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Competitive Cationic Pathways and the Asymmetric Synthesis of Aryl-Substituted Cyclopropanes

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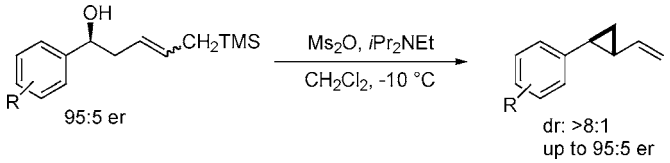
ABSTRACT

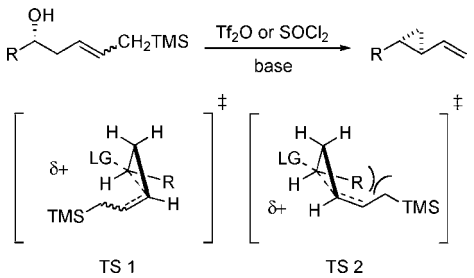


1,2-Disubstituted cyclopropanes were synthesized in a nonracemic fashion via activation of the corresponding homoallylic alcohols in excellent yields. A series of substituted phenyl rings showed higher enantiospecificity for the cyclization as the electron-withdrawing ability of the group increased. The results offer strong support for the existence of competing cation mechanisms.

New methods for the generation of cyclopropane motifs are ever present in the literature due to interesting structure and reactivity and their frequent appearance in biologically active compounds.[1] One particular class of reactions, Michael-initiated ring closures (MIRCs),[2] is a highly efficient and stereoselective route to cyclopropanes. MIRC substrates include phosphorus, sulfur, and tellurium ylides which generate cyclopropanes through an anionic process. Conversely, the realm of cationic cyclizations is less widely explored.[3] Several years ago, Suzuki and co-workers[4] demonstrated that homoallylic triflates can be trapped to access diastereomerically pure trans-1,2-disubstituted cyclopropanes. Contemporaneously, we investigated the use of allylsilane homoallylic alcohols as a source of vinylcyclopropanes through an intermediate β-silylcyclopropylcarbinyl cation.

We have demonstrated the ability of this method to produce diastereomerically and enantiomerically pure 1,2-disubstituted and 1,2,3-trisubstituted cyclopropanes from readily available homoallylic alcohols in excellent yields. The high diastereoselectivity of this process is rationalized by a preference for transition state 1 (TS 1) (Scheme 1).[5]

Scheme 1. Cationic Cyclopropanation



Moreover, our previous work in this area, focusing on alkyl and heteroatom-substituted alkyl substrates (R = alkyl),

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(1) de Meijere, A.; Editor for special thematic issue on Cyclopropanes and Related Rings. *Chem. Rev.* **2003**, *103*, 931.

(2) For a review of stereoselective cyclopropanation reactions, see: Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977 and references therein.

(3) For a recent review of cation approaches to cyclopropanes, see: Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623.

(4) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739.

(5) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964.

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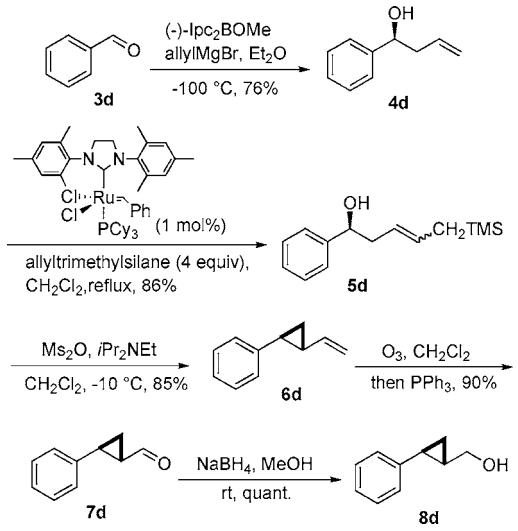
found that the reaction proceeds with complete stereospecificity with inversion. In this manuscript, we report an extension of our methodology to the synthesis of aryl-substituted cyclopropanes (R = aryl). In contrast to our previous observation, the intermediate benzyl sulfonates may be prone to ionization and, thus, lead to products with reduced enantiomeric purity.

The general synthetic route for the formation of aryl-substituted cyclopropanes is illustrated by the phenyl-substituted case in Scheme 2. Benzaldehyde (**3d**) was first

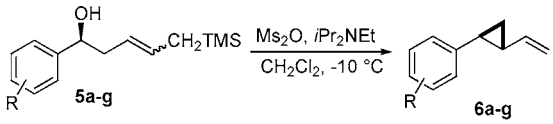
Scheme 2. General Sequence to Cyclopropylmethyl Alcohols



subjected to Brown's asymmetric allylation conditions,[6] to furnish homoallylic alcohol **4d** with 95:5 er. Olefin cross metathesis[5,7] with allyltrimethylsilane yielded allylsilane homoallylic alcohol **5d** in 66:34 selectivity for the *E* geometry. We have previously demonstrated that olefin geometry has little effect on the cyclization, and thus the mixture of olefin isomers was used directly.

