Scaffold Diversity

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Sequential Transformations to Access Polycyclic Chemotypes: Asymmetric Crotylation and Metal Carbenoid Reactions**

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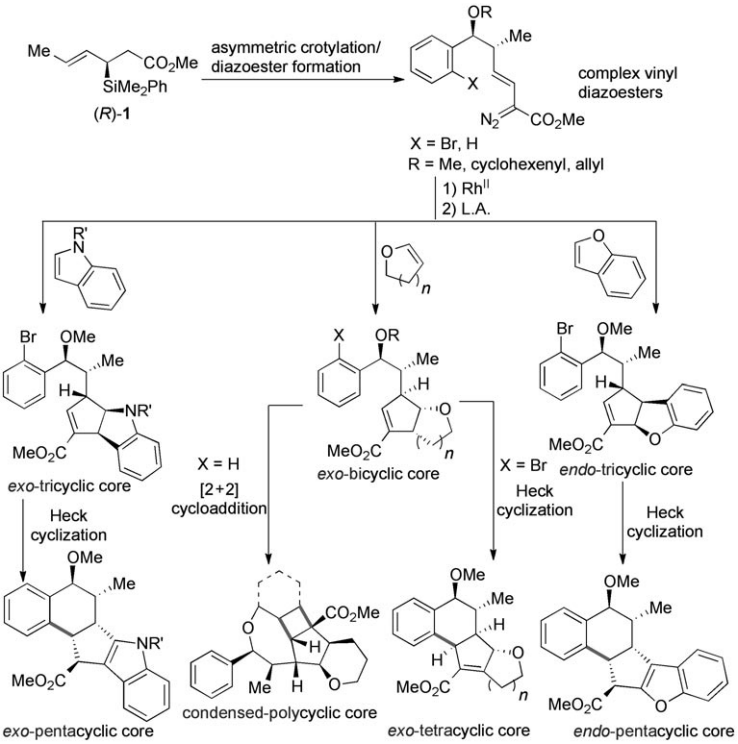
The development of sequential, asymmetric transformations can provide rapid access to novel molecules with a high degree of skeletal and stereochemical diversity.[1] However, efficient control of the regio- and stereoselectivity during each step remains a significant challenge.[2] In this regard, stereochemically well-defined building blocks obtained from our organosilane-based enantioselective crotylation methodology[3] have been successfully employed for the preparation of libraries of complex molecules.[4] We anticipated that the sequential use of the organosilane methodology with the rhodium(II)-catalyzed asymmetric cyclopropanation[5] would produce stereochemically well-defined cyclopentene compounds with unprecedented structural complexity. In the context of diversity-oriented synthesis (DOS),[6,7] these materials would in turn retain additional reaction sites for "functional-group pairing"[8] to enable further enhancement in the complexity of the polycyclic frameworks (Scheme 1).



Scheme 1. Skeletal and stereochemical variation by sequential asymmetric transformations. L.A. = Lewis acid.

The decomposition of unbranched vinyl diazoesters in the presence of a rhodium catalyst and an appropriate olefin donor has been extensively explored.[9] However, reports of the use of more complex diazoesters that have branching at the positions α and β to the vinyl group are less common.[4c] In this context, we envisioned that organosilane-based crotylation products would be ideally suited for the synthesis of complex diazoesters, and could thus potentially expand the scope of asymmetric transformations that utilize vinyl diazoester intermediates. Accordingly, our study was initiated with a three-component enantioselective crotylation[3] using silanes (*R*)-**1** and (*S*)-**1**, and a subsequent diazotization to afford complex α-diazoesters **2** in high stereoselectivity. Both bromoaryl (**2a**, **2b**; Scheme 2) and allyl ether functionalities (**2c**, **2d**), both of which are necessary for further ring construction at a later stage, were readily introduced using this methodology.

