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Free-Radical Carbocyanation of Cyclopropenes: Stereocontrolled Access to All-Carbon Quaternary Stereocenters in Acyclic Systems

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Supporting Information

ABSTRACT: Free-radical carbocyanation of cyclopropenes offers straightforward access to tetrasubstituted cyclopropanes in satisfying yields with moderate diastereoselectivity. The incorporation of various functional groups on the cyclopropane ring allows a subsequent base-mediated ring-opening reaction leading to functionalized acyclic systems having an all-carbon quaternary stereocenter.

Polysubstituted cyclopropanes are useful intermediates in organic synthesis[1] that have attracted a lot of interest due mainly to their easy ring opening under acidic, basic, or free-radical conditions.[2] Cyclopropanes are readily available in enantiopure form using now well-established organometallic and organocatalyzed processes.[3] Recent progress in the stereocontrolled synthesis of cyclopropanes also includes the functionalization of substituted cyclopropenes.[4] (1) Organometallic and (2) free-radical additions onto the π system of cyclopropenes thus offer a complementary route to polysubstituted cyclopropanes, which may be functionalized further (Figure 1). It is worthy of note that cyclopropenes may also be

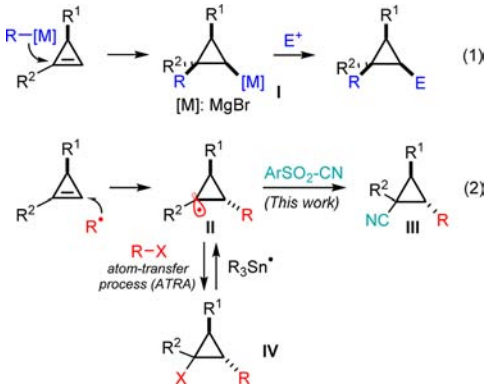

Figure 1. Carbometalation and free-radical additions onto cyclopropenes.

prepared in enantiopure form through rhodium-mediated cyclopropanation of the corresponding alkynes using commercially available diazo esters.[5] Recent work by Marek and coworkers[6] has elegantly shown that *syn*-carbometalation of cyclopropenes (Figure 1, eq 1) leads to the corresponding metalated cyclopropanes **I**, which can be trapped by various electrophiles or undergo selective ring opening. Free-radical atom-transfer processes using cyclopropenes leading to cyclopropanes in moderate to good yields were reported earlier by Saicic,[7a] Zard,[7b] and Nakamura[7c] and more recently by Miyata and Ueda.[8] In contrast, radical addition of two carbon fragments across the cyclopropene π system has, to our knowledge, not been explored to date. This may be attributed to the high reactivity of cyclopropyl radical **II**, which is involved in fast atom-transfer processes (ATRA product **IV**),[9] preventing further reaction of **II** with other radical traps. Steric hindrance in the neighborhood of the radical center may also preclude any approach of reagents to **II**. Finally, the weaker nucleophilicity of the cyclopropyl σ radical compared with those of other alkyl radicals is another factor that may hamper carbofunctionalization of cyclopropenes.[10]

Here we report a new multicomponent carbocyanation addition onto substituted cyclopropenes that gives rise to tetrasubstituted cyclopropyl nitriles **III** bearing a quaternary center in satisfying yields with moderate diastereocontrol. The structure of these cyclopropanes also allows subsequent base-mediated ring opening, offering straightforward and stereodivergent access to acyclic systems having functionalized all-carbon quaternary stereocenters, present in many biomolecules and natural products.

Preliminary experiments were carried out using iodoester **1a** as a radical precursor, cyclopropene **2a**, and commercially available *p*-tosyl cyanide (**3**) as a cyanide source. Initiation of the process was performed using di-*tert*-butoxyhyponitrite (DTBHN) and $(Bu_3Sn)_2$ as a chain carrier.[11] First reaction attempts by mixing the three components, DTBHN, and ditin produced less than 20% yield of the desired nitrile as a mixture of two stereoisomers, **4aa** and **4ab**, in the presence of a large amount of the iodine atom transfer product (not shown). The two diastereomers were easily separated through chromatography, and their structures assigned through ^{1}H NMR analysis. A slightly better yield was obtained by slow addition of a mixture of *p*-TsCN and DTBHN to the medium through a syringe pump (Table 1, entry 1). Considering that the ATRA product (i.e., **IV** with X = I; Figure 1) was likely the intermediate in the reaction process, it was envisioned that the

