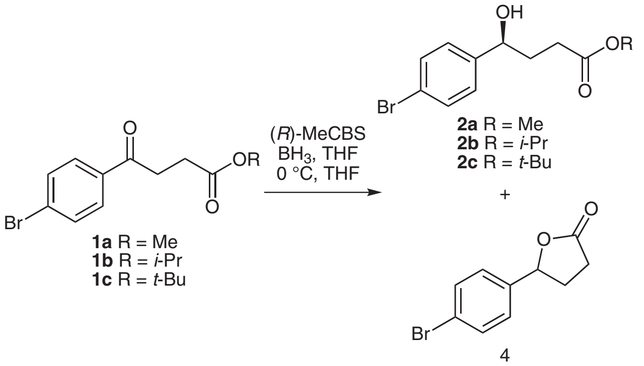
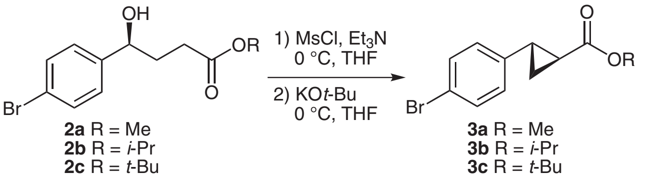
Table 1 (*R*)-MeCBS-Catalyzed Asymmetric Reduction of **1**



Product	Yield (%)	er
2a	75	97:3
2b	84	96:4
2c	88	98:2

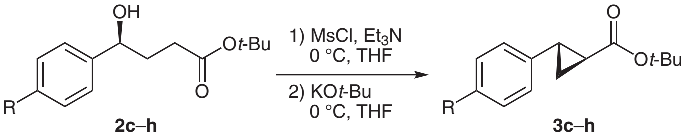
Table 2 Effect of Ester Group on Ring Closure

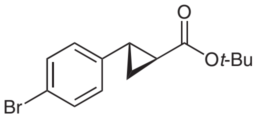
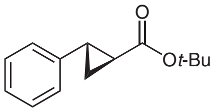
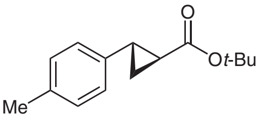
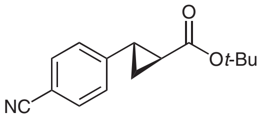
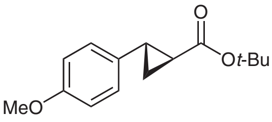
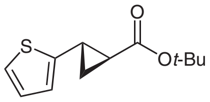


Product	Yield (%)	er of **2**	er of **3**	dr (*trans*/*cis*)
3a	68	96:4	96:4	91:9
3b	89	97:3	96:4	90:10
3c	93	98:2	98:2	93:7

With the chiral alcohols in hand, the influence of the ester group was evaluated in the ring-closing reaction. Activation of the alcohols **2a**–**c** with MsCl/Et$_3$N followed by intramolecular ring closure by addition of KO*t*-Bu readily afforded the cyclopropane products **3a**–**c** in high diastereoselectivities (Table 2). In all cases, the *trans*-diastereomer

Table 3 Substrate Scope of Disubstituted Cyclopropanes



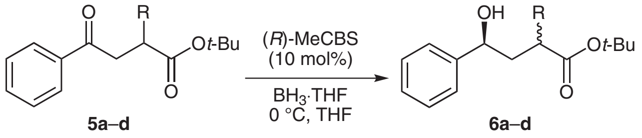
Product	Yield of **3** (%)	er of **2**	er of **3**	dr of **3** (*trans*/*cis*)
 **3c**	93	98:2	98:2	93:7
 **3d**	83	98:2	98:2	94:6
 **3e**	89	97:3	96:4	93:7
 **3f**	90	87:13	86:14	90:10
 **3g**	76	96:4	86:14	92:8
 **3h**	84	92:8	66:34	95:5

was favored, with slight increase in diastereoselectivity for the larger *tert*-butyl ester of **3c**. In addition, the enantiospecificity for this reaction was high with <0.5% isomerization observed. The *tert*-butyl ester was chosen for additional studies as it provided the highest yield, enantio-, and diastereoselectivities.

