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Development of a C–C Bond Cleavage/Vinylation/Mizoroki–Heck Cascade Reaction: Application to the Total Synthesis of 14- and 15-Hydroxypatchoulol

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Abstract

A C–C bond cleavage/vinylation/Mizoroki–Heck cascade reaction has been developed to provide access to densely functionalized bicyclo[2.2.2]octane frameworks. The sequence proceeds through the coupling of dihydroxylated pinene derivatives, prepared from carvone, with *gem*-dichloroalkenes. The method was applied to 12-step total syntheses of both 14- and 15-hydroxypatchoulol, which provided unambiguous support for the structure of the natural products and corrects a misassignment in the isolation report.

The combination of transition-metal-catalyzed C–C bond cleavage and cross-coupling reactions has been shown to be a powerful strategy for rapidly generating molecular complexity from simple building blocks.[1] When applied to total synthesis, such methods can underpin nonintuitive strategies to access various complex molecular frameworks in an expedient fashion.[2] Our group has previously explored the transition-metal-catalyzed C–C bond cleavage/cross-coupling reactions of dihydroxylated pinene derivatives (e.g., **1**, Figure 1A),[3] prepared from carvone, to provide functionalized cyclohexenone derivatives (see **1** → **3**).[4] The cyclohexenones thus obtained were further elaborated to bicyclo[3.3.1]nonane frameworks (e.g., **4**) using a radical cyclization approach, which enabled the total synthesis of xishacorene B.[4d] Overall, this strategy of “chiral pool” remodeling has enabled access

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Accession Codes

CCDC 2203888 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c09201

Supporting Information

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Experimental procedures and spectral data for all new compounds. (PDF)

to a unique chemical space starting from readily available, enantioenriched small molecules such as carvone.[5]

As part of our ongoing interest in the development of C–C bond cleavage/cross-coupling reactions and their application to total synthesis, we sought to access bicyclo[2.2.2]octanes (e.g., **7**, Figure 1B) in a single operation from cyclobutanol **1** and *gem*-dihaloalkene electrophiles (**5**).[6] These frameworks were expected to arise from cross-coupled product **6** through a subsequent C–C bond formation with the α-carbon of the enone moiety in an intramolecular Mizoroki–Heck reaction.[7] Highly substituted bicycles such as **7** bearing various functional groups present many opportunities for derivatization and therefore application in complex molecule synthesis. In one such application, we envisioned that this transformation could provide short access to the hydroxylated patchoulols (Figure 1C).

14-Hydroxypatchoulol (**9**) and 15-hydroxypatchoulol (**10**) are tricyclic sesquiterpenoids that were isolated in 2015 from *Valeriana stenoptera*, a plant used in traditional medicine and in the fragrance industry.[8,9] These molecules contain the skeleton characteristic of patchouli alcohol (**8**) adorned with additional hydroxy groups. We hypothesized that our planned C–C bond cleavage/cross-coupling/Mizoroki–Heck cascade reaction would allow for a concise synthesis of **10**.

Mechanistically, we envisioned a dual Pd(0)/(II) catalytic cycle, first involving insertion of a Pd(0)-complex into *gem*-dihaloalkene **5** to provide Pd(II)-species **12** (Figure 2A). Ligand exchange with cyclobutanol **11** would form Pd(II)-alkoxide **13**, which could undergo β-carbon elimination to yield alkyl-substituted Pd(II)-complex **14**. Reductive elimination would then give vinyl chloride **6** to