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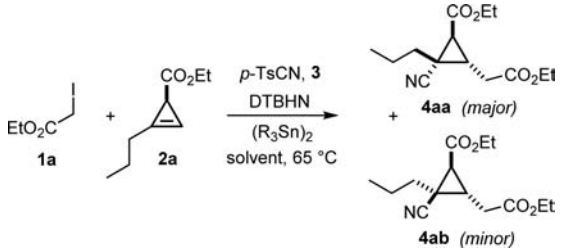
Table 1. Optimization of the Carbocyanation of Cyclopropenes[a]



entry	rate of addition (time)	solvent	yield (%)[b,c]	dr[d]
1	0.5 mL/h (5 h)	benzene	24[e]	n.d.
2	0.5 mL/h (5 h)	benzene	60	72:28
3	0.25 mL/h (10 h)	benzene	16	n.d.
4	1 mL/h (2.5 h)	benzene	64	76:24
5	1 mL/h (2.5 h)	DCE	33	78:22
6	1 mL/h (2.5 h)	CH_3CN	–	–
7[f]	1 mL/h (2.5 h)	benzene	41	77:23

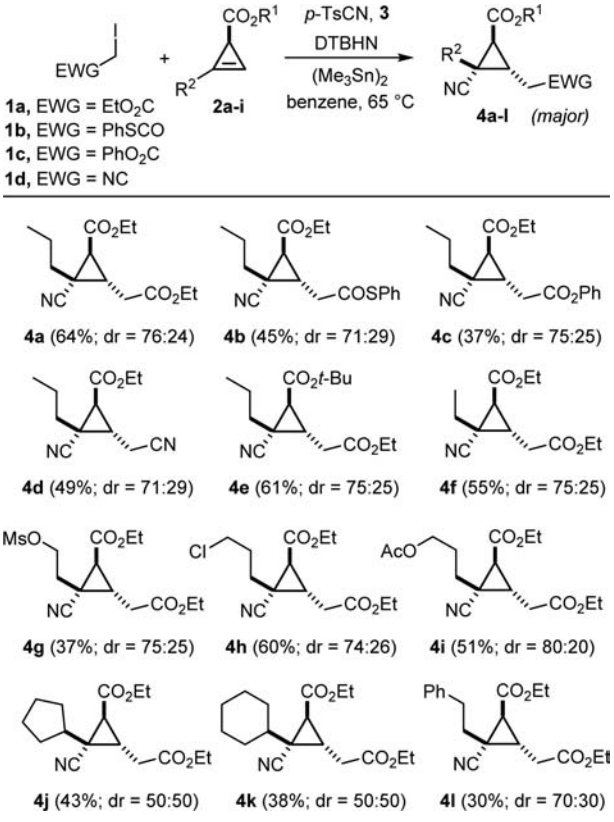
[a]The reactions were carried out by mixing **1a** (1 equiv), **2a** (2 equiv), and $(Me_3Sn)_2$ (unless otherwise indicated) (2 equiv) in the solvent and then adding a mixture of DTBHN (40 mol %) and **3** (2 equiv) at 65 °C through a syringe pump. [b]Isolated yields. [c]Isolated ATRA product (~10−15%). [d]Estimated by ^{1}H NMR analyses of the crude reaction mixtures after a short filtration column. [e]$(Bu_3Sn)_2$ was used. [f]The reaction was performed at 45 °C.

Bu_3Sn radical might be too sterically hindered to abstract the iodine atom and regenerate the cyclopropyl radical **II** for further cyanation. This proved to be the case, as the reaction using instead the smaller Me_3Sn radical led to cyclopropyl nitriles **4aa−ab** in a much improved yield of 60%, albeit with modest diastereocontrol (Table 1, entry 2). Reducing the rate of addition surprisingly had a deleterious effect (Table 1, entry 3). The best yield was observed when DTBHN and *p*-TsCN were added at a rate of 1 mL/h (Table 1, entry 4). Variation in the nature of the solvent using DCE or CH_3CN led to a reduced yield compared with benzene or no conversion (Table 1, entries 5 and 6). Finally, an attempt with a lower reaction temperature of 45 °C (instead of 65 °C) to slow the decomposition of DTBHN also led to a lower yield (Table 1, entry 7).

The optimized conditions above (Table 1, entry 4) were then applied to a series of cyclopropenes **2a−i**, leading to cyclopropyl nitriles **4a−l** in moderate to good yields with modest diastereocontrol (Scheme 1). The variation in the yield depending on the nature of the substituents on the cyclopropane ring suggests that steric hindrance is the main issue in this process. For instance, variation of the size of the added ester group (i.e., **1a−c**) as in **4a−c** led to decreased yield in going from CO_2Et to CO_2Ph. Similarly, increasing bulk of the resident R^2 group in the cyclopropene as in **4j** and **4k** also led to a lower yield and more importantly to a loss of diastereocontrol. In all cases, a small amount of the ATRA product was also isolated (10−15% yield). This approach allows access to orthogonal carbonyl functions as in **4b−e**, which will be useful for further functionalizations. Finally, it is worth noticing that although the diastereocontrol is modest, the diastereomers of **4b−l** are easily separable through silica gel chromatography.

