Efficient and stereodivergent synthesis of unsaturated acyclic fragments bearing contiguous stereogenic elements

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Abstract

Synthetic organic strategies that enable the catalytic and rapid assembly of a large array of organic compounds possessing multiple stereocenters in acyclic systems are somewhat rare, especially when it comes to reaching today's high standards of efficiency and selectivity. In particular, the catalytic preparation of a three-dimensional molecular layout of a simple acyclic hydrocarbon skeleton possessing several stereocenters from simple and readily available reagents still represents a vastly uncharted domain. Here, we report a rapid, modular, stereodivergent and diversity-oriented unified strategy to construct acyclic molecular frameworks bearing up to four contiguous and congested stereogenic elements, with remarkably high levels of stereocontrol and in only three catalytic steps from commercially available alkynes. A regio- and diastereoselective catalytic Heck migratory insertion reaction of alkenylcyclopropyl carbinols merging selective C–C bond cleavage of a cyclopropane represents the key step.

In light of many transformative advances, organic synthesis is expected to allow a chemist to create, prepare and investigate any organic molecule at will, regardless of its complexity. Despite the ever-increasing synthetic toolbox available to practitioners, the perfect "atomic scale manipulation of matter for the synthesis of anything and everything"[1] represents a never-ending and yet unmet challenge. Growing expectations to provide faster, more cost-efficient and highly selective transformations, however, sets a high bar for modern chemical synthesis[2–6]. Tending towards these ideals, research efforts have not only been focusing on

the development of newly diverse and more efficient methodologies, but also on expanding the realm of new possibilities through original conceptual advances. For instance, introducing the notion of chemical space in organic synthesis has spurred chemists to explore more efficiently all the potential structural and geometric isomers of a given scaffold[7]. Accordingly, the catalytic preparation of a three-dimensional molecular layout of a simple acyclic hydrocarbon skeleton possessing several stereocenters from simple and readily available reagents still represents a vastly uncharted domain (Fig. 1a).

Molecular complexity rapidly rises with the number of stereogenic elements, their degree of substitution and the additional presence of neighboring functional groups[8]. Although considerable progress has been made these last decades in stereoselective synthesis[9,10], general catalytic examples implemented for non-cyclic systems are still scarce, inherently due to the difficulty to discriminate between the different possible conformers of these flexible chains. Furthermore, the elaboration of congested systems adds another level of complexity as exemplified by the difficulty to selectively construct quaternary carbon stereocenters[11–15]. One ambitious task would entail selectively preparation of all possible isomers of a simple acyclic hydrocarbon motif featuring adjacent and congested stereogenic elements[16], by means of a unified assembly-line[17] approach concomitantly, allowing stereodivergency[18] and diverse functionalization[19–21]. An emerging approach to address concurrently the aforementioned issues involves taking advantage of the exergonic ring-opening reactions of strained cycles[22–26]. Cyclopropanes, diversely and readily accessible with high levels of enantio- and diastereocontrol[22,23,27,28], have been successfully utilized as precursors to stereodefined acyclic systems. Nonetheless, to ensure a selective outcome for such an approach concomitantly requires: (*i*) to control the selectivity of the C-C bond cleavage[29–35] and (*ii*) to prevent epimerization at the resulting released stereocenters during the transformation. On the basis of the utility of this latter strategy, we have previously developed sequential protocols, based on various metal-assisted and controlled ring-opening modes of strained carbocycles to access stereodefined acyclic hydrocarbon fragments that contain sp^2 and/or sp^3 carbon stereogenic element(s)[36–44].

As an example, we have been investigating the Pd-catalyzed Mizoroki–Heck intermolecular arylation of terminal olefins as a versatile and selective trigger for a remote cyclopropane unfolding event[44]. Despite the numerous chemical events that transpire, including critical long distance Pd-walk and selective Pd-assisted β-carbon fragmentation, the overall transformation was remarkably selective. Spurred by these central features, we set out to devise a strategy to address the highly challenging selective and stereodivergent preparation of a three-dimensional molecular layout with adjacent and congested stereogenic elements; importantly, this would be achieved in just three catalytic steps and involve readily available reagents (Fig. 1c). Herein, we disclose a unified, robust and modular approach for efficient synthesis of acyclic aldehydes, which are structurally complex and feature up to four contiguous congested stereogenic elements.

