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A Stereoselective Arylative-Cyclopropanation Process

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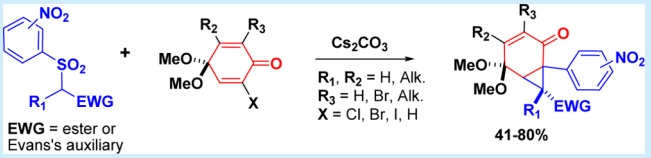
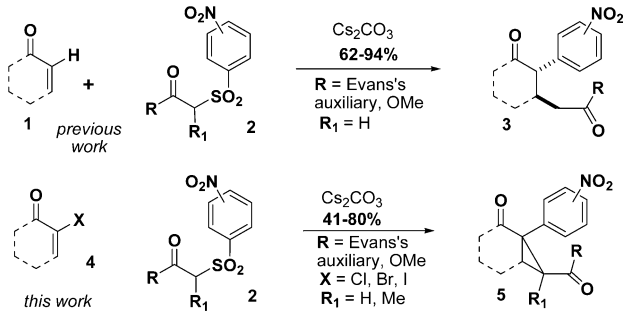
Supporting Information

ABSTRACT: A new stereoselective arylative cyclopropanation process involving treatment of halogenated dienone systems in the presence of a Michael donor containing a nitro-aryl-sulfone has been developed. This transformation enables production of an arylated cyclopropane under mild conditions and occurs via a Michael−Smiles ring closure cascade process, reflecting the concepts of green chemistry and atom economy.



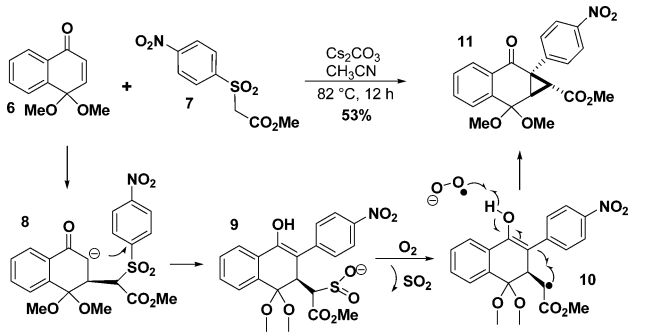
Cyclopropanation is an important process in organic synthesis, yielding three-membered ring structures that are useful as precursors for the elaboration of advanced intermediates. Cyclopropanes are formed in several processes such as the Simmons−Smith[1] method or its variants mediated by diazo compounds or iodonium ylides,[2] Corey−Chaykovsky[3] or Kulinkovich transformations,[4] or intramolecular alkylation.[5] There is increasing sentiment that transformations should be atom economical[6] and should respect the concept of "green chemistry." To this end, we developed a methodology enabling the formation of functionalized scaffolds **3** mediated by a Michael−Smiles tandem process.[7] In this paper we describe a new application of this approach on a halogenated enone to develop an arylative cyclopropanation strategy, Scheme 1.

Scheme 1. Michael−Smiles Tandem Process Avenues



One advantage of the Smiles rearrangement[8] is its capacity for rapid reconfiguration of a structure into a more elaborated one under slightly basic and mild thermal conditions. A judicious combination of this process with a tandem Michael addition leads to α−β-disubstituted cyclohexanones **3**.[7] Indeed, a malonate derivative containing a nitro-aryl sulfonyl moiety[9] **2** may be used as an activating group, enabling an initial Michael addition on enone moiety **1** to produce an enolate and triggering a Smiles rearrangement yielding **3** (Scheme 1) in which SO_2 serves as a leaving group and is released as the sole byproduct. During our efforts to extend the scope of this process, we observed that the presence of enone **6** resulted in formation of an interesting cyclopropanated byproduct **11** with very good diastereoselectivity instead of **3**. The yield of this transformation product was increased in the presence of oxygen and decreased in the presence of TEMPO, suggesting a free radical process[10] via oxygen-mediated electron transfer was responsible. A potential mechanism is described in Scheme 2.

Scheme 2. Radical-Based-Cyclopropanation Mechanism



It should be noted that compound **11** represents a polyfunctionalized core obtained in a diastereoselective and environmentally benign manner in one step from simple starting materials. However, we were unable to extend this method to other substrates and only one other cyclopropanated example **13** was obtained from **12** under similar conditions, Scheme 3.

