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Communication

Catalytic, Asymmetric Dearomative Synthesis of Complex Cyclohexanes via a Highly Regio- and Stereoselective Arene Cyclopropanation Using α-Cyanodiazoacetates

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ABSTRACT: Arene cyclopropanation offers a direct route to higher-order, non-aromatic carbocycles; however, the inherent issue of dictating site selectivity has cumbered the development of novel intermolecular reactions that directly engage the arene pool. This paper describes a highly regio- and stereoselective, $Rh_2[(S)\text{-PTTL}]_4$-catalyzed arene cyclopropanation using α-cyanodiazoacetates to afford stable norcaradienes bearing three stereogenic centers, one of which is an all-carbon quaternary center. The enantioenriched norcaradienes served as tunable templates for further transformation into stereochemically dense, fused and bicyclic carbocycles containing transmutable functionality.

Benzenoid compounds are important feedstock chemicals in organic synthesis. Their abundance from petrochemical refining and emergent availability from renewable resources have provided an impetus for the development of new methodologies that use the aromatic pool.[1] Dearomatization reactions, transformations that mobilize the aromatic π-system for the generation of new bonds at the expense of aromatic stabilization, have allowed for the upcycling of simple benzenoid feedstocks into higher-order carbocyclic products. The ample supply of benzenoid chemicals has fueled the development of dearomative strategies, resulting in a fertile research field spanning a diverse range of chemical approaches.[2] In particular, the direct dearomative monofunctionalization of benzenoids holds high synthetic value (Scheme 1a) by engaging a single π-bond of the aromatic system, thereby revealing a latent 1,3-cyclohexadiene motif that can be further decorated to complex molecules. Asymmetric dearomatization reactions of this type would enable the rapid conversion of the aromatic pool to an array of complex, chiral cyclohexane building blocks.

Transition metal-catalyzed arene cyclopropanations are powerful reactions for the synthesis of non-aromatic structures, with their feasibility established in foundational work from Noels and Hubert in 1981,[3] and built upon by numerous other laboratories in substantial ways in the intervening time.[4] Scheme 1b illustrates inherent challenges in such reactions: regiocontrol for the three non-equivalent sites, stereoselectivity, and tautomeric composition. For the former, tethering strategies have proven to be effective by restricting access to distal sites,[4] and the illustrated case from Mander (Scheme 1c) is an excellent representative example from a substantial corpus of work.[5,6] Much of the work on absolute stereocontrol has focused on intramolecular cases; however, Beeler and Fleming recently showed that flow chemistry improves the site selectivity in intermolecular enantioselective Buchner reactions with electron-rich arenes, allowing for the preparation of enantioenriched cycloheptatrienes (CHTs, Scheme 1c).[7] Within this landscape, we wondered if a direct, intermolecular arene cyclopropanation that afforded enantioenriched, regioisomerically pure *norcaradienes* (NCDs) might serve as a useful contribution to this evergreen field.[8] Herein, we report an asymmetric, intermolecular arene cyclopropanation to prepare enantiomerically enriched 7-carboxyalkyl-7-cyanonorcaradienes bearing three stereogenic centers, one of which is an all-carbon quaternary center, from simple benzene congeners.

The electronic identities of the C-7 substituents influence the NCD−CHT equilibrium, with strong π-acceptors favoring the norcaradiene valence tautomer (Scheme 2a).[9,10] Access to the desired NCD tautomer necessarily mandates a C-7 disconnection to a geminally disubstituted carbene/carbenoid bearing the requisite stabilizing groups, which can arise from acceptor/acceptor diazo compounds. α-Cyano-acceptor diazo compounds exhibit high reactivity and selectivity in catalytic cyclopropanation reactions of π-systems by virtue of the enhanced carbenoid electrophilicity conferred by the inherent cylindrical symmetry of the nitrile.[11] We considered the intermolecular, photolytic carbene cyclopropanation of benzene with 4-diazo-1,2,3-triazoles reported by Shechter (Scheme 2b) as reasonable precedent for the proposed catalytic transformation.[12] Furthermore, β-cyanoesters are versatile handles for translation into other functional groups.[4b,13] These considerations directed our attention to the development of an intermolecular cyclopropanation