Results and Discussion

Straightforward and stereodivergent strategy for the synthesis of alkenylcyclopropyl carbinols

A unique attribute of our strategy is that the vinylcyclopropyl carbinol moiety is made to serve as temporal auxiliary for promoting high levels of stereochemical control[45]. Accordingly, we devised a step-economical, modular and highly stereoselective pathway for synthesis of compounds represented by **3** from simple and readily accessible alkynes by means of two catalytic processes. Alkenylcyclopropane motifs are found in various natural products and other biologically active compounds[46], and have been used in transition-metal catalyzed transformations leading to various desirable scaffolds[47]. Yet, there are just a limited number of diastereo- and enantioselective protocols for generating alkenylcyclopropanes with a quaternary carbon in a non-fused system[48]. Based on our recently acquired experience on the catalytic enantioselective 1,2-bisalkylation of cyclopropenes[49], we surmised that polysubstituted alkenylcyclopropyl carbinols **3** could be synthesized diastereo- and enantioselectively starting from a common cyclopropene precursor. Indeed, cyclopropenyl esters **1** may be accessed through Rh-catalyzed decomposition of diazoesters in the presence of terminal alkynes. Key to the success of our plan was that enantioselective versions of this [2+1] cycloaddition process have been reported (Fig. 2)[50]. Compounds of the general structure **1** were thus engaged in regio- and diastereoselective copper-catalyzed carbomagnesiation (with R^2MgBr), leading to stereodefined cyclopropyl Grignard reagents[51]. Subsequent to transmetalation, the *in situ* generated organozinc compounds were coupled with stereodefined alkenyl halides **2** (stereospecifically generated from their corresponding terminal alkynes either by *syn* hydrometalation or by carbometalation and halogenolysis; see the Supplementary Information) catalyzed by a phosphine–Pd complex in a medium of increased polarity (through addition of THF or DMF). Importantly, the sp^3-sp^2 Negishi-type cross-coupling involving two congested and stereodefined systems did not cause scrambling at the stereogenic carbon centers. Reduction of the ester moiety then provided the desired diastereomerically enriched alkenylcyclopropyl carbinols **3a-3v** in good overall yields (either pure *E* or *Z* olefins, dr   95:5:0:0 in all cases). Therefore, through this unified strategy, an assortment of bench-stable polysubstituted alkenylcyclopropanes **3** was prepared expeditiously, by a readily modifiable route, in high stereoisomeric purity, and on a multi-gram scale (see Figure 2).

Stereoselective Pd-catalyzed Heck arylation of alkenylcyclopropyl carbinols with aryl boronic acids

With a relatively straightforward and general method for preparation of **3** in hand, we focused on probing the feasibility of an ensuing Heck-type arylation process. Following a thorough optimization, we discovered that, similar to the findings reported by Sigman et al. [52,53], with an aerobic Pd(II)-based catalyst (derived from [Pd(OTs)$_2$(MeCN)$_2$] and Cu(OTf)$_2$) and 5-(2-pyridyl)-1,3-oxazole as the ligand (L), arylboronic acids may be coupled to **3**, affording aldehydes **4** with excellent selectivity (3Å molecular sieves, DMA, 55 °C; Fig. 3). The presence of this particular ligand was necessary for achieving higher yields as well as more selective aryl migratory insertion. Under these optimal conditions, (*Z*)-**3c** could

be converted to $(3R^*,6R^*)$-**4a** in 78% yield, as a single alkene isomer (E/Z>99:1), and with exceptional diastereoselectivity (d.r.>95:5); this latter transformation was diastereospecific as well, because $(3S^*,6R^*)$-**4b** and $(3S^*,6S^*)$-**4c** could be accessed with an nearly identical stereoisomeric purity by simply permuting the stereochemistry of the alkene in the corresponding starting materials (**3d** and **3e**, respectively). The relative 1,4-configuration of **4d** was determined by X-ray analysis of its 2,4-dinitrophenylhydrazone derivative **6a** (see the Supplementary Information). Other relative configurations were assigned by analogy. It is especially noteworthy that the transformation of **3g** was chemoselective, as the unsubstituted cyclopropane was preserved in product **4f**. Substituting the olefin with bulkier alkyl chains (secondary or tertiary) led to a slight decrease in diastereoselectivity (**4e**) and regioselectivity (**4g**). However, to our delight, substrates containing more electron-rich and bulkier trisubstituted olefins (**3o-v**) could be similarly converted – in a single chemical step and with remarkably high levels of 1,4-diastereocontrol – to products bearing a second acyclic quaternary stereocenter (**4p-ae**, Fig. 3c). Varying substrate substituent patterns (**3o**, **3p**, **3q** and **3s**) did not hamper yields and selectivities. The use of electron-rich arylboronic acids did not dramatically influence yields nor selectivities. Reactions with relatively electron-deficient arylboronic acids (**4l-n**, **4ab-4ae**) were typically sluggish, and those involving substrates bearing an ortho-substituent were inefficient (i.e., low conversion to **3**).