We therefore investigated alternative methods of generating this cyclopropane scaffold, beginning with introduction of a bromine on the enone moiety **14** to replace the uncertain oxidative cyclopropanation step with an intramolecular alkylation. We were pleased to observe that cyclopropane **11** was produced in 80% yield by this strategy, Scheme 4.

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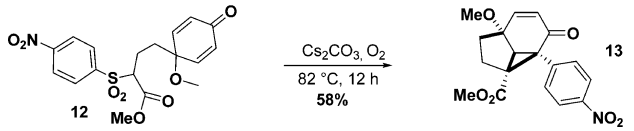
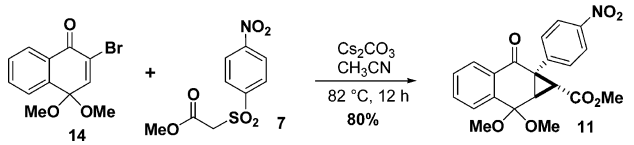
Scheme 3. Intramolecular-Radical-Based Cyclopropanation

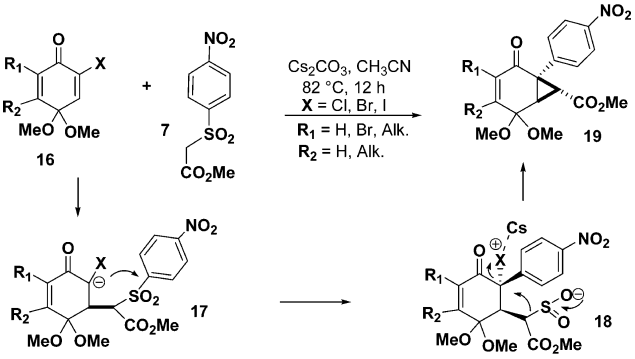


Scheme 4. Halide-Mediated Cyclopropanation Alternative



We assume that the mechanism is similar to the mechanism described in Scheme 2 and the prototypical transformation involves a Michael–Smiles cyclopropanation cascade process. We suppose that the aryl migration occurs with retention of configuration leading to **18** from **17** and enabling an antiperiplanar attack to produce cyclopropane **19**. One interesting aspect is the potential intramolecular nucleophilic substitution that would occur on a tertiary alkyl bromide with inversion of configuration. We suspect that a partial carbocation leading to a potential enolonium ion[11] could be involved due to the presence of a conjugated system; this species could be generated in the presence of a cesium ion acting as a Lewis acid. When radical processes were excluded by performing the reaction in the absence of oxygen or in the presence of TEMPO, the cyclopropane **19** was still obtained in comparable yields, Scheme 5.

Scheme 5. Michael–Smiles Cyclopropanation Mechanism



Encouraged by this result, we investigated different halides as nucleofuges. These attempts have been performed on dienone **16**, which represents a good Michael acceptor obtained by direct oxidation of halogenated phenols **15** in the presence of methanol and a hypervalent iodine reagent.[12] Iodine and bromine provided slightly improved results, Scheme 6. Unfortunately, this process was not efficient with a simple halogenated enone.

The transformation was subsequently performed on several bromo-dienones **21**, derivatives of **16**. Bromine was selected as the halogen atom because it was easily introduced on the phenol precursor. The *ortho*- and *para*-nosyl derivatives **20** have both been tested. An interesting aspect of this process is the good stereoselectivity observed, with only one diastereomer observed in NMR spectra.[13] The corresponding systems **22** that were obtained are described in Table 1.

Scheme 6. Rapid Elaboration of Functionalized Tricycles

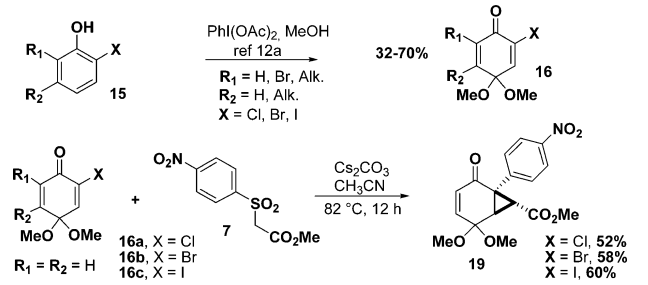
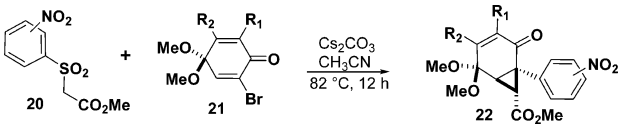