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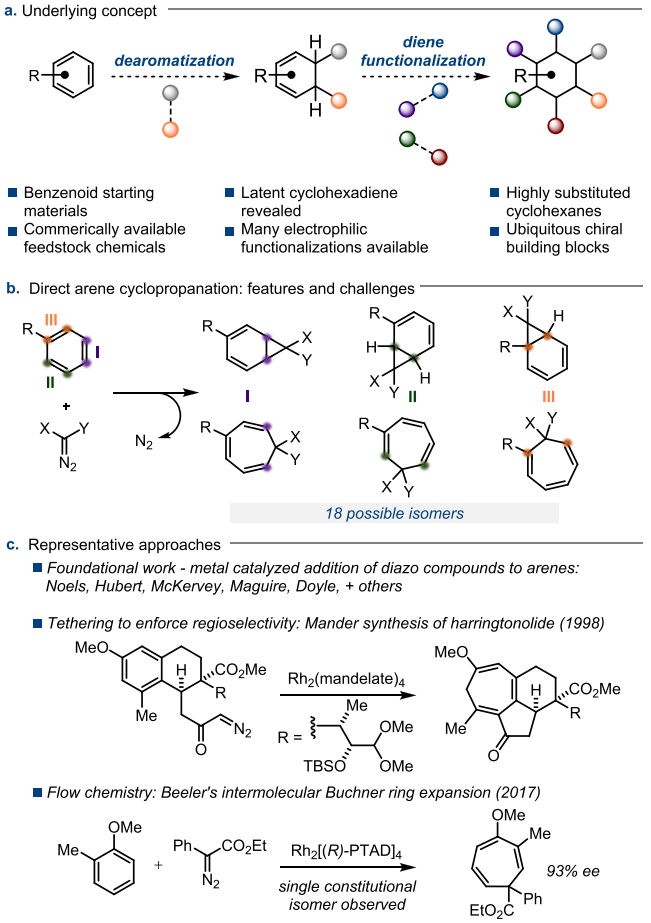
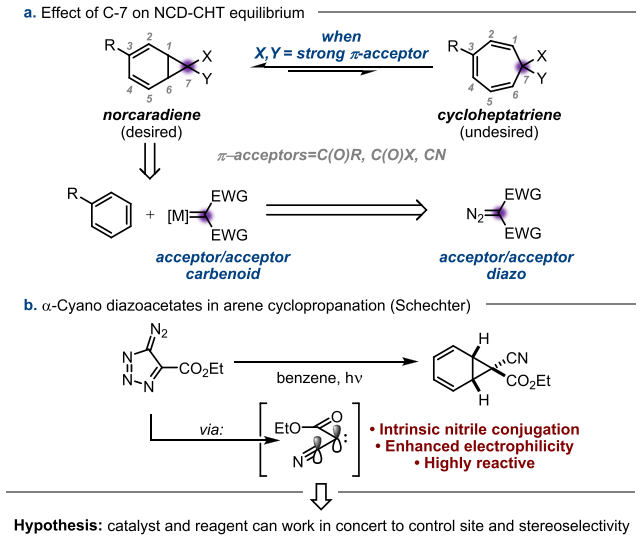
Scheme 1. Using Norcaradienes to Streamline the Synthesis of Chiral Cyclohexane Building Blocks



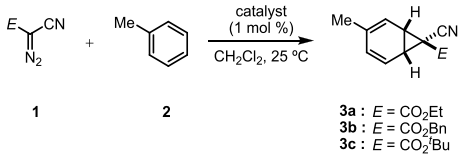
Scheme 2. Substituent Effects on NCD−CHT Equilibrium: Stable 7-Carboxyalkyl-7-cyanonorcaradienes



employing α-cyanodiazoacetates, which are readily prepared following known diazo transfer protocols.[14]