The resultant alcohol **5d** was subjected to various conditions for the key cyclization step. After optimization, vinyl cyclopropane **6d** was isolated in 85% yield as a 9:1 mixture of trans/cis isomers. The enantiomeric ratio of **6d** was determined by a two-step conversion to the cyclopropylmethyl alcohol **8d**. ^{19}F NMR analysis of the corresponding Mosher esters of **8d** and comparison to the racemic series were performed as well.[8] With regards to the key cyclization, our standard conditions of triflic anhydride and 2,6-lutidine provided the activated sulfonate intermediates necessary for cyclization. However, much to our surprise, vinyl cyclopropanes were isolated in reduced yield. Under these conditions, a significant amount of silyl-protected starting material was

Table 1. Aryl-Substituted Cyclopropane Formation[a]



entry	cyclopropanes	yield	*trans:cis*[c]	er[d]
1	**6a**	88%	8:1	84:16
2	BnO **6b**	95%	9:1	90:10
3	AcO **6c**	96%	9:1	90:10
4	**6d**	85%	9:1	93:7
5[b]	Br **6e**	94%	9:1	95:5
6	MeO_2C **6f**	95%	9.5:1	95:5
7	F_3C **6g**	85%	9:1	95:5

[a] Starting er's for alcohols **5a**−**g** were 95:5 for enantiomers shown. [b]Starting er for bromo-substituted aryl alcohol **5e** was 98:2. [c]Ratios determined by NMR integration of the corresponding aldehyde proton in intermediate **7**. The cis product was found to have been formed with a similar er. [d]Product er determinations were made on their corresponding cyclopropylmethyl alcohols.

isolated which effectively shut down triflate formation and prevented cyclization. Thus, it appears that cyclization is significantly faster than triflation of **5d**. However, mesyl anhydride was an efficient alternative and vinylcyclopropane **6d** was isolated in high yields with no observable silylation byproducts.

The series of aryl-substituted aldehydes was subjected to the identical reaction sequence to gain insight on the stereochemical outcome of the reaction. The homoallylic alcohols **4a**−**d** and **4f**,**g** were synthesized using Brown's asymmetric allylation conditions,[6] and homoallylic alcohol **4e** was prepared via Soderquist's method with higher enantioselectivity.[9] Homoallylic alcohols **4b** and **4c** were synthesized from **4f** (see Supporting Information). Alcohols **4a**−**g** were further elaborated via cross metathesis with allyltrimethylsilane yielding allylsilane homoallylic alcohols **5a**−**g** (75−90%) in good yield and moderate *E*/*Z* selectivity.

Regardless of substitution, the cyclization proved to be extremely efficient. Moreover, the study of aryl-substituted substrates revealed two unique aspects of reactivity not previously observed in the aliphatic system.

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(7) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
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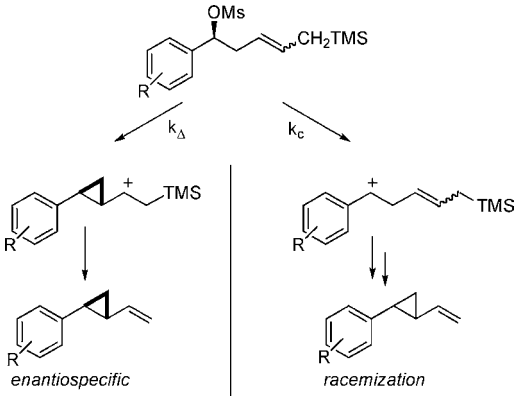
Previous work with aliphatic-substituted systems, ours as well as Suzuki's, reported exclusive formation of *trans*-cyclopropanes. In contrast, aryl-substituted cyclization substrates provided a consistent ratio of *trans*-/*cis*-cyclopropane products (9:1). This observation suggests that competing transition states (TS1 and TS2, Scheme 1) are closer in energy for aryl-substituted substrates. A number of qualitative differences could account for the greater stability of TS2 in aryl-substituted substrates including greater dipole minimization or simple steric differences.

The enantiomeric purity of the cyclopropane products, reported in Table 1, illustrated a clear trend between aryl group and reaction stereospecificity. Although aryl groups substituted with electron-withdrawing substituents cyclized with complete stereospecificity (Table 1, entries 6 and 7), an appreciable loss in enantiomeric purity was observed in electron-rich systems (Table 1, entries 1−3).