A number of electronically distinct aryl groups were evaluated in the ring-closing reaction (Table 3). High yields and diastereoselectivities were observed for a range of aryl groups. High enantioselectivities were observed for substrates containing electronically deficient or neutral arenes, however, lower enantioselectivities were observed for substrates containing electron-rich arenes or hetereocycles. These results are consistent with competing S_N2 and S_N1 reaction pathways where the benzylic cation intermediate of the S_N1 pathway is more stabilized in electron-rich arenes resulting in higher amounts of isomerization.

With the high enantiospecificities and diastereoselectivities observed in the ring closure to form disubstituted cyclopropanes, we desired to extend this methodology to the formation of chiral trisubstituted cyclopropanes. The stereoselective preparation of trisubstituted cyclopropanes containing an ester functional group is highly dependent on the nature of the substituent, with acceptable selectivity and scope when donor–acceptor carbenes are used,[5] but a limited scope exists for the incorporation of alkyl substituents.[18] Asymmetric reduction of 4-phenyl-4-oxobutanoic esters **5a–d** containing methyl, benzyl, isopropyl, and phenyl substituents in the 2-position afforded chiral alcohols **6a–d** as a mixture of diastereomers (Table 4).

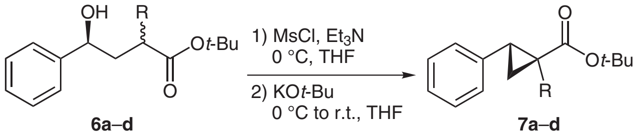
Table 4 (*R*)-MeCBS Catalytic Asymmetric Reduction of **5**



Product	Yield (%)	dr	er (major)	er (minor)	er (combined)
6a R = Me	89	52:48	97:3	93:7	95:5
6b R = Bn	89	51:49	97:3	92:8	94:6
6c R = *i*-Pr	83	51:49	97:3	89:11	93:7
6d R = Ph	95	51:49	95:5	90:10	93:7

The mixture of diastereomers **6a–d** were subjected to the MsCl activation and the KO*t*-Bu ring-closure reactions to afford the desired cyclopropane products **7a–d** in moderate to high yields with high enantiospecificty (Table 5). For compounds **7a–c**, substituted with methyl, benzyl, or isopropyl groups, high diastereoselectivities are also observed, comparable or better to that of the disubstituted product **3d**. For compound **7d**, where the substituent is phenyl, only moderate diastereoselectivity is observed. To test the influence of the chiral center in the 2-position on the ring closure, the diastereomers of **6c** were separated and independently subjected to the ring-closing reaction. Both diastereomers of **6c** formed **7c** with high enantiospecificity and diastereoselectivity. The convergence of both diastereomers of **6c** to the single product **7c** is consistent with the formation of an enolate intermediate and demonstrates that the diastereomeric mixtures of the chiral alcohols **6** can be directly used without affecting the diastereoselectivity of the ring-closure reaction.

Table 5 Substrate Scope of Trisubstituted Cyclopropanes



Product	Yield of **7** (%)	er of **6**	er of **7**	dr of **7** (*trans*/*cis*)
7a R = Me	69	95:5	95:5	96:4
7b R = Bn	95	94:6	94:6	97:3
7c R = *i*-Pr[a]	77	97:3	97:3	91:9
7d R = Ph	95	93:7	91:9	65:35

[a] Major diastereomer of **6c**. Minor diastereomer of **6c** (er 89:11) afforded **7c** with er 89:11 and dr 92:8.

In conclusion, we have developed an intramolecular ring-closing reaction to form di- and trisubstituted cyclopropanes in high enantio- and diastereoselecitivies from readily accessible starting materials. This methodology opens access to broad classes of ester-substituted cyclopropanes which have proven difficult to prepare stereoselectively while avoiding hazardous reagents typically employed in cyclopropanation reactions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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