The structures of the two isomers of cyclopropanes **4a−l**, assigned through ^{1}H NMR analyses, showed that the addition of the radical precursor occurred *anti* with respect to the

Scheme 1. Scope of the Carbocyanation of Cyclopropenes 2a−i



cyclopropene ester group, leading to a pyramidalized cyclopropyl σ radical, which is known to rapidly invert (10^8 s^{-1}).[10] The latter then abstracts the iodine atom of the precursor **1a−d**, providing the corresponding ATRA product (i.e., **IV**; Figure 1) as an intermediate (vide infra). Reaction of this iodide with the trimethyltin radical then returns the cyclopropyl σ radical (i.e., **II**; Figure 1), which may react under two configurations **A** and **B**, with *p*-tosyl cyanide (**3**) preferably approaching *anti* with respect to the resident ester group in configuration **A** (Figure 2).[8a] Configuration **B** is less favored due to steric

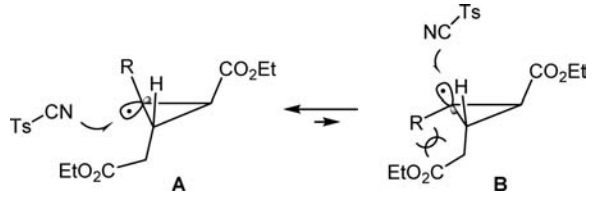


Figure 2. Transition state model for the carbocyanation of cyclopropenes.

interactions between the R group and the CH_2CO_2Et chain. When the R substituent becomes too bulky, as in **4j** and **4k**, steric interactions with CO_2Et develop, and configurations **A** and **B** likely have similar energies, resulting in a loss of diastereocontrol.

Interestingly, cyanation of diastereomerically pure iodocyclopropane **5**[12] with **3** under the above conditions led to cyclopropane **4a** with the same diastereomeric ratio observed in the above one-pot reaction (Scheme 2), indicating that the

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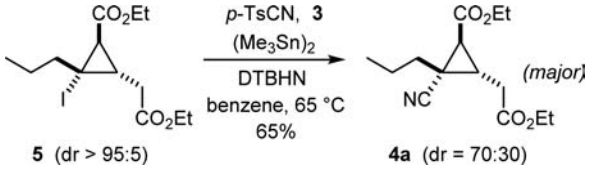
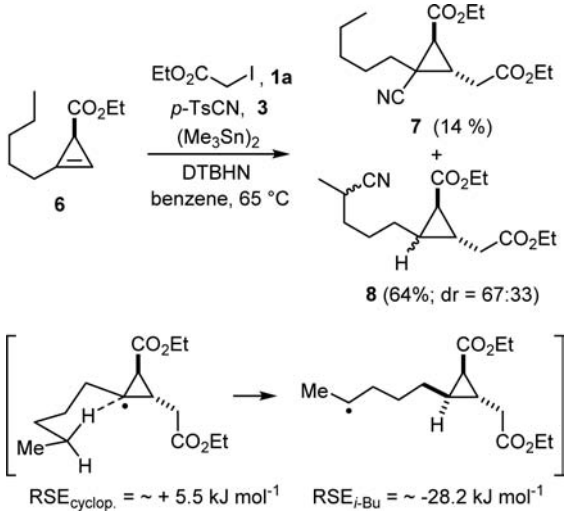
inversion at the radical center is faster than the cyanation, in good agreement with earlier studies.[10]

Scheme 2. Cyanation of Iodocyclopropane 5



The high reactivity of the cyclopropyl radical was further illustrated during carbocyanation of cyclopropene **6**. Treatment of **6** under the above carbocyanation conditions led to the desired cyclopropyl nitrile **7** in low yield along with nitrile **8** (as a mixture of two diastereomers), which results from a 1,5-hydrogen shift (Scheme 3). This unexpected C−H activation is

