Letter

Enantioselective Assembly of Congested Cyclopropanes using Redox-Active Aryldiazoacetates

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Enantioselective Assembly of Congested Cyclopropanes using Redox-Active Aryldiazoacetates

Zhunzhun Yu[a] and Abraham Mendoza[a,*]

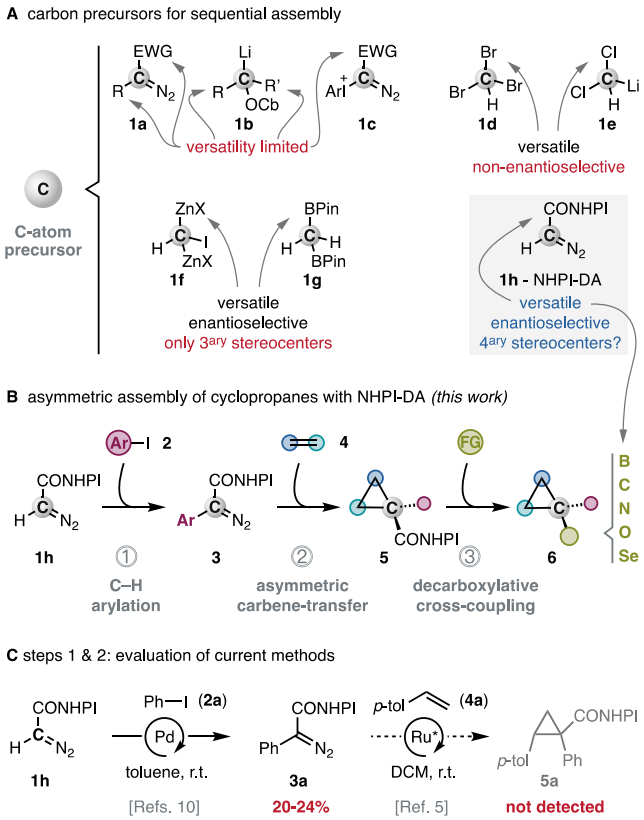
Dept. of Organic Chemistry, Stockholm University, Arrhenius laboratory 106 91 Stockholm (Sweden)

ABSTRACT: The enantioselective assembly of quaternary stereocenters through sequential functionalization of versatile carbon-atom precursors has the potential to systematize the synthesis of these ubiquitous stereogenic elements. Herein, we report two catalytic processes that allow the realization of this concept in the enantioselective synthesis of cyclopropanes. We demonstrate that C–H functionalization, carbene-transfer and decarboxylative cross-coupling can sequentially take place in the same carbon atom to obtain highly enantioenriched cyclopropane products. The reactions reported herein give access to redox-active analogs of privileged aryldiazoacetates and demonstrate their enantioselective carbene transfer with a simple and practical rhodium catalyst.

KEYWORDS: Asymmetric catalysis, C–H arylation, Cyclopropanes, Quaternary centers, Carbenes.

Chemoselective methods that evade protecting group manipulations[1] have significantly simplified synthesis,[2] and enabled relevant applications in bio-orthogonal coupling and chemical biology.[1, 3] While chemoselective manipulations in poly-functional molecules have been extensively developed,[1-3] the orthogonal functionalization of a single carbon atom has proven more challenging due to the easier mutual interference of reactive handles upon co-localization.[3c, 4] To address this challenge, functionalized carbene and carbyne equivalents **1a-c** have been explored (Scheme 1A), but taming their extreme reactivity still requires static substituents (EWG, R, R') that remain in the resulting products.[3c, 4a-h,s,t] Other carbon precursors such as haloforms and their derivatives (**1d,e**) are yet unsuitable for enantioselective catalysis,[4i-l] and those with organozinc and organoboron manifolds are yet confined to the asymmetric synthesis of tertiary stereocenters (**1f,g**).[4m-r]