Next, we probed the reactivity of 1,1,2,2,3-pentasubstituted vinylcyclopropyl carbinols (R H), presenting an additional stereocenter (**3k-n** and **3s**). The presence of adjacent cyclopropyl quaternary stereocenters did not impact fragmentation selectivity, and, what is more, the same conditions led to the formation of the corresponding aldehydes without epimerization of the somewhat sensitive Cα stereogenic center (Fig. 3d). As before, aryl migratory insertion was diastereospecific (**4ag**, **4ah**). The relative stereochemistry of such 1,4,5-stereochemical triad was determined by X-ray crystallographic analysis of the 2,4-dinitrophenylhydrazone derivative (**6b**) of **4ah.** By engaging **3m**, we were able to access **4ak**, which features three tertiary stereocenters, including one that is rather labile (benzylic and α-to a carbonyl group), further illustrating the notably mild conditions and the excellent selectivity of the Pd-assisted carbon-carbon bond cleavage. Our findings clearly illustrate that these reaction conditions tolerate several potentially sensitive functional groups such as ethers (**4d**, **4v**, **4w–z**), halides (**4j**, **4l–n**, **4aa–4ad**), nitro (**4z**), ketone (**4o**) and ester moieties (**4ae**). Notably, this approach enabled us to fuse alkenylcyclopropyl carbinol **3e** with a steroid framework (derived from estrone), affording **4o** as a single alkene isomer (E) and in high diastereomeric ratio.

To assess further the stereodivergency of our approach, we decided to synthesize all possible stereoisomers of a three-dimensional molecular scaffold possessing adjacent and congested stereogenic centers by permuting the substitution pattern at the quaternary stereocenter and at the olefin (**3p**, **3t**, **3u**, **3v**). We were pleased to note that the exact similar protocol led us to access the corresponding four stereoisomers (respectively, **4p**, **4am**, **4an**, **4ao**) with remarkably comparable isolated yields and high stereoselectivities (Fig. 4). This set of experiments confirmed that the diastereoselective outcome was essentially dictated by the geometry of the original olefin moiety in **3** (either E or Z), independently of the nature at the other alkyl substituents (R^1, R^2, R^3 and R^4). Such results explicitly showed the exceptional

diastereodivergence and robustness of our strategy, as the different substituent groups could easily be permutated without affecting the stereoselective outcome of the key Pd-catalyzed aryl migratory insertion coupled with the selective carbon-carbon bond cleavage nor the *E/Z* ratio (see Fig. 4).

Stereoselective Pd-catalyzed Heck arylation of alkenylcyclopropyl carbinols with different nucleophiles

The present method is applicable to coupling reagents other than aryl boronic acids. For instance, by a similar protocol, the union of cyclohexenyl triflate or furanylboronic acid and **3c** was accomplished, affording **4ap** and **4aq**54. As demonstrated previously by the use of alkenyl alcohols55, Fujiwara-Moritani (or dehydrogenative Heck)56 reactions in the presence of *N*-methylindole could be performed to generate the desired heterocyclic compounds (e.g., **4ar** and **4as**) with exceptional selectivity (Fig. 5a). Few others heterocycles were tested in the dehydrogenative Heck reaction such as *N*-methyl pyrrole, 2-methylfurane and thiophene without any success.