Two well-described mechanistic pathways for cationic processes are relevant here: neighboring group displacement (NGD, k_Δ) and ionization (k_c) (Scheme 3). The NGD pathway

Scheme 3. Competitive Cationic Pathways



involves direct displacement of the intermediate sulfonate by the allylsilane through a stereospecific inversion. Alternatively, ionization provides an achiral benzylic cation and the formation of a racemic product. Thus, relative enantiomeric purity between the starting material **5a**−**g** and the cyclopropane products **6a**−**g** provides an estimate of the relative rates of each mechanistic pathway.[10] Moreover, there was a good correlation between the enantiospecificity of the cyclization and σ^+ values[11] for the aryl substituent (Table 2).

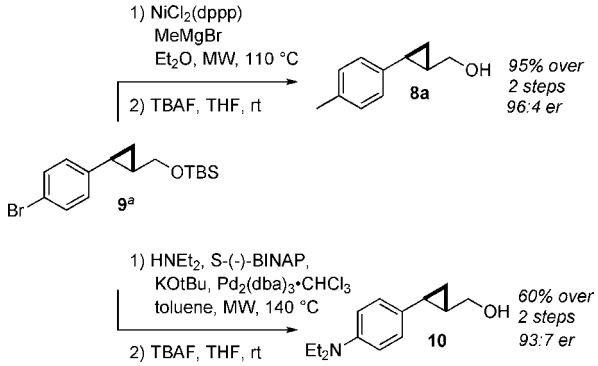
Table 2. Competitive Cationic Pathways

R group	Δee	k_Δ/k_c	σ_p^+
CH_3	−32	76:24	−0.31
CH_2OBn	−10	89:11	–
CH_2OAc	−10	89:11	–
H	−5	94:6	0.00
Br	−6	93:7	0.23
CO_2Me	0	100:0	0.49
CF_3[a]	0	100:0	0.46

[a] σ_m value used for the *m*-CF_3 substituent.

As illustrated in Tables 1 and 2, electron-rich aromatic systems showed a loss of enantioselectivity upon cyclization. As a synthetic solution to this problem, we envisioned *p*-bromo-aryl-substituted cyclopropanes **9** (Scheme 4) as a

Scheme 4. Aryl Bromide Cross Coupling



[a] Starting er for **9** was 95:5 for enantiomer shown.

common precursor to enantiomerically pure cyclopropanes with electron-rich aryl substituents. Couplings of aryl bromides with Grignard reagents or dialkylamines mediated by nickel or palladium are frequent in the literature, such as those described by Kumada[12] and Hartwig.[13]

TBS ether **9** was cleanly generated from alcohol **8e**.[14] Coupling with methylmagnesium bromide in the presence of Ni(II) salts, followed by deprotection of the TBS group, afforded alcohol **8a** in 95% yield. The enantiomeric ratio of the product was consistent with the starting cyclopropane **9**. Thus, substitution of aryl bromide **9** circumvents the loss of enantioselectivity observed in the cyclization of **5a**.

A logical extension of this process would allow the preparation of electron-rich aryl cyclopropanes not likely accessible through cationic cyclization processes. For example, diethylamino-substituted aryl cyclopropane **10** was procured through a similar two-step sequence from **9**. Pd-(0)-catalyzed aryl amination in the presence of *S*-(−)-BINAP cleanly generated the desired coupling product. After TBAF deprotection and Mosher's ester analysis, the enantiomeric ratio of **10** (93:7) was similar to the starting material **9** (95:5). On the basis of σ^+ values for an amino substituent (−1.3), one would expect essentially complete loss of stereoselectivity and/or an inefficient cyclization.

In summary, we have expanded on our first-generation methodology for the formation of cyclopropanes through

(10) Detailed kinetic analysis also supports this correlation. Creary, X.; O'Donnell, B. D.; Vervaeke, M. *J. Org. Chem.*, **2007**, *9*, in press.
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(14) See Supporting Information for the preparation of **8e**.

cationic processes. The method is concise and provides access to vinyl cyclopropanes from readily available, non-racemic homoallylic alcohols. The stereoselective generation of aryl-substituted cyclopropanes with good diastereo- and enantioselectivity was demonstrated for most substrates. Marked loss of enantioselectivity was observed in the cyclization of electron-rich aryl-substituted precursors. However, the same substrates were generated with enhanced enantioselectivity through the use of transition-metal coupling methods. This chemistry is amenable to the synthesis of complex cyclopropane targets including natural products, natural product analogues, and medicinal agents. Results to this end will be reported separately.

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Supporting Information Available: Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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