With the complex vinyl diazoester building blocks **2** available in useful amounts, the asymmetric synthesis of vinyl cyclopropanes was conducted using the cyclic vinyl ethers 2,3-dihydrofuran and 2,3-dihydropyran (Table 1). The reactions generally proceeded in good yields, and the diastereoselectivity was dependent on the structure of the carbenoid and the configuration of the metal catalyst. Unsurprisingly, the cyclopropanations exhibited varying levels of selectivity, which resulted from the combination of the chiral rhodium catalyst and diastereomeric α-diazoester. For instance, vinyl diazoester **2a**, which is derived from silane (*R*)-**1**, exhibited good diastereoselectivity with [Rh_2{(*S*)-dosp}$_4$], but low selectivity with [Rh_2{(*R*)-dosp}$_4$] (Table 1, entries 1 and 3). In contrast,

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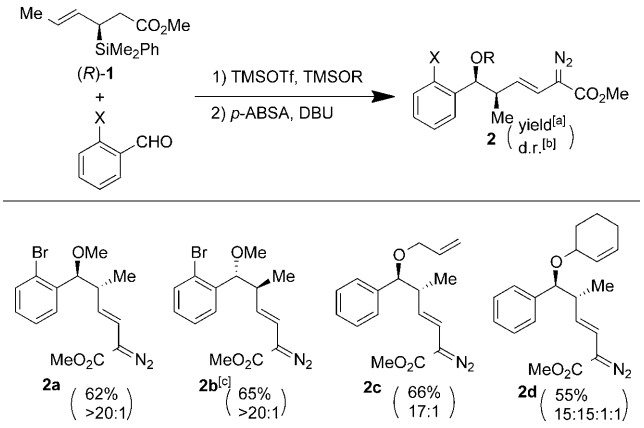
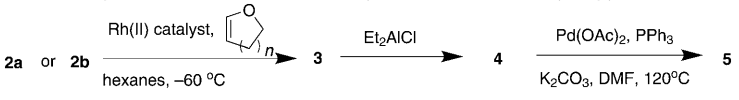
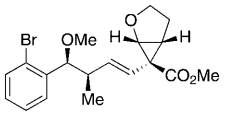
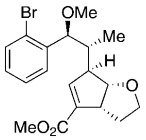
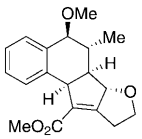
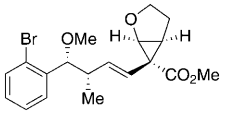
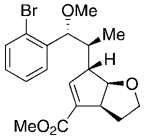
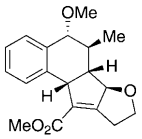
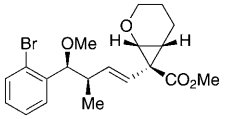
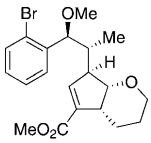
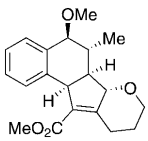
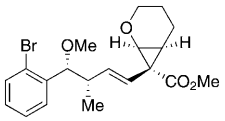
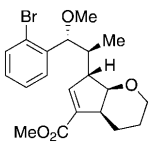
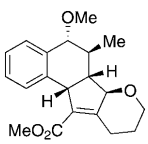


Scheme 2. Preparation of the complex diazoester **2** from (*R*)-**1**.
[a] Yield over two steps after column chromatography on silica gel.
[b] The d.r. is based on ^{1}H NMR analysis of the crude reaction mixture.
[c] The opposite enantiomer was obtained with (*S*)-**1**. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, *p*-ABSA = *para*-acetamidobenzene sulfonyl azide, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Table 1: Sequential reactions with 2,3-dihydrofuran and 2,3-dihydropyran.[a,b]