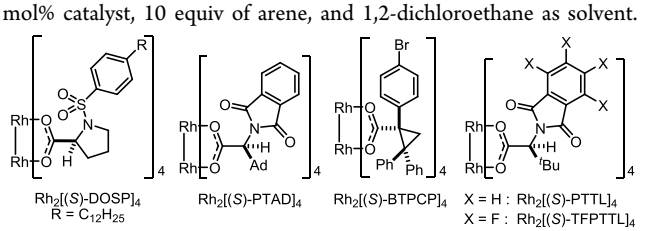
The reaction catalyzed by the achiral $Rh_2(esp)_2$ dimer afforded norcaradiene **3a** in 57% yield as a 10:1 mixture of regioisomers (Table 1, entry 1). Encouraged by the high regioselectivity observed, various chiral rhodium(II) bis-

Table 1. Optimization of the Asymmetric Cyclopropanation



entry[a]	catalyst	E	yield (%)[b]	rr[c]	er[d]
1	$Rh_2(esp)_2$	CO_2Et	57	10:1	–
2	$Rh_2[(S)\text{-DOSP}]_4$	CO_2Et	55	6:1	69:31
3[e]	$Rh_2[(S)\text{-PTAD}]_4$	CO_2Et	58	13:1	74:26
4[e]	$Rh_2[(S)\text{-BTPCP}]_4$	CO_2Et	56	8:1	66:34
5[e]	$Rh_2[(S)\text{-PTTL}]_4$	CO_2Et	63	11:1	83:17
6[f]	$Rh_2[(S)\text{-PTTL}]_4$	CO_2Et	55	11:1	83:17
7[f]	$Rh_2[(S)\text{-PTTL}]_4$	CO_2Bn	27	7:1	76:24
8[f]	$Rh_2[(S)\text{-PTTL}]_4$	$CO_2{}^tBu$	66	14.5:1	94:6
9[f]	$Rh_2[(S)\text{-TFPTTL}]_4$	$CO_2{}^tBu$	57	11:1	84:16

[a]Reactions performed using 0.10 mmol of cyanodiazoacetate, 1 mol% catalyst, 20 equiv of arene, and CH_2Cl_2 as solvent. [b]Determined by ^1H NMR spectroscopic analysis of the crude mixture using mesitylene as an internal standard. [c]Determined by integral ratio of the olefinic ^1H NMR resonances. [d]Determined by HPLC using a chiral stationary phase. [e]Reaction performed at 0 °C. [f]Reaction performed using 0.25 mol% catalyst, 10 equiv of arene, and 1,2-dichloroethane as solvent.



(carboxylate) dimers were surveyed in an effort to develop the asymmetric cyclopropanation. Davies's $Rh_2[(S)\text{-DOSP}]_4$ gave modest enantioselectivity accompanied with a decrease in regioselectivity in the cyclopropanation. (Table 1, entry 2). $Rh_2[(S)\text{-PTAD}]_4$ and $Rh_2[(S)\text{-BTPCP}]_4$ displayed high reactivity and enantioinduction in an asymmetric Buchner ring expansion reported by Beeler.[7] Increases in both regioselectivity and enantioselectivity to 13:1 and 74:26, respectively, were observed when $Rh_2[(S)\text{-PTAD}]_4$ was employed at 0 °C (Table 1, entry 3). The *tert*-leucine-derived dimer $Rh_2[(S)\text{-PTTL}]_4$ disclosed by Hashimoto[15] displayed enhanced performance, leading to increases in reaction yield as well as both regio- and enantioselectivity (Table 1, entries 5 and 6). Increasing the steric demand of the ester by switching to the *tert*-butyl ester had a positive effect, affording **3c** in 66% yield with 14.5:1 rr and 94:6 er (Table 1, entry 8).