Issues of mechanism

To account for the remarkably selective catalytic transformation of **3** into **4**, the following mechanism might be suggested (Fig. 5b). Based on the available experimental data, we postulate that the high diastereoselectivity with which **4** is generated might be due to the following factors: (*i*) The alkenylcyclopropyl carbinol adopting a conformation to minimize steric repulsion involving a sizeable alkyl chain (*s-trans* preferred to *s-cis* conformation in **3**). (*ii*) Chelation of $L_nPd(Ar)^+X^-$ species (**I**) with the hydroxyl and the alkenyl moieties, leading to a diastereoselective aryl migratory insertion (**II**). Such remarkable diastereofacial discrimination offers a plausible rationale for the complete diastereospecificity when various R^1, R^2, R^3 and R^4 units are involved (Fig. 4); in line with our hypothesis, selectivity depended largely on the initial geometry of the olefin moiety in **3**. The β-cyclopropyl organopalladium complex **II** would then undergo selective *syn* β-carbon elimination, furnishing **III** exclusively as an *E*-alkene isomer (cf. **4**). It therefore appears that selectivity in C–C bond cleavage is directly dependent on the presence of a chelating alcohol moiety, rather than as a consequence of substitution pattern at C_5 or C_6 (e.g., **4ak**). The final carbonyl complex **VI** is thus formed by subsequent chain walking within the organopalladium intermediate **III** (i.e., β-hydride elimination/re-insertion). Moreover, when R ≠ H, not only does the purported tertiary organopalladium compound seems to be configurationally stable, the hydride re-addition probably takes place on the same diastereoface (**V**); this is manifested by the finding that the overall process did not lead to epimerization of the tertiary stereocenter in **4af-al**. Furthermore, by means of a labeling experiment (**4al**, Fig. 3d), we are able to rule out the possibility of direct extrusion via the corresponding enol form (**IV**)57–61. Release of the carbonyl-containing product (**4**), containing up to three stereochemically defined sp^3–carbon sterogenic centers and an (*E*)-1,2-disubstituted alkene moiety, regenerates the Pd-based complex. There was no observable transformation when the corresponding methyl ether was used (vs. alcohol), underscoring the importance of rapid extrusion of the catalytically active Pd complex.

Conclusions

We have designed a strategy that entails a succession of highly stereoselective carbon–carbon forming reactions catalyzed by a transition metal complex. As such, complicated and otherwise difficult-to-access acyclic fragments may be prepared from simple and readily available reagents. We illustrate that various acyclic hydrocarbon motifs may be synthesized in a step-wise manner by the following chemo- and stereoselective C–C forming bond processes: Rh-catalyzed [2+1] cycloaddition, Cu-catalyzed carbomagnesiation/Pd-catalyzed cross-coupling followed by ester reduction, and regio- and diastereoselective Pd-catalyzed oxidative Heck migratory insertion to trigger selective unfolding of a cyclopropane intermediate (see Figs 2, 3 and 5). Notably, products bearing adjacent quaternary carbon stereogenic centers were synthesized from readily accessible terminal alkynes through just three catalytic reactions. The stereodivergence of this new approach was highlighted through preparation of four different stereoisomers of compounds that represent the same constitutional isomer (see Fig. 4). The investigations described above demonstrate that by judicious implementation of distinct transformations, carried out in a particular sequence, synthesis routes may be conceived that are of considerable utility, render streamlined access to previously unknown stereoisomeric motifs a realistic possibility.

Methods

General procedure for the Heck arylation of alkenylcyclopropyl carbinols with aryl boronic acids