Scheme 3. 1,5-Hydrogen Atom Abstraction in Carbocyanation Processes

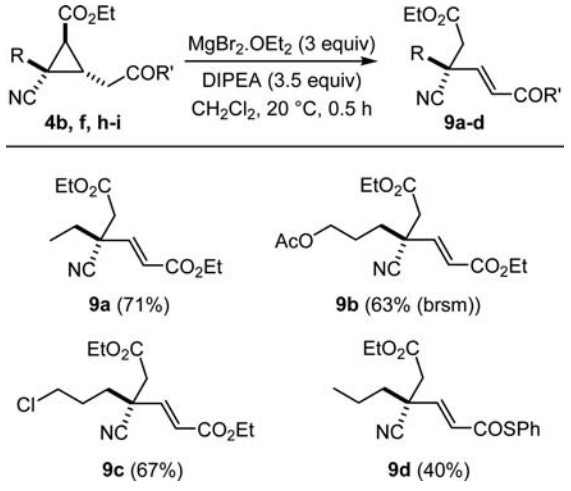


driven by radical stability, with secondary radicals being much more stable than cyclopropyl ones, as suggested by radical stabilization enthalpies (RSEs)[13] measured for cyclopropyl and isobutyl radicals.

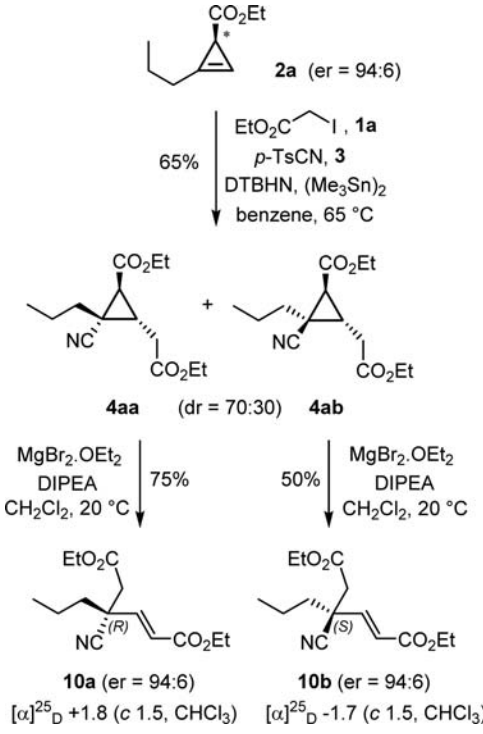
With cyclopropyl nitriles **4** in hand, the base-mediated ring-opening process was then studied.[14] Preliminary attempts using LDA led to low conversion and yield. In contrast, soft enolization of the cyclopropanes **4b**, **4f**, **4h**, and **4i** using *i*-Pr_2NEt (DIPEA) and $MgBr_2$ in CH_2Cl_2 was found to be more appropriate,[15] leading to clean cyclopropane ring opening and the formation of highly functionalized acyclic systems **9a−d** bearing an all-carbon quaternary center in generally good yields (Scheme 4).[16] The reaction was relatively fast, except with **9b**, where the starting material could not be totally consumed even after 12 h.

The carbocyanation/cyclopropane ring opening sequence was finally applied to enantioenriched cyclopropene **2a** (er = 94:6), which is readily available through cyclopropanation of pent-1-yne using Corey's chiral rhodium catalyst (see the Supporting Information) (Scheme 5).[5c] Carbocyanation of enantioenriched **2a** led to a 7:3 mixture of diastereomers **4aa** and **4ab**, which were separated through silica gel chromatography. Separate treatment of the two isomers under the soft

Scheme 4. Base-Mediated Ring Opening of Cyclopropanes 4b, 4f, 4h, and 4i



Scheme 5. Stereodivergent Access to Diesters 10a and 10b Having an All-Carbon Quaternary Stereocenter



enolization conditions above finally led to enantiomers **10a** and **10b**, the enantiomeric purity of which was shown by chiral HPLC to be the same as that of the starting cyclopropene **2a**, indicating that no erosion of the enantioselectivity occurred during the whole sequence. This straightforward transformation thus provides stereodivergent access to both enantiomers of diester **10** having all-carbon quaternary stereocenters.[16]

In summary, we have reported the first free-radical carbofunctionalization of cyclopropenes. This one-pot multicomponent carbocyanation offers a straightforward entry to tetrasubstituted cyclopropanes in satisfying yields with moderate diastereoselectivity. This radical addition installs functionalizations allowing further base-mediated cyclopropane ring opening, leading to acyclic diesters having an all-carbon

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quaternary stereocenter. This methodology makes use of readily available enantioenriched cyclopropenes and leads to regioselectivity complementing that observed in carbometalation of cyclopropenes.[4,6]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03163.

Experimental details and characterization data for the starting material and products (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Iodocyclopropane **5** was obtained in 87% yield (88:12 dr) through addition of α-iodoester **1a** to **2a** using $(Bu_3Sn)_2$ (50 mol %) and DTBHN (10 mol %).

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