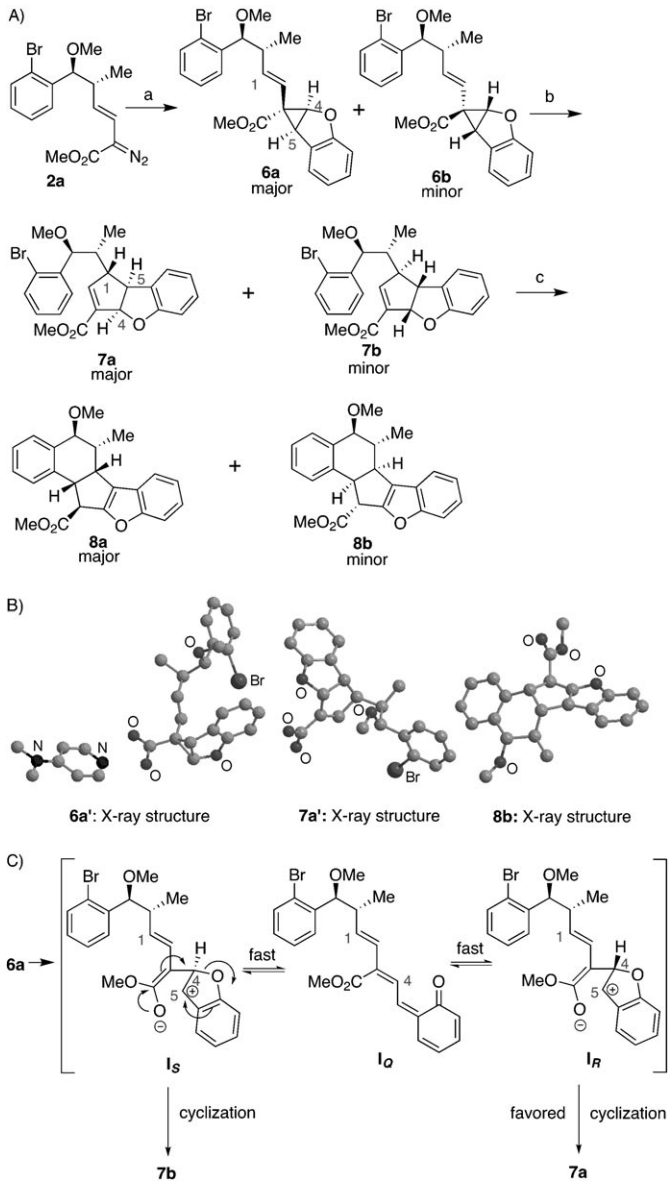
Entry	2	Product 3 (Yield [%], d.r.)[c]	Product 4 (Yield [%], d.r.)[c]	Product 5 (Yield [%], d.r.)[c]
				
1	**2a**	**3a** [Rh$_2${(*R*)-dosp}$_4$] (70, 1:1.2) [Rh$_2${(*S*)-dosp}$_4$] (73, 3.5:1)	**4a** (77, 3.2:1)	**5a** (75, 3.2:1)
				
2	**2b**	**3b** [Rh$_2${(*R*)-dosp}$_4$] (73, 3.3:1) [Rh$_2${(*S*)-dosp}$_4$] (73, 1:1.5)	**4b** (75, 3.2:1)	**5b** (77, 3.1:1)
				
3	**2a**	**3c** [Rh$_2${(*R*)-dosp}$_4$] (75, 1.1:1) [Rh$_2${(*S*)-dosp}$_4$] (77, 7.1:1)	**4c** (80, 6.8:1)	**5c** (72, 6.2:1)
				
4	**2b**	**3d** [Rh$_2${(*R*)-dosp}$_4$] (80, 7.3:1) [Rh$_2${(*S*)-dosp}$_4$] (75, 1:1.2)	**4d** (81, 6.8:1)	**5d** (70, 6.7:1)

[a] For detailed reaction conditions see the Supporting Information. [b] The major diastereomer is shown. [c] The yield is of the isolated product, and the d.r. is based on ^{1}H NMR analysis of the crude reaction mixture. DMF = *N*,*N*′-dimethylformamide, dosp = *N*-dodecylbenzenesulfonylprolinate.

diazoester **2b**, which is prepared from silane (*S*)-**1**, afforded products with good levels of selectivity only with [Rh$_2${(*R*)-dosp}$_4$] (entries 2 and 4). Treatment of cyclopropane products **3** with Et_2AlCl provided the rearranged cyclopentenes **4** with a minimal loss of selectivity.[10]

