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Free-radical Carbo-cyanation of Cyclopropenes. A Stereocontrolled Access to All-Carbon Quaternary Stereocenters in Acyclic Systems

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

Polysubstituted cyclopropanes are useful intermediates in organic synthesis,¹ which 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 should also include the functionalization of substituted cyclopropenes.⁴ Organometallic (1) and free-radical additions (2) onto the π -system of cyclopropenes thus offer a complementary route to polysubstituted cyclopropanes, which may be functionalized further (Figure 1). It is worth of note that cyclopropenes may also be prepared in enantiopure form through rhodium-mediated cyclopropanation of the corresponding alkynes, using commercially available diazo esters.⁵ Recent work by Marek et al.⁶ has elegantly shown that *syn*-carbometallation of cyclopropenes (Figure 1, eq 1) led to the corresponding metallated cyclopropane **I**, which could be trapped by various electrophiles or undergo selective ring opening. Free-radical atom-transfer processes using cyclopropenes have been reported earlier by Saicic,^{7a} Zard,^{7b} et al. and more recently by Miyata, Ueda et al.⁸ leading to cyclopropanes in moderate to good yields. In contrast, radical addition of two carbon fragments across cyclopropene π -system has, to our knowledge, not been explored so far. This may be attributed to the high reactivity of the 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 onto **II**. Finally, the weaker nucleophilicity of the cyclopropyl σ -radical as compared to that of other alkyl radicals is another factor, which may hamper carbo-functionalization of cyclopropenes.¹⁰

We report here on a new multicomponent carbo-cyanation addition onto substituted cyclopropenes, which gives rise to tetrasubstituted cyclopropyl nitriles **III**, bearing a quaternary center, in satisfying yields and moderate diastereocontrol. The

structure of these cyclopropanes also allow further base-mediated ring opening, offering a straightforward and stereodivergent access to acyclic systems having functionalized all-carbon quaternary stereocenters, present in many biomolecules and natural products.

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

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-*t*-butoxyhyponitrite (DTBHN) and $(\text{Bu}_3\text{Sn})_2$ as a chain carrier.¹¹ First reaction attempts by mixing the three components, DTBHN and ditin, produced less than 20% 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). Both diastereomers were easily separated through chromatography and their structure assigned through ¹H NMR. Slightly better yield was obtained by adding slowly to the medium, a mixture of *p*-TsCN and DTBHN

through a syringe pump (Table 1, entry 1). Considering that the atom transfer product (ATRA) (*i.e.* **IV**, X = I, Figure 1) was likely the intermediate in the reaction process, it was envisioned that the Bu₃Sn radical might be sterically too hindered to abstract the iodine atom and regenerate the cyclopropyl radical **II** for further cyanation. This proved to be the case, as reaction using instead the smaller Me₃Sn radical led to much improved yield, cyclopropyl nitriles **4aa-4ab** being formed in 60% yield, albeit with modest diastereocontrol (Table 1, entry 2). Reducing the rate of addition had surprisingly 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 per hour (Table 1, entry 4). Variation in the nature of the solvent using DCE or CH₃CN led to a reduced yield as compared to benzene or no conversion (Table 1, entries 5-6). Finally, an attempt at lowering the reaction temperature to 45 °C, instead of 65 °C, to slow down the decomposition of DTBHN, also led to a lower yield (Table 1, entry 7).

Table 1. Optimization of the carbo-cyanation of cyclopropene.

entry	rate of addition (time)	solvent	yield ^{b,c} (%)	dr ^d
1 ^a	0.5 mL/h (5 h)	benzene	24 ^d	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 ₃ CN	-	-
7 ^e	1 mL/h (2.5 h)	benzene	41	77:23

^a Reaction was carried out mixing **1a** (1 equiv), **2a** (2 equiv) and (Me₃Sn)₂ (unless otherwise indicated) (2 equiv) in the solvent, then a mixture of DTBHN (40 mol %) and **3** (2 equiv) was added at 65 °C through a syringe pump. ^b Isolated yields. ^c Isolated ATRA product (~ 10-15%). ^d Estimated through ¹H NMR of the crude reaction mixture after a short filtration column. ^e (Bu₃Sn)₂ was used. ^e Reaction performed at 45 °C.