In a dry one-neck flask under O_2 (balloon, 1 atm), 5-(2-pyridyl)-1,3-oxazole (9 mol%), [Pd(MeCN)$_2$(OTs)$_2$] (7.5 mol%), Cu(OTf)$_2$ (5 mol%), 3 Å molecular sieves (100% w/w substrate) and alkenylcyclopropyl carbinol **3** (1 equiv.) were dissolved in DMA (8 mL/mmol substrate). The arylboronic acid (3 equiv.) was then rapidly poured into the reactional mixture, which was allowed to stir for 18 h at 55 °C. After the reaction was judged to be complete, the mixture was diluted by the addition of brine and EtOAc. The phases were separated and the aqueous phase was successively washed three times with EtOAc. The combined organic phases were then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (gradient eluent 100% hexane to 5% Et$_2$O/hexane) afforded aldehyde **2**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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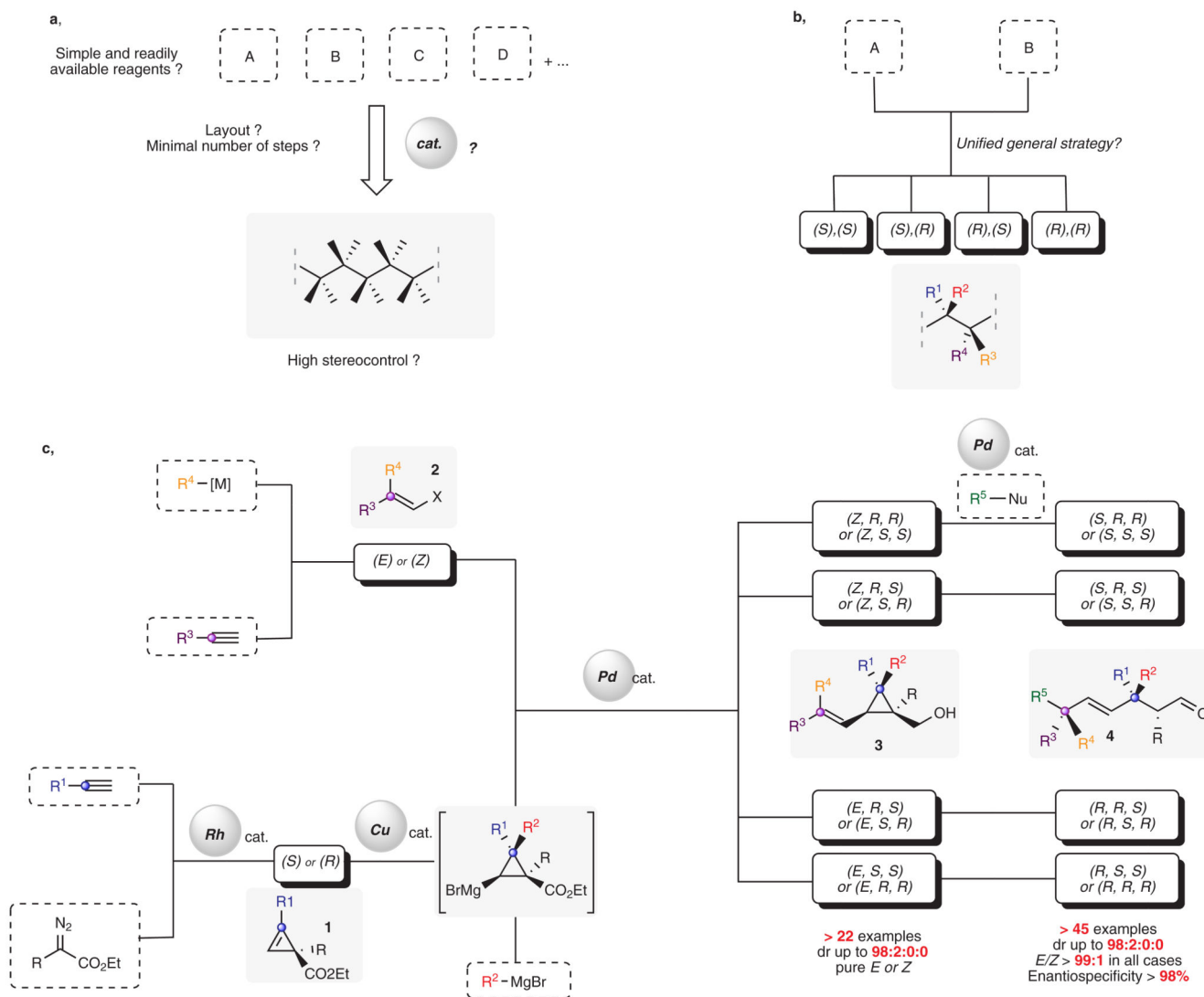
Figure 1. Challenges for easily diversifiable and stereoselective preparation of acyclic hydrocarbon motifs.