Additional skeletal variation was achieved by diversification of the products from the vinyl cyclopropane rearrangement through a Heck cyclization, which afforded tetracyclic products **5**. The stereochemical course of the reaction indicated that the insertion of the arylpalladium intermediate occurred from the convex face of the bicyclic framework. Subsequent elimination involved the only available *syn* hydride.[11] At this point, careful separation allowed the isolation of the individual diastereomers, and the structural conformation was determined by X-ray crystal structure analysis.[11] The configuration of the new stereocenters in the Heck-cyclization products **5** was the result of the diastereomeric preference in the rhodium-catalyzed cyclopropanation. Combined with NOE analysis, these studies allowed assignment of the stereochemistry of the major and minor diastereomers of each precursor. The stereoselectivity observed in the cyclopropanation of **2a** was in agreement with the predictive model for the asymmetric induction of the simpler vinyl diazoesters using [Rh$_2$(dosp)$_4$].[5b]

Cyclopropanation of **2a** using [Rh$_2${(*S*)-dosp}$_4$] in the presence of benzofuran provided cyclopropa[*b*]-benzofuran **6** with 8.5:1 diastereoselectivity (Scheme 3A). Treatment of **6** with $AlCl_3$ (1.1 equiv) led to the rearrangement product **7** with a slightly lower selectivity. Careful analysis of the NOE and HMBC spectra for **7**[11] suggested that both the major and minor rearranged products possessed an *endo* configuration. The Heck cyclization afforded the more thermodynamically stable product **8**, in which the double bond was isomerized to give a conjugated system. The absolute stereochemistry of compounds **6a**, **7a**, **8a**, and **8b** was confirmed by NOE measurements and X-ray crystal structure analysis (Scheme 3B).[12] As previously reported, the major cyclopropanation products were derived from the initial bond formation at C4 of the benzofuran with diazoester **2a**.[5c] Interestingly, the C4 and C5 stereocenters of adduct **6a** were both reversed during the rearrangement step; this is in contrast to the racemized products obtained with simple vinyl diazoesters.[5b] To probe the mechanistic pathway for the rearrangement, a control experiment was conducted using a 1:1 mixture of diastereomers **6a** and **6b**. Surprisingly, compound **7** was obtained with 6:1 diastereoselectivity, with **7a** as the major product. We propose that, after the cyclopropane ring opening promoted by a Lewis acid, the resulting zwitterionic intermediate $\mathbf{I}_S$ may undergo rapid and reversible equilibration with the highly conjugated quinone intermediate $\mathbf{I}_Q$. In this manner, the C4 stereocenter may epimerize through both $\mathbf{I}_S$ and $\mathbf{I}_R$ (Scheme 3C). To understand the stereochemical outcome, we performed computational analyses



Scheme 3. A) Sequential reactions with benzofuran: a) $[Rh_2\{(S)\text{-dosp}\}_4]$, benzofuran, toluene, −40 °C, 55 %, d.r. = 8.5:1; b) $AlCl_3$, CH_2Cl_2, −20 °C, 82 %, d.r. = 6:1; c) $Pd(OAc)_2$, tri-*o*-tolylphosphine, K_2CO_3, DMF, 120 °C, 65 %, d.r. = 6:1. For detailed reaction conditions see the Supporting Information. B) Stereochemistry assigned by X-ray crystal structure analysis. C) Possible mechanism for the rearrangement.

(B3LYP/3-21G*) of the proposed equilibrating zwitterionic intermediates $\mathbf{I}_S$ and $\mathbf{I}_R$ (Figure 1). DFT structural optimization of the ground-state conformer of the zwitterionic intermediate $\mathbf{I}_S$ indicated that the enolate anion and the C5 carbocation may have an n→p interaction to delocalise the positive charge. Through this interaction, the C5 carbocation may take on partial sp^3 character, thus rendering $\mathbf{I}_S$ less reactive toward the C1–C5 cyclization. Moreover, the C1–C5 distance for $\mathbf{I}_R$ (3.23 Å) should be advantageous for cyclization in comparison to $\mathbf{I}_S$ (4.55 Å), thereby favoring production of the major product **7a**.