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 and modest diastereocontrol (Scheme 1). Variation in yields 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 going from CO₂Et to CO₂Ph. Similarly, increasing bulk of the resident R² group in cyclopropene as in **4j-k** also led to lower yields and more importantly to a loss of diastereocontrol. In all cases, a small

amount of the ATRA product was also isolated (from 10 to 15% yield). This approach allows an access to orthogonal carbonyl functions as in **4b-e**, which will be useful for further functionalizations. Finally, it is worth noticing that, although diastereocontrol is modest, diastereoisomers of **4b-l** are easily separable through silica gel chromatography.

Scheme 1. Scope of the carbo-cyanation of cyclopropenes **2a-i**.

The structure of the two isomers of cyclopropanes **4a-l**, assigned through ¹H NMR, showed that the addition of the radical precursor occurred *anti* relative to the cyclopropene ester group, leading to a pyramidalized cyclopropyl σ-radical, known to rapidly invert (10⁸ 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**, the *p*-tosyl cyanide **3** preferably approaching *anti* relative to the resident ester group in configuration **A** (Figure 2).^{8a} Configuration **B** is less favored due to steric interactions between the R group and the CH₂CO₂Et chain. When R substituent becomes too bulky as in **4j-k**, steric interactions with CO₂Et develop and configurations **A** and **B** likely have similar energies, resulting in a loss of diastereocontrol.

Figure 2. Transition state model for the carbo-cyanation of cyclopropanes.

Interestingly, cyanation of diastereomerically pure iodocyclopropane **5**¹² with *p*-tosyl cyanide **3** under the above conditions led to the cyclopropane **4a** with the same diastereomeric ratio observed in the above one-pot reaction, indicating that the inversion at the radical center is faster than the cyanation, in good agreement with earlier studies (Scheme 2).¹⁰

Scheme 2. Cyanation of iodocyclopropane **5**.

The high reactivity of the cyclopropyl radical was further illustrated during carbo-cyanation of cyclopropane **6**. Treatment of the latter under the above carbo-cyanation conditions led to the desired cyclopropyl nitrile **7** in low yield along with nitrile **8** (as a mixture of two diastereomers), resulting from a 1,5-hydrogen shift (Scheme 3). This unexpected C-H activation is driven by radical stability, secondary radicals being much more stable than cyclopropyl ones, as suggested by radical stabilization enthalpies (RSE),¹³ measured for cyclopropyl and isobutyl radicals.

Scheme 3. 1,5-Hydrogen atom abstraction in carbo-cyanation processes.

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** and **4h-i** using *i*-Pr₂NEt (DIPEA) and MgBr₂ in CH₂Cl₂ was found to be more appropriate,¹⁵ leading to a 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 Reaction were relatively fast, except with **9b** where starting material could not be totally consumed even after 12h.

Scheme 4. Base-mediated ring-opening of cyclopropanes **4b**, **4f** and **4h-i**.

The carbo-cyanation/cyclopropane ring-opening sequence was finally applied to enantioenriched cyclopropane **2a** (er 94:6), readily available through cyclopropanation of pent-1-yne using Corey's chiral rhodium catalyst (supporting information).^{5c} The carbo-cyanation of enantioenriched **2a** led to a 7:3 mixture of diastereomers **4aa** and **4ab**, which were separated through silica gel chromatography (Scheme 5). Separate treatment of both isomers under the soft enolization conditions above, finally led to enantiomers **10a** and **10b**, the enantiomeric purity of which was shown (chiral HPLC) to be the same to that of the starting cyclopropane **2a**, indicating that no erosion of the enantioselectivity occurred during the whole sequence. This straightforward transformation thus provides a stereodivergent access to both enantiomers of diester **10** having all-carbon quaternary stereocenters.¹⁶

Scheme 5. Stereodivergent access to diesters **10a-b** having an all-carbon quaternary stereocenter.

In summary, we reported the first free-radical carbo-functionalization of cyclopropenes. This one-pot multicomponent carbo-cyanation offers a straightforward entry to tetrasubstituted cyclopropanes in satisfying yields and moderate diastereoselectivity. This radical addition installs functionalizations allowing further base-mediated cyclopropane ring-opening, leading to acyclic diesters having an all-carbon quaternary stereocenter. This methodology makes use of readily available enantioenriched cyclopropenes and leads to regioselectivity, which complements those observed in carbo-metallation of cyclopropenes.^{4,6}

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