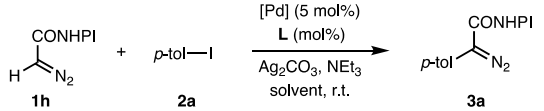
Recently, our group has reported on the orthogonality of redox-active esters towards carbene-transfer, using the diazoacetate reagent NHPI-DA (**1h**; NHPI, *N*-hydroxyphtalimide).[5] Despite the versatility demonstrated in the asymmetric synthesis of cyclopropanes, the carbene transfer of **1h** was limited to products with tertiary stereocenters.[5] Overcoming this limitation would enable a systematic and enantioselective assembly of congested cyclopropanes,[6] using their quaternary carbon[6f-i, 7] as the key connective unit (Scheme 1B). If the functionalization of the C–H bond in **1h** could be orthogonal to the existing diazo and redox-active ester groups, it could enable a rapid entry into more complex redox-active diazocompounds (*i.e.* **3**). In principle, enantioselective cyclopropanation with these reagents would deliver enantiopure cyclopropane intermediates **5**, direct precursors of a wide range of densely-functionalized products **6**. In particular, the C–H arylation of **1h** is an attractive entry into redox-active analogs of privileged aryldiazoesters (**3**).[4b-h] However, the arylation of diazocompounds is an inherently challenging transformation due to the competitive formation of metal carbenes.[8] In this case, the reaction is further complicated by the redox-active ester moiety, which can undergo oxidative addition and/or single electron transfer with palladium intermediates through its activated N–O bond.[9] Even after successful arylation, the electron-rich redox-active diazocompounds **3** are stereoelectronically distinct from **1h**, and would require specific developments to achieve high turnover and enantioselectivity in cyclopropanation reactions. Evaluation of current arylation and



Scheme 1. Background, approach and initial evaluation. EWG = $CO_{(2)}R$, $PO(OR)_2$, SO_3R, CF_3; NHPI, *N*-hydroxyphtalimide.

cyclopropanation methods showcased their unsuitability for this purpose (Scheme 1C). The redox-active diazocompound **1h** extensively decomposes under the arylation conditions that are efficient with conventional diazoesters.[10] Also, the resulting aryldiazocompound **3a** was found to be much less reactive than **1h** in cyclopropanation reactions, even towards activated styrene substrates such as **4a**.[5]

Table 1. Optimization of the C–H arylation of NHPI-DA (**1h**).