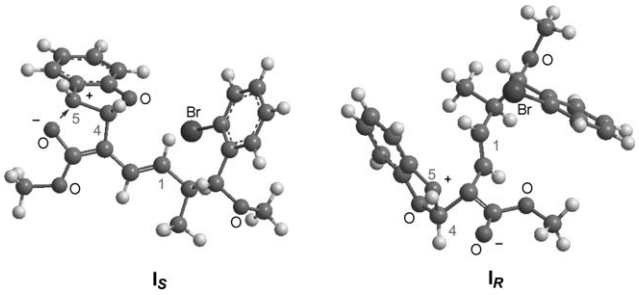


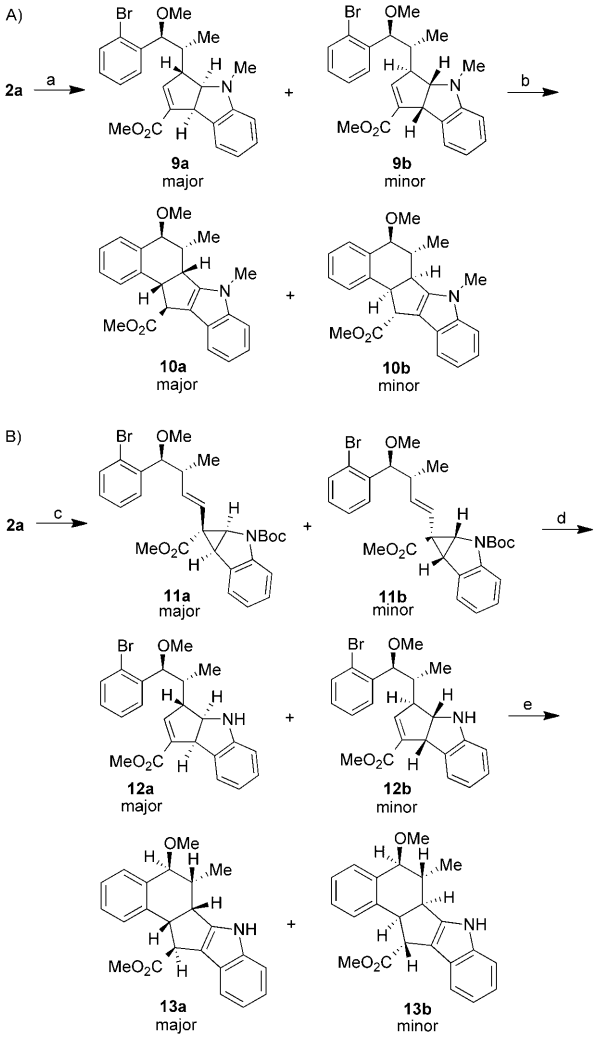
Figure 1. DFT ground-state conformers for zwitterionic intermediates en route to **7**.

The $[Rh_2\{(S)\text{-dosp}\}_4]$-catalyzed reaction of **2a** with the electron-rich heterocycle *N*-methylindole resulted in the production of the [3+2] cycloaddition products **9** and no cyclopropane products were detected (Scheme 4 A). However, in contrast to the mixtures of *exo* and *endo* products, which were observed for the simpler substrate,[5d] **2a** only afforded the *exo* product **9** (d.r. = 4.2:1) along with small amounts of alkylation by-products.[11] The Heck cyclization afforded the more thermodynamically stable product **10**. The absolute conformation of the major and minor diastereomers of **10** was confirmed by X-ray crystal structure analysis and 2D NMR measurements.[11,12] The absolute stereochemistry of the major diastereomer obtained from the rhodium(II)-promoted [3+2] cycloaddition was in agreement with the reactions previously reported for the unbranched vinyl diazoesters.[5d]