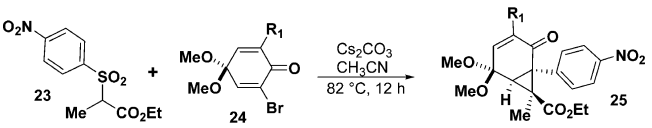
Table 1. Michael–Smiles Cyclopropanation Process



entry	NO_2	R_1	R_2	yield (%)
a	ortho	Me	Me	64
b	para	Me	Me	68
c	ortho	Et	H	61
d	para	Me	H	70
e	ortho	*t*-Bu	H	74
f	para	*t*-Bu	H	73
g	ortho	Me	H	63
h	para	allyl	H	70
i	para	Br	H	50
j	para	Et	H	71

In order to produce a highly substituted cyclopropane subunit, the process was extended to compound **23**, a methyl derivative of **20**. We were pleased to observe that, once again, only one diastereomer was observed by NMR[13] in the substituted cyclopropane **25**.[14] The diastereoselectivity was further verified using NMR NOE. Some examples are described in Table 2.

Table 2. Formation of Highly Substituted Cyclopropanes



entry	R_1	yield (%)
a	*t*-Bu	67
b	allyl	61
c	Et	60
d	Me	49

Interestingly, in the presence of a methyl-substituted malonate derivative **23**, the ester functionality was *anti* to the nitro-aryl segment. The difference of diastereoselectivity observed between the formation of cyclopropane **22** and its more substituted analogous **25** could be explained by their enolate precursors **26**. Indeed, if R_1 is a hydrogen, we supposed that conformer **26a** was favored and led to compound **22**. However, in the presence of a methyl group (R_1 = Me) a potential steric interaction between the aryl and methyl groups would favor conformer **26b** yielding cyclopropane **25**, Scheme 7.

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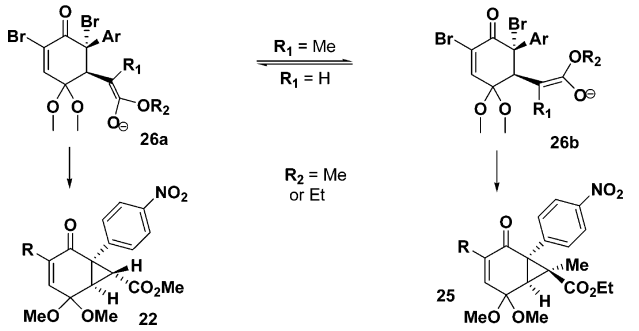
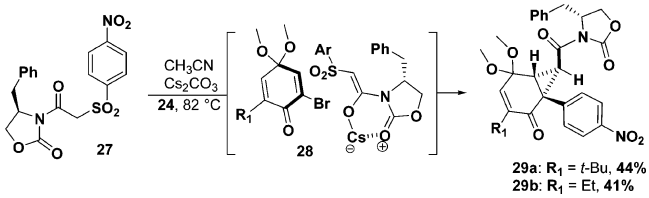
Scheme 7. Diastereoselectivity Issues



An asymmetric variant containing an Evans auxiliary[15] was developed, and the corresponding cyclopropanes **29** were obtained in 41% and 44% yields with an excellent stereoselectivity of 95% based on NMR.[13] A potential approach suggesting an opened transition state to explain the observed stereoselectivity is depicted in Scheme 8.

Scheme 8. Asymmetric Avenue



In summary, we have developed a novel stereoselective arylative cyclopropanation transformation mediated by a Michael−Smiles ring closure cascade process. These methods occur under slightly basic conditions at moderate temperatures with sulfur dioxide as the only byproduct. Very good diastereoselectivity is observed during this multistep transformation even during the formation of highly substituted cyclopropane moieties. We are currently looking for novel applications for these transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00248.

Experimental procedures and spectral data for key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Only one diastereomer was observed by NMR, and the stereoselectivity was verified by nuclear Overhauser effect (NOE). The coupling constants for the cyclopropane hydrogens **22** were close to 6 Hz and in agreement with a *trans* isomer.

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