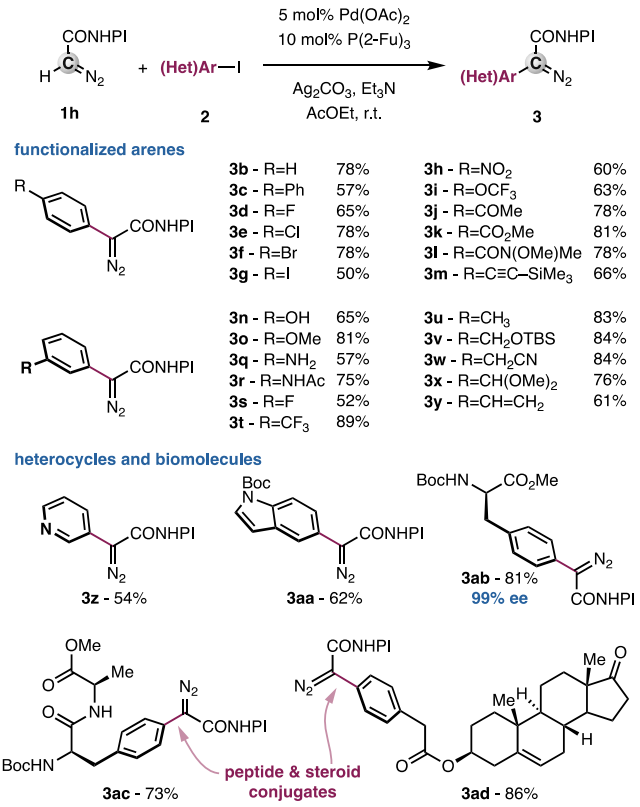


#	[Pd]	L (mol%)	L	solvent	**3a** (%)
1	$[Pd(PPh_3)_4]$[10a,b]	-	-	toluene	24
2	$[Pd(PPh_3)_4]$[10c]	10	PPh_3	toluene	25
3	$[Pd(PPh_3)_4]$	-	-	EtOAc	35
4	$Pd(OAc)_2$	10	PPh_3	EtOAc	<5
5	$Pd(OAc)_2$	10	PCy_3	EtOAc	<5
6	$Pd(OAc)_2$	10	XPhos	EtOAc	<5
7	$Pd(OAc)_2$	10	DPEPhos	EtOAc	<5
8	$Pd(OAc)_2$	10	XantPhos	EtOAc	<5
9	$Pd(OAc)_2$	10	dppbz	EtOAc	<5
10	$Pd(OAc)_2$	10	**$P(2\text{-Fu})_3$**	**EtOAc**	**77**
11[a]	$Pd(OAc)_2$	10	$P(2\text{-Fu})_3$	EtOAc	<5[b]
12[c]	$Pd(OAc)_2$	10	$P(2\text{-Fu})_3$	EtOAc	<5

[a]no Et_3N; [b]rapid decomposition of **3a** detected by TLC at low conversion; [c]no Ag_2CO_3.

Exploration of palladium catalysts for the arylation of NHPI-DA (**1h**) revealed that $[Pd(PPh_3)_4]$, the only catalyst known for the arylation of conventional diazocompounds,[11] proved unsuitable in this case (Table 1, entries 1,2). We found that other Pd(0) pre-catalysts based on phosphines and NHCs as ligands also lead to extensive decomposition of **1h** (see Table S1).[10-11] We observed that its degradation is slower in ethyl acetate (entry 3), and hypothesized that Pd(0) pre-catalysts were incompatible with the redox-active diazocompound.[10-11] Although most ligands were unsuitable using Pd(II)-sources (entries 4-9, see Table S2 for details), we discovered that the simple tris-(2-furyl)phosphine – $P(2\text{-Fu})_3$ – is singular at promoting this coupling in high yield (entry 10). This is likely the result of its strong binding to Pd(0) and weak coordination to Pd(II).[12] The Et_3N additive, which is common in previous arylations of diazocompounds,[10] prevents the rapid decomposition of **3a** (entry 11), and Ag_2CO_3 is required as iodide scavenger (entry 12).

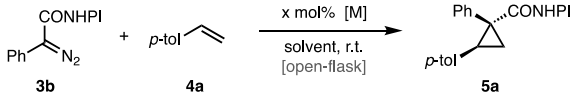
The C–H arylation conditions for the redox-active diazoacetate **1h** can be applied in a wide range of arenes and heteroarenes (Scheme 2). In the aryl iodide, neutral substituents (**3b,c**) and the complete halogen series (**3d-g**) were included with total chemoselectivity, including the monoarylation of 1,4-diiodobenzene (**3g**). Various electron-poor substituents (**3h-l**) with particular emphasis on distinct carbonyl derivatives (**3j-l**) could be seamlessly installed. The alkyne in **3m** allows for further diversification and click reactions. Unfortunately, diazocompounds with electron-rich functions in the 4-position proved to be unstable. However, strong electron-donors are suitable in the 3-position (**3n-r**), as well as fluorinated groups (**3s,t**), and functionalized aliphatics (**3u-x**) containing alcohol (**3v**), nitrile (**3w**), and aldehyde derivatives (**3x**). Interestingly, activated alkene (**3y**), phenol (**3n**) and aniline (**3q**) functions prove to be orthogonal to the redox-active diazocompound. Also, unprotected π-deficient (**3z**), and even π-excessive (**3aa**) heterocycles engaged in the cross-coupling. Importantly, this reaction can be utilized in the late-stage modification of biomolecules and their conjugates. For example, we could obtain the redox-active diazocompound derived from iodophenylalanine (**3ab**) in high enantiomeric purity. Moreover, peptide and steroid conjugates (**3ac,ad**) could also be functionalized with the potent redox-active diazoacetate moiety to enable further coupling reactions. This adds to the value of these compounds in medicinal chemistry particularly to construct fluorinated scaffolds (**3d,i,s,t**).