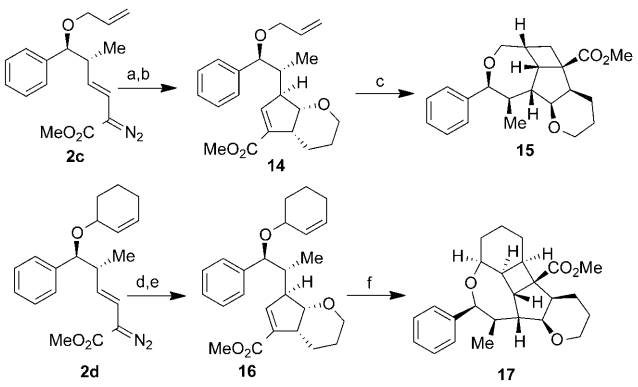
In contrast to the reaction with *N*-methylindole, the incorporation of an electron-withdrawing Boc group on the indole nitrogen atom may reduce the formation of the zwitterionic intermediates, thereby allowing the isolation of the cyclopropane products **11a** and **11b** (4:1 ratio of diastereomers) when promoted by $[Rh_2\{(S)\text{-dosp}\}_4]$ (Scheme 4 B). Subsequent treatment with Et_2AlCl afforded the rearranged products **12a** and **12b** as a 3:1 mixture within 40 minutes, with accompanying removal of the Boc group .[13] The relative configurations of **13a** and **13b**, which were obtained from the Heck cyclization, were confirmed by 2D NMR measurements.[11,14] Notably, the pentacyclic indoles **13** had the same configuration as the *N*-methylindole sequential-reaction products **10**.

To explore further skeletal diversification, we anticipated that an intramolecular [2+2] cycloaddition between the unsaturated ester group in the rearranged cyclopentene moiety and the allyl ether incorporated from the crotylation would offer convenient access to novel fused-ring systems, which have unique three-dimensional architectures (Scheme 5). Cycloaddition precursors **14** and **16** were prepared using a similar sequence to that used for cyclopentene **4**. The $[Rh_2\{(S)\text{-dosp}\}_4]$-promoted asymmetric cyclopropanation between vinyl diazoacetate **2c** or **2d** and 2,3-dihydropyran, followed by the Et_2AlCl-catalyzed vinyl cyclopropane rearrangement, furnished cyclopentenes **14** and **16** in good yield and diastereoselectivity.

Although [2+2] enone–olefin photochemical reactions are well studied in both the inter- and intramolecular



Scheme 4. A) Sequential reactions with *N*-methylindole: a) $[Rh_2\{(S)\text{-dosp}\}_4]$, *N*-methylindole, hexanes, CH_2Cl_2, −40 °C, 65 %, d.r. = 4.2:1; b) $Pd(OAc)_2$, tri-*o*-tolylphosphine, K_2CO_3, DMF, 120 °C, 60 %, d.r. = 4:1. B) Sequential reactions with *N*-Boc indole: c) $[Rh_2\{(S)\text{-dosp}\}_4]$, 1-Boc-indole, hexanes, −50 °C, 53 %, d.r. = 4:1; d) Et_2AlCl, CH_2Cl_2, 45 %, d.r. = 3:1; e) $Pd(OAc)_2$, tri-*o*-tolylphosphine, K_2CO_3, DMF, 120 °C, 52 %, d.r. = 3:1. For detailed reaction conditions see the Supporting Information. Boc = *tert*-butoxycarbonyl.