Using the optimal conditions obtained, the reactivities of various arenes were surveyed in the reaction (Table 2). An interesting trend emerged with haloarenes, where considerable amounts of a bis(cyclopropanated) side product were present using the standard conditions. The electronegative substituent deactivates the arene nucleus to dearomative cyclopropanation, thereby allowing the competitive cyclopropanation of the more reactive norcaradiene. Increasing the haloarene charge to 60 equiv allowed for the obtention of acceptable yields of halogenated norcaradienes **3e**−**3g** with high enantiopurities and regiopurities. Cyclopropanation of methyl benzoate under the standard conditions gave results consistent with our hypothesis regarding the reactivity of haloarenes. Accordingly, employing methyl benzoate (60 equiv) in the reaction allowed for preparation of acrylate **3h**, albeit in low yield and

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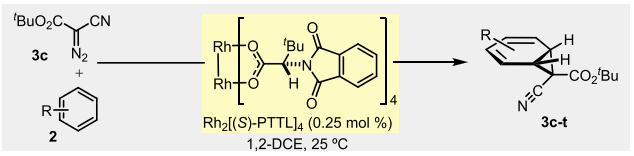
Table 2. Survey of Substituted Arenes in the Asymmetric Cyclopropanation



rr = regioisomer ratio; *er* = enantiomer ratio

entry	R'	yield	rr	er
3c	^{t}Bu	66%	14.5:1	94:6
3c[a]	^{t}Bu	68%	13:1	92:8

entry	R	yield	rr	er
3d	^{i}Pr	67%	11:1	90:10
3e	Cl	42%	19:1	96:4
3f	F	47%	>20:1	94:6
3g	Br	41%	13:1	95:5
3h	CO_2Me	17%	5:1	96:4
3i	Ph	37%	18:1	91:9
3j	CH_2NHTs	45%	>20:1	91:9
3k	CH_2OTBS	49%	13:1	92:8
3l	$(CH_2)_3$OTBS	65%	10:1	91:9

entry	yield	entry	yield	rr	er
3m	69%	3n	65%	11:1 7:1 dr	97:3

entry	yield	rr	er
3o	47%	>20:1	94:6

entry	yield	rr	er
3p	53%	14:1	95:5

entry	yield	rr	er
4q[b]	43%	>20:1	79:21

entry	yield	rr	er
3r[b]	10%	>20:1[a]	n/a

entry	yield	rr	er
3s/s'	67%	1:1	92:8/94:6

entry	yield
3t	0%

[a]Reaction performed on 5 mmol scale. [b]Refer to the Supporting Information.

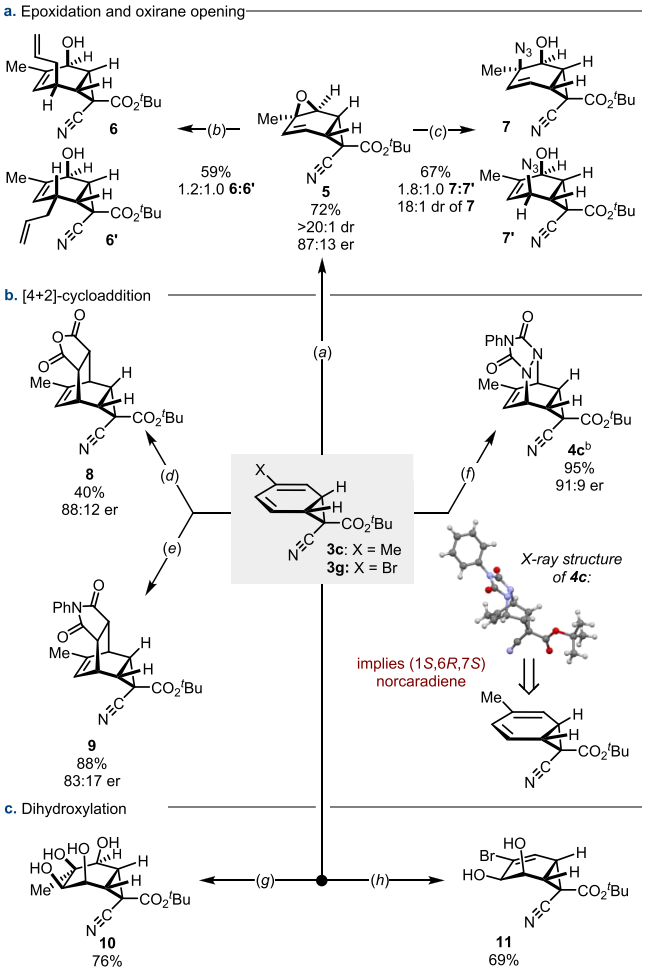
diminished regioselectivity. Sulfonamides and protected alcohols were tolerated in the reaction as evident by products **3j**, **3k**, and **3l**. Notably, the lower yield with **3k** compared to the chain-extended **3l** highlights the sensitivity of the reaction to steric factors on the arene. Cyclopropanation of anisole furnished the formal C−H insertion product **3m**, likely arising from facile rearomatization of the transiently generated norcaradiene. Enantiotopic group selection was feasible under the conditions allowing for the desymmetrization of TBS-protected benzhydrol, furnishing **3n** with good diastereoselectivity and high enantioselectivity.