Scheme 2. Scope of the C–H arylation of NHPI-DA (**1h**).

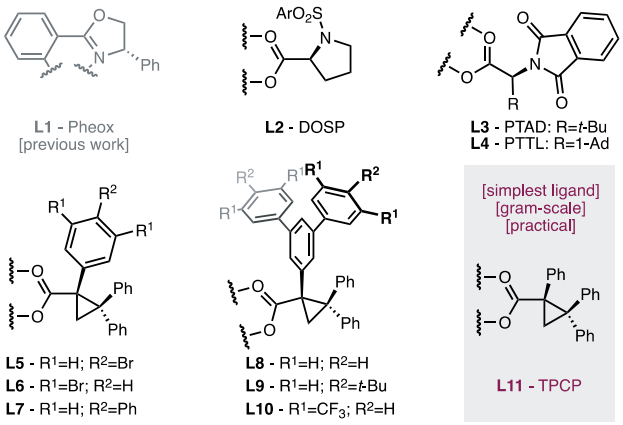
Unfortunately, the cyclopropanation of styrene **4a** with diazocompound **3b** using privileged cyclopropanation catalysts based on ruthenium and rhodium lead to only low yields and/or enantioselectivities (Table 2, entries 1-4).[13] Moderate activity and enantioselectivity was observed using Davies' rhodium catalyst with the cyclopropane carboxylate ligand **L5** (entry 5).[13c] It was discovered that the enantioselectivity is significantly higher in ethyl acetate (entries 4,5, see Table S4 for details). This result is remarkable in the context of carbene transfer reactions, in which solvents of lower polarity such as CH_2Cl_2 or pentane are commonplace.[13-14] However, more evolved catalysts in the same ligand series (**L6-L10**)[4c-h] displayed variable efficiencies and lower enantioselectivities (entries 7-11). We reasoned that a catalyst with a more open and flexible environment could be more suited to accommodate the bulkier redox-active carbene derived from **3b**. To our delight, the simplest catalyst in this series 1,2,2-triphenylcyclopropane carboxylate (**L11**),[15] provided quantitative yield and the highest enantioselectivity (entry 12), even with as low as 0.5 mol% loading and without inert atmosphere (entry 13). Remarkably, **L11** has never been reported to be effective in asymmetric cyclopropanation,[13a, 13b] and is known to produce less efficient and stereoselective catalysts than **L5-L10** in other reactions.[16]

Table 2. Optimization of the enantioselective cyclopropanation with redox-active aryl-diazocompounds **3**.