a, General synthetic challenges related to access stereodefined acyclic hydrocarbon fragments. **b**, Stereodivergent coupling of **A** and **B** to create 1,2-stereocenters. **c**, Our proposed synthetic approach consisting in three sequential catalytic steps to prepare aldehydes featuring up to four contiguous stereogenic elements, from readily available reagents.
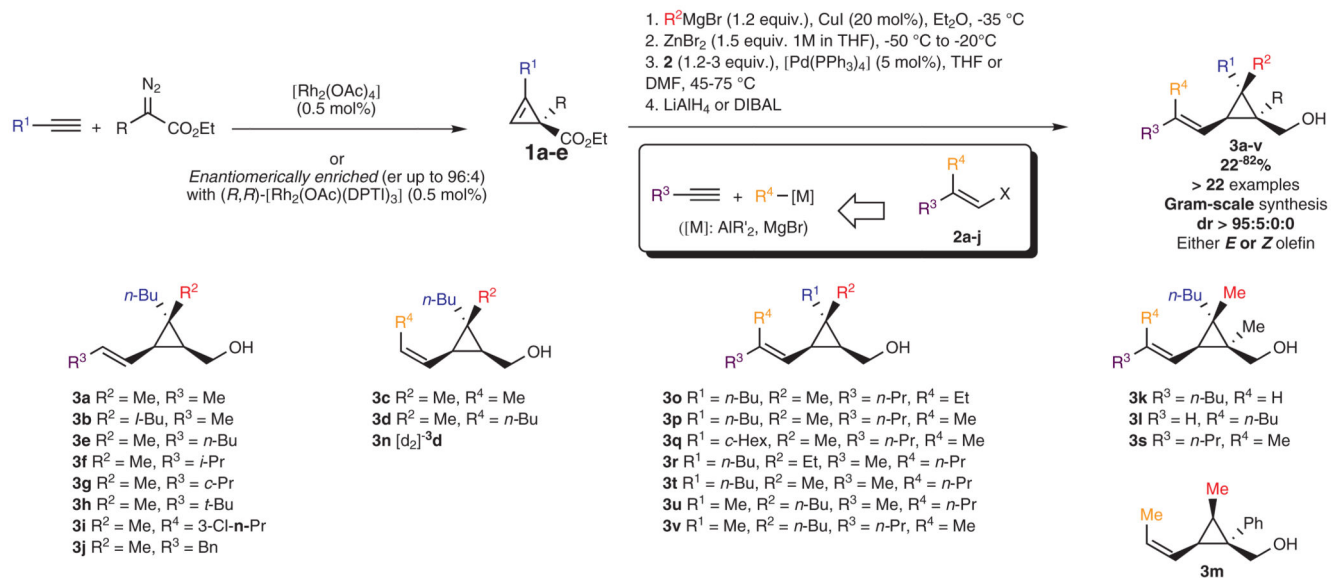
Figure 2. Stereoselective preparation of polysubstituted alkenylcyclopropyl carbinols 3a-v.
Catalytic carbenoid insertion into terminal alkynes enabled the synthesis of cyclopropenyl