Norcaradienes from cyclopropanation of the xylene series displayed unique stability profiles. Cyclopropanation of *o*-xylene proceeded with high regioselectivity for C3−C4 to generate **3p** which was easily isolated post-reaction. The *m*-xylene-derived norcaradiene was isolated as its 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) cycloadduct **4q** given the instability of norcaradiene to conventional chromatography. The *p*-xylene norcaradiene exhibited disparate reactivity; cyclopropanation occurred with slight kinetic regioselectivity at C1−C2; however, the product isomerizes to *meso*-**3r** during purification. The catalyst did not show site selectivity in the reaction with *o*-chlorotoluene, furnishing an equimolar mixture of enantioenriched norcaradienes **3s** and **3s′**. Cyclopropanation of 1,3,5-mesitylene was unsuccessful, likely due to the distributed increase in steric hindrance around the ring.

With enantioenriched norcaradienes available, we explored the synthetic viability of the products in further transformations. A convex facial approach to the bicyclo[4.1.0]-heptane should reinforce highly diastereoselective transformations; however, careful determination of downstream transformations that would not sensitize the norcaradiene to rearomatization was paramount. Previously reported norcaradiene functionalizations largely rely on substituted NCDs that restrict rearomatization or *in situ*-generated NCDs from the CHT valence tautomer.[4b,6] Chemoselective epoxidation has been used extensively to prepare vinyl epoxides from 1,3-dienes.[16] Furthermore, vinyl oxiranes readily serve as electrophiles in epoxide opening reactions by carbon and heteroatom nucleophiles.[17] Treating **3c** with *m*-CPBA/KF effected clean mono-epoxidation, affording norcaradiene oxide **5** in 72% yield as a single diastereomer (Scheme 3a).[18,19]

BF_3·OEt_2-promoted opening of epoxide **5** with allyltributylstannane supplied the diastereomeric S_N2' products **6**/**6′** in a combined 63% yield.[20] Alternatively, azidolysis of **5** using $TMSN_3$ mediated by $Ti(OEt)_4$ generated allylic azides **7**/**7′** as

Scheme 3. Selected Transformations of Norcaradienes 3b/3g



[a]Reagents and conditions: (a) *m*-CPBA (1.2 equiv), KF (1.2 equiv), CH_2Cl_2; (b) BF_3·Et_2O (1.5 equiv), allylBu_3Sn (3 equiv), CH_2Cl_2; (c) $TMSN_3$ (5 equiv), $Ti(OEt)_4$ (1 equiv), PhMe; (d) maleic anhydride (10 equiv), brine, 110 °C; (e) *N*-phenyl maleimide (5 equiv), brine, 110 °C; (f) PTAD (3 equiv), Et_2O; (g) OsO_4 (10 mol%), NMO (5 equiv), THF:^{t}BuOH:H_2O; (h) OsO_4 (10 mol%), NMO (1.5 equiv), THF:^{t}BuOH:H_2O. [b]Isolated mixture of regioisomeric cycloadducts.

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an equilibrating mixture by virtue of a [3,3]-Winstein rearrangement.[21,22] None of the analogous cyclopropane opening products were observed, illustrating the high chemoselectivity toward epoxide activation.