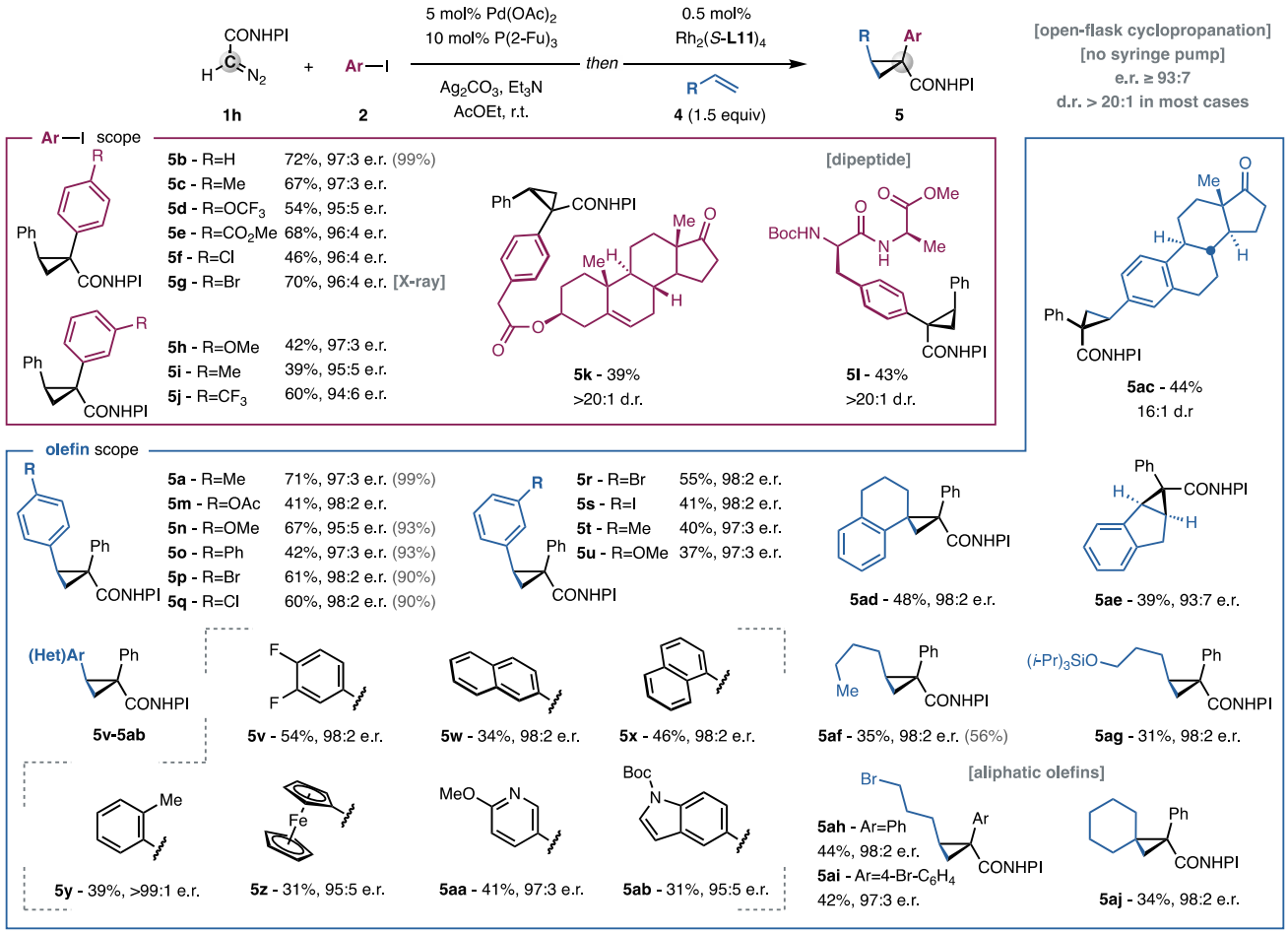
3b **4a** **5a**

#	x (mol%)	[M]	solvent	**5a** (%)	d.r.	ee (%)
1	1	[Ru(**L1**)(MeCN)$_4$]PF$_6$	DCM	–	–	–
2	1	Rh$_2$(*R*-**L2**)$_4$	DCM	58	>20:1	8
3	1	Rh$_2$(*R*-**L3**)$_4$	DCM	57	>20:1	7[a]
4	1	Rh$_2$(*R*-**L4**)$_4$	DCM	97	>20:1	17
5	1	Rh$_2$(*S*-**L5**)$_4$	DCM	76	>20:1	72[a]
6	1	Rh$_2$(*S*-**L5**)$_4$	EtOAc	65	>20:1	91[a]
7	1	Rh$_2$(*R*-**L6**)$_4$	EtOAc	64	>20:1	16
8	1	Rh$_2$(*R*-**L7**)$_4$	EtOAc	46	>20:1	77
9	1	Rh$_2$(*R*-**L8**)$_4$	EtOAc	99	>20:1	67
10	1	Rh$_2$(*R*-**L9**)$_4$	EtOAc	48	>20:1	88
11	1	Rh$_2$(*R*-**L10**)$_4$	EtOAc	51	>20:1	77
12	1	Rh$_2$(*R*-**L11**)$_4$	EtOAc	99	>20:1	94
13	**0.5**	**Rh$_2$(*R*-L11)$_4$**	**EtOAc**	**99**	**>20:1**	**94**[b]