esters **1a-e**, either racemic or enantiomerically enriched for specific examples.50 Then, a diastereoselective copper-catalyzed carbomagnesiation afforded diastereomerically pure cyclopropylmagnesium halide compounds, which could be subjected to catalytic cross-coupling with alkenyl halides **2** (generated from terminal alkynes) to provide, after ester reduction, stereoisomerically enriched alkenylcylopropyl carbinol derivatives **3**.
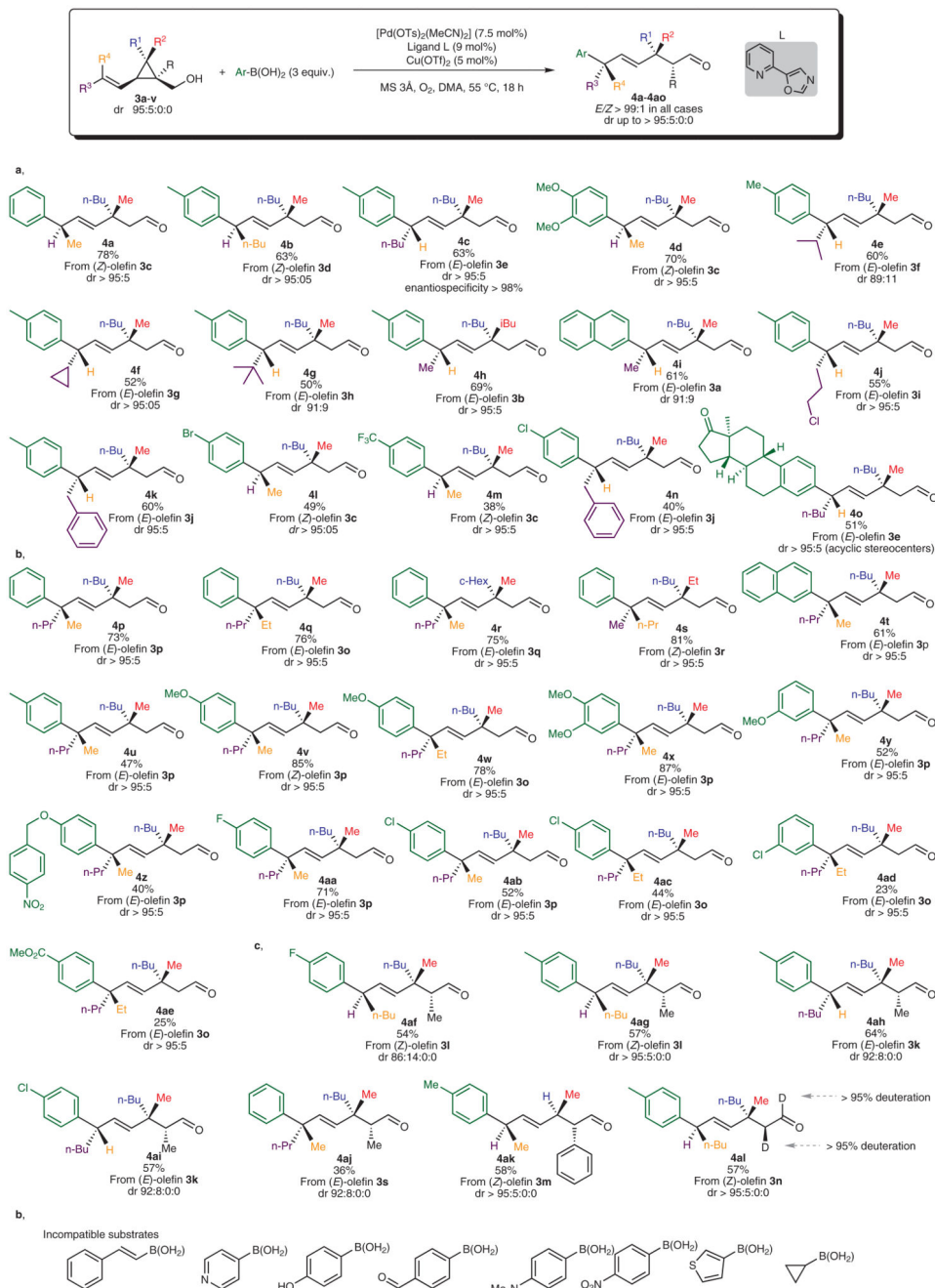
Figure 3. Oxidative Pd-catalyzed Heck coupling of aryl boronic acids with alkenylcyclopropyl carbinols.