Scheme 5. Preparation of polycyclic chemotypes using [2+2] cycloaddition. a) $[Rh_2\{(S)\text{-dosp}\}_4]$, 2,3-dihydropyran, hexanes, −50 °C; b) Et_2AlCl, CH_2Cl_2, two step 58 % yield, d.r. = 9:1; c) *hν*, pyrex tube, quartz filter, benzene/acetone (3:1), 60 %, d.r. = 9:1; d) $[Rh_2\{(S)\text{-dosp}\}_4]$, 2,3-dihydropyran, hexanes, −50 °C, 63 %, d.r. = 6:6:1:1; e) Et_2AlCl, CH_2Cl_2, 80 %, d.r. = 5:5:1:1; f) *hν*, pyrex tube, quartz filter, benzene/acetone (3:1), 20–30 %, single diastereomer. For detailed reaction conditions see the Supporting Information.

variants,[15] there are few examples of the [2+2] cyclization between α,β-unsaturated esters and isolated olefins.[16] The [2+2] cycloaddition of cyclopentene **14** proceeded smoothly to afford tetracyclic product **15** when irradiated through a quartz UV filter with benzene/acetone (3:1) as the solvent.[17] NOESY NMR measurements indicated that the product possessed a *cis-syn-cis* structure.[11] We believed that the observed facial selectivity of the cycloaddition may be due to the terminal olefin approaching the unsaturated ester from the convex face of bicyclic precursor **14**. Treatment of compound **16** under the photocycloaddition reaction conditions afforded the fused-ring product **17** as a single diastereomer in 20–30 % yield. Notably, the cycloaddition precursor **16** contained two major diastereomers, which resulted from the utilization of either chiral or racemic cyclohex-2-enol; however, only the *S*-allylic ether participated in the photocycloaddition.[18] The stereochemistry of **17** was assigned by NOESY NMR experiments, which indicated that the cycloaddition occurred from the convex face of the bicyclic framework in a similar manner as **15**. Overall, the photocycloaddition incorporates extended substituents for further diversification and illustrates the effective final pairing of the functionality installed by both of the asymmetric operations (crotylation and cyclopropanation/rearrangement) of the reaction sequence.

In summary, we have demonstrated the utility of sequential asymmetric processes utilizing organosilane-based crotylation followed by a rhodium(II)-catalyzed asymmetric carbenoid transformation, thereby enabling a significant extension of the substrate scope of vinyl diazoacetates. Diastereomeric rhodium carbenoids exhibited good to moderate levels of selectivity in the cyclopropanation, while a substrate-dependent *endo*/*exo* selectivity was observed with vinyl cyclopropane rearrangements. Further elaboration of the cyclopentene products through Heck cyclization and [2+2] photocycloaddition allowed for the effective pairing of functional groups installed in the sequential process, resulting in tetracyclic, pentacyclic, and condensed polycyclic chemotypes, which are not readily accessible by other methods. Each final compound was prepared in either four or five steps from silane (*R*)-**1** or (*S*)-**1**. A similarity search in PubChem (score ≥ 80 %)[19] of one structural type from this study, that is the pentacyclic indole framework of **13**, revealed a number of structures, including several indoloterpene alkaloid natural products with biological activity.[20] Biological evaluation of the polycyclic chemotypes from this study are currently underway and will be reported in due course.

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Keywords: carbenoids · cyclization · diastereoselectivity · diversity-oriented synthesis · sequential transformations

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[10] In a control reaction, a 1:1 mixture of diastereomers of **3c** afforded product **4c** as a 1:1 mixture of diastereomers.

[11] See the Supporting Information for complete mechanistic and conformational analyses and NOE measurements.

[12] X-ray crystal structure analysis was carried out on DMAP salt derivative **6a′** and acid derivative **7a′** and **10a′**. CCDC 808910 (**5a**), CCDC 809096 (diastereomer of **5a**), CCDC 809097 (diastereomer of **5c**), CCDC 809098 (**6a′**), CCDC 809099 (**7a′**), CCDC 809100 (**8b**), and CCDC 809101 (**10a′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] A possible mechanism for the partial racemization is provided in the Supporting Information.

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[18] Attempts to prepare enantioenriched **2d** were unsuccessful because of racemization of the allylic ether under the crotylation reaction conditions.

[19] A structural-similarity search of the framework **13** at $\geq 90\,\%$ threshold showed no hits. Structural similarity is measured using the Tanimoto equation and the PubChem. dictionary-based binary fingerprint (http://pubchem.ncbi.nlm.nih.gov/).

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