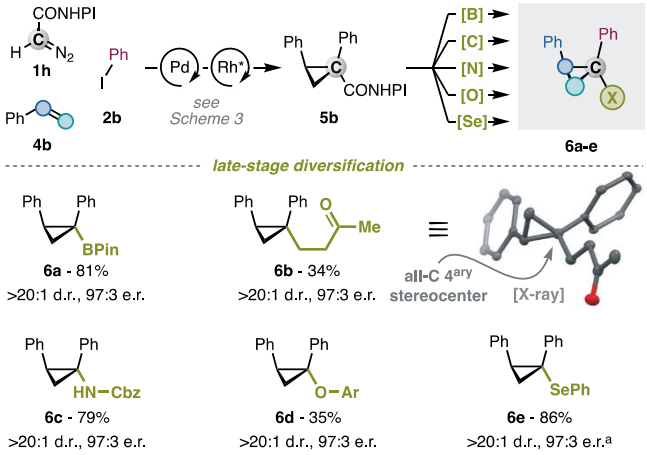
[a]opposite enantioselectivity; [b]yield, diastereo- and enantioselectivity was identical under an inert atmosphere of Ar.

A telescoped arylation-cyclopropanation protocol poses an additional challenge for the rhodium catalyst to maintain its turnover efficiency and enantioselectivity. Previous systems required the isolation of the aryldiazoacetate before the carbene transfer step,[10] and slow addition or inert atmosphere during the cyclopropanation reaction.[10c] To our delight, the simple Rh$_2$(*S*-**L11**)$_4$ allowed for cyclopropanation with the same enantioselectivity and without slow addition, after filtration of the cross-coupling mixture (Scheme 3). Without this filtration the cyclopropanation reaction does not occur. On the aryl iodide (**2**), the cyclopropanation can engage electron-rich (**5c,h,i**) and electron-poor (**5d-g,j**) aryl sources in good yields and high enantioselectivities. This includes medicinally-relevant fluorinated moieties (**5d,j**) and interesting handles that enable further manipulation of the products (**5e-g**), which can be incorporated in various positions in the aromatic ring. However, *ortho*-functionalized diazocompounds have proven to be particularly unstable.[17] The absolute configuration of compound **5g** was confirmed by X-ray diffraction.[18]



Scheme 3. Scope of the telescoped assembly of cyclopropanes from aryl iodides (**2**), olefins (**4**) and NHPI-DA (**1h**). In parenthesis, yield obtained using isolated **3** (identical e.r. was obtained). Diastereoselectivities have been determined by ^{1}H-NMR analysis of the reaction crude.

The chemoselectivity and functional group tolerance of both arylation and cyclopropanation enable the incorporation of biomolecules with complete stereocontrol. This way, steroids with a phenylacetate linker (**5k**), and the more polar dipeptide (**5l**) can be selectively arylated and cyclopropanated. On the olefin component (**4**), this process accommodates styrenes with electron-rich (**5a,m-o,t,u,w-y**) and electron-poor (**5p-s,v**) *m*- or *p*-substituents. High enantioselectivities are observed with the *o*-functionalized styrenes (**5x,y**). Moreover, interesting organometallic (**5z**), heterocyclic (**5aa,ab**), and stereoidal frameworks (**5ac**) of importance in non-linear optics and medicinal chemistry can engage in this process. The 1,1- and 1,2-disubstituted styrenes produce the corresponding enantioenriched cyclopropanes (**5ad,ae**), albeit with slightly lower enantioselectivity in the latter class. Aliphatic olefins are traditionally more challenging substrates in the context of asymmetric cyclopropanation reactions.[5, 19] However, we observe surprisingly high enantioselectivities using unactivated mono- (**5af-ai**) and disubstituted olefins (**5aj**), which can include halide (**5ah,ai**) and masked alcohol functions (**5ag**). The high enantioselectivities obtained without isolation nor slow addition of the aryldiazoacetates (**3**) are remarkable, and seem to originate in the particular topology of the redox-active carbene intermediate.[5]