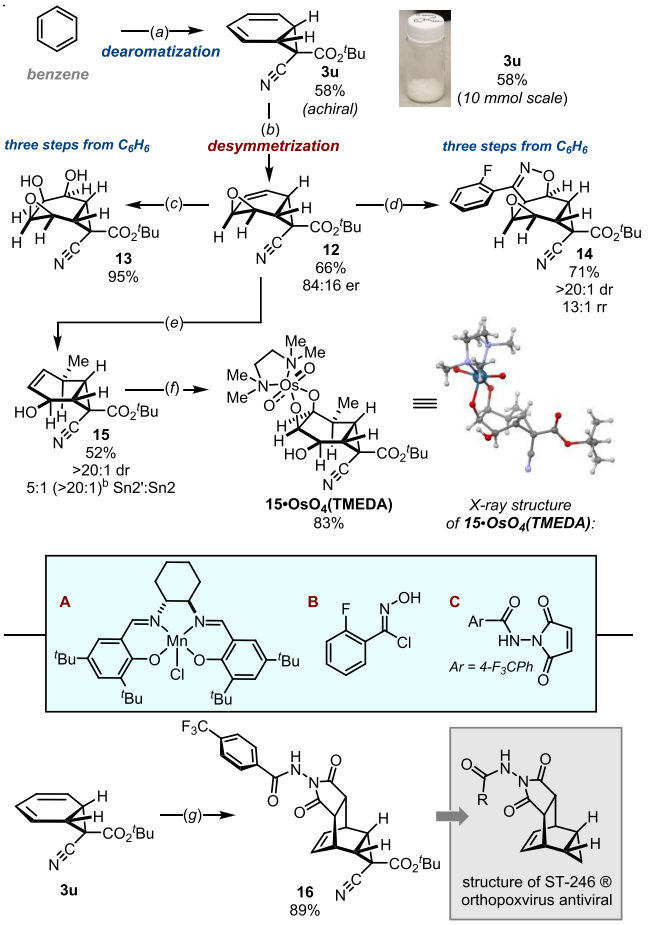
NCDs readily engage activated dienophiles in [4+2]-cycloadditions.[23] Indeed, [4+2]-cycloadditions of NCD **3c** in brine under microwave heating offered access to cycloadducts **8** and **9** (Scheme 3b). The poor yield of the maleic anhydride cycloadduct **8** can be understood in light of significant rearomatization and maleic anhydride hydrolysis that transpired during the reaction. The combination of elevated temperature and acidic medium would amplify an undesired acid-promoted rearomatization. Bicyclic urazole **4c** was obtained in excellent yield after exposure to PTAD in ethereal solvent. X-ray diffraction studies on a single crystal assigned the absolute configuration of **4c**, indirectly assigning the [1*S*,6*R*,7*S*] enantiomer of **3c**.

Cyclohexene dihydroxylation has been employed routinely toward the preparation of highly oxygenated cyclohexane scaffolds such as those seen in the isocarbostyryl alkaloid family (Scheme 3c).[24] Upjohn conditions effected clean global dihydroxylation of NCD **3c**, furnishing tetraol **10** in good yield and diastereoselectivity. Achieving mono-dihydroxylation of **3c** posed a challenge due to over-oxidation; however, we conjectured that the electronically differentiated bromo-NCD **3g** would present an avenue for mono-dihydroxylation by relying on the comparatively slow oxidation of vinyl halides.[2c,25] Under similar conditions, NCD **3g** was readily oxidized to diol **11** in 69% yield as a single diastereomer with no indication of bis(dihydroxylation).

We next targeted the direct dearomatization of benzene (Scheme 4). Applying the standard catalytic conditions to benzene gave the Schecter *meso*-norcaradiene **3u** in 58% yield. Desymmetrization reactions are useful for the preparation of enantioenriched, stereochemically complex products from *meso* starting materials.[26] Jacobsen demonstrated the enantioselective epoxidation of unactivated dienes using sterically and electronically tuned (salen)Mn complexes.[27] Desymmetrization of **3u** under similar conditions afforded norcaradiene oxide **12** in 66% yield in 84:16 er as a single diastereomer. Subsequent dihydroxylation furnished diol **13** in excellent yield. Nitrile oxide cycloaddition of alkene **12** enabled the preparation of tricyclic isoxazoline **14** in 71% yield and high regioselectivity, representing a tunable three-step sequence that upcycles benzene[24a] to value-added fused tetracyclic compounds bearing seven stereocenters. Alkylative opening of **12** with methyl Gilman reagent proceeded smoothly, affording preferentially allylic alcohol **15** resulting from S_N2' addition in 52% yield.[28] Employing a recent protocol reported by Rychnovsky, preparation of crystalline osmate ester **15·OsO$_4$(TMEDA)** allowed for unambiguous assignment of its absolute configuration, therefore identifying the [1*R*,2*R*,4*S*,7*S*,8*R*] enantiomer of epoxide **12**.[29] Microwave-assisted [4+2]-cycloaddition of **3u** with a hydrazide-derived maleimide delivered the cycloadduct **16** as a single diastereomer in 89% yield. Structurally, tetracycle **16** maps onto the class of ST-246 orthopox antivirals.[30,31]