a, Reactions were carried out on a 0.15 – 0.5 mmol scale. Yields were determined after silica gel chromatography. Diastereoisomeric and *E/Z* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures. **b**, Heck arylation of alkenylcyclopropanes bearing 1,2-disubstituted olefin moieties; these reactions provide access to stereodiads that contain a tertiary and a quaternary stereogenic center at a distance of four methylene units. **c,** Heck arylation of alkenylcyclopropanes bearing 1,1,2-trisubstituted olefin moieties; such

processes allow access to stereodiads with two quaternary stereogenic centers at a distance of four methylene units (we obtained **4t** by using 1.5 equiv. of the corresponding aryl boronic acid). **d**, When R   H, the transformation selectively afforded 1,4,5-stereotriads, without any observable epimerization at the tertiary stereocenter adjacent to the aldehyde moiety. **e**, Unsuccessful boronic acids tested. Tf: triflyl, *n*-Pr: *n*-propyl, *n*-Bu: *n*-butyl, *c*-Hex: cyclohexyl, *i*-Bu: *iso*-butyl, Ts: tosyl, DMA: *N,N*-dimethylacetamide.
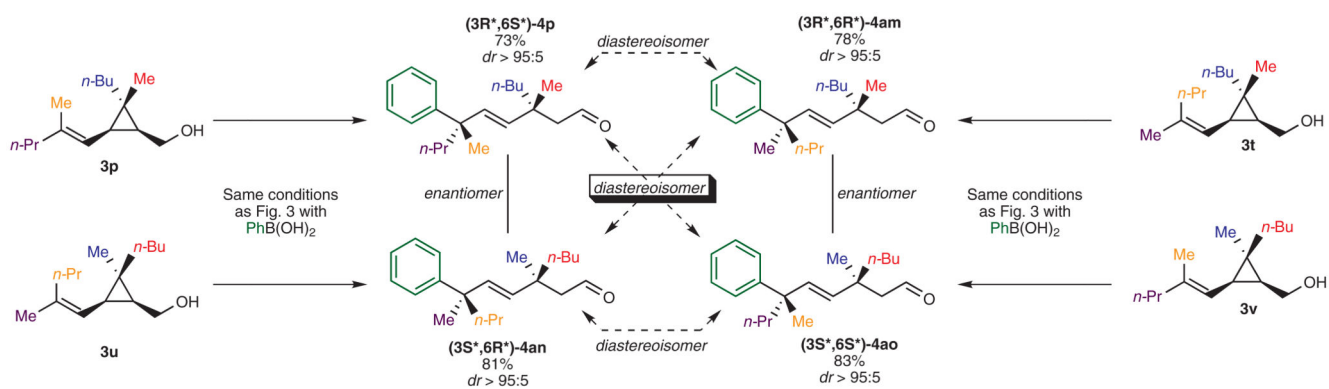
Figure 4. Stereodivergent and selective construction of four stereoisomers of a similar scaffold.
Reaction conditions employed were similar as in Fig. 3. Reactions were carried out on a 0.25 mmol scale. Yields were determined after silica gel chromatography. Diastereoisomeric and *E/Z* (>99:1) ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures. Ph: phenyl.
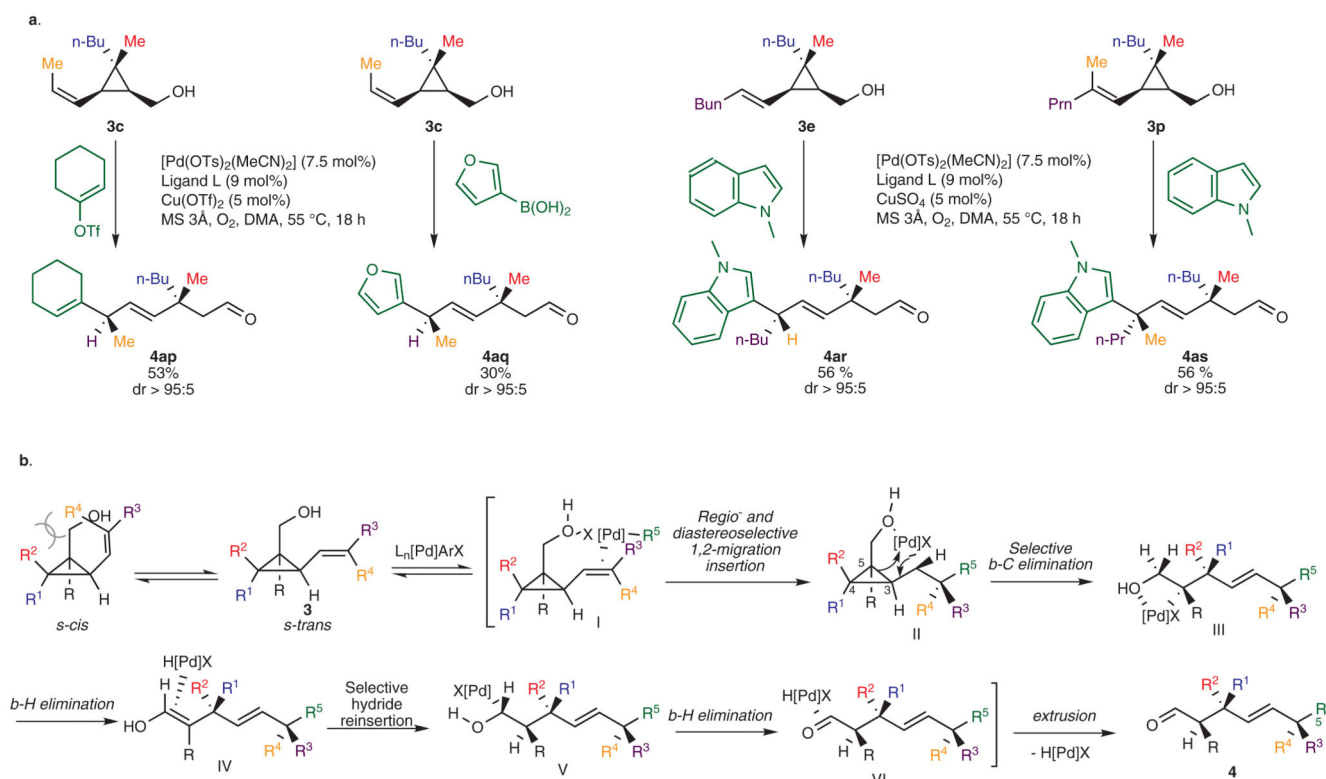
Figure 5. Oxidative Pd-catalyzed Heck coupling of other nucleophiles with alkenylcyclopropyl carbinols and proposed rationale regarding stereoselective migratory insertion.

a, Extension to other nucleophiles, reactions were carried out on 0.25 mmol scale. Yields were determined after silica gel chromatography. Diastereoisomeric and *E/Z* ratios (>99:1 in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures.
b, Proposed mechanistic model for Pd-catalyzed Heck regio- and diastereoselective aryl migratory insertion / selective *β*-carbon elimination. Ar: aryl, L$_n$: ligand, X: couterion.