Scheme 4. Two-step enantioselective assembly of diverse cyclopropanes from a carbon-atom precursor. Diasteroselectivities determined by ^{1}H-NMR analysis of the reaction crude; [a]Relative stereochemistry could not be confirmed. Conditions (see SI for details): *[B]* B_2cat_2, blue LEDs, *then* pinacol, Et_3N, r.t.; *[C]* Methyl vinyl ketone, Et_3N, Eosin Y cat., blue LEDs, r.t.; *[N]* NaN_3, HCl, r.t., *then* 90 °C, *then* BnOH, 90 °C; *[O]* 2-Methoxyphenol, Ir(III) cat., Cu(I) cat., Et_3N, blue LEDs, r.t.; *[Se]* $(PhSe)_2$, Hantzsch ester, Et_3N, Ru cat., blue LEDs, r.t.; Cbz, benzyloxycarbonyl; Ar, 2-methoxyphenyl.

The highly enantioenriched cyclopropane product **5b** now accessible through assembly of NHPI-DA (**1h**), iodobenzene (**2b**) and styrene (**4b**), was used to demonstrate the unified approach towards densely functionalized cyclopropanes **6** (Scheme 4). Decarboxylative borylation proceeded efficiently to provide highly enantioenriched cyclopropylboronate **6a**, which required three-steps before to be obtained as a racemate using existing diborylmethane (**1d**; Scheme 1) functionalization methods.[4i] Radical Giese-type addition delivers the all-carbon quaternary enantiopure cyclopropane **6b**, whose absolute configuration was confirmed by X-ray crystallography.[18] Our direct Curtius protocol[5] can be used to obtain the congested cyclopropylamine **6c**, precursor of histone demethylase inhibitors.[20] The chiral cyclopropylether **6d** can be obtained[21] avoiding routes involving unstable 1-arylcyclopropanol intermediates. Likewise, a versatile selenyl unit can be introduced (**6e**) to drive downstream radical and polar reactions.

To summarize, two catalytic systems have been developed for the synthesis and asymmetric cyclopropanation of redox-active aryldiazoesters. It has been found that these reactions can be combined in the telescoped assembly of arylcyclopropanes from abundant iodoarenes and olefins of relevance in biomolecules, heterocycles, and organometallics. The enantioselective carbene transfer of redox-active aryldiazoesters requires only a simple catalyst, and opens the door for further developments with push-pull redox-active diazocompounds. Late-stage decarboxylative coupling reactions deliver distinct chiral products with identical enantiomeric excess. These results demonstrate the viability of unified synthetic strategies towards ubiquitous carbon stereocenters using orthogonal and stereoselective manipulations of programmable carbon-atom precursors.

AUTHOR INFORMATION

Corresponding Author

* E-mail: abraham.mendoza@su.se

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)
Crystallographic information files (CIF)

Raw data for this article can be downloaded from Zenodo DOI: 10.5281/zenodo.3350527

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18. CCDC 1909222 (**5g**), and 1909223 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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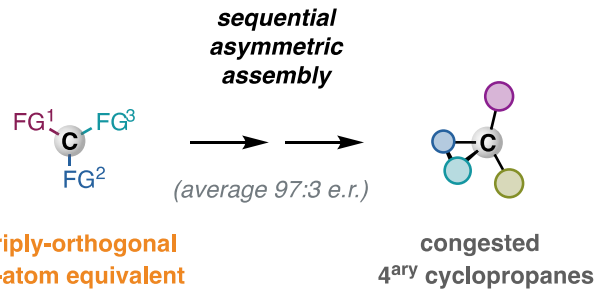
sequential
asymmetric
assembly
FG1
FG3
C
FG2
(average 97:3 e.r.)
C
triply-orthogonal
C-atom equivalent
congested
4ary cyclopropanes