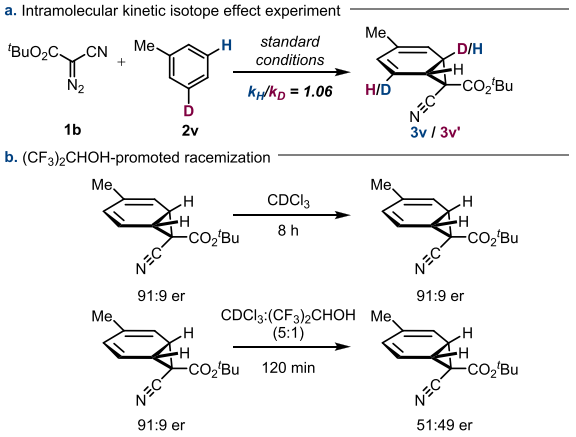
Intrigued by the high regioselectivities observed in the reaction, an isotopic labeling study was performed (Scheme 5). Rhodium carbenoid cyclopropanations have been reported to proceed through asynchronous, concerted carbene transfers, displaying small secondary isotope effects.[32] An intramolecular competition study of mono-deuterated toluene **2v** gave a

Scheme 4. Benzene Dearomatization and Norcaradiene Desymmetrization



[a]Reagents and conditions: (a) standard conditions using 40 equiv of benzene; (b) **A** (5 mol%), NaOCl (4 equiv), 4-phenylpyridine *N*-oxide (19 mol%), EtOAc; (c) OsO_4 (10 mol%), NMO (3 equiv), THF:^{t}BuOH:H_2O; (d) **B** (3 equiv), Et_3N (3.5 equiv), CH_2Cl_2; (e) Me_2CuLi (3 equiv), $ZnCl_2$ (3 equiv), THF; (f) OsO_4 (1 equiv), TMEDA (1 equiv), CH_2Cl_2; (g) **C** (3 equiv), brine, 110 °C. [b]Ratio after purification.

Scheme 5. Isotopic Labeling and Racemization Studies



1.06:1.00 product mixture of **3v**, with the ratio determined by ^{2}H NMR spectroscopy. During the course of our investigation, we observed enantioerosion of older samples of **3b**. A slow

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[1,5]-migration by a polar C−C bond scission/closure sequence could account for the racemization.[4f,33,34] Given the instability of norcaradienes **3q** and **3r** to chromatography, we considered that exposure of **3b** to a sufficiently ionizing Brønsted or Lewis acidic reagent should promote racemization. Indeed, exposure of enantioenriched **3b** to $(CF_3)_2CHOH$[35] led to complete racemization in 120 min, with partial rearomatization.

In summary, a highly regioselective, intermolecular arene cyclopropanation was developed that provided access to a diverse set of enantioenriched 7-carboxyalkyl-7-cyanonorcaradienes. The products were subjected to a range of transformations that allowed for the modular syntheses of unique bicyclo[4.1.0]heptanes that would be difficult to access via alternative methods. Further investigations into the origins of the regioselectivity and the use of these norcaradienes in target-based synthesis are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13080.

X-ray crystallographic data for compound **4c** (CCDC 1857545) (CIF)

X-ray crystallographic data for compound **15·OsO$_4$(TMEDA)** (CCDC 1990391) (CIF)

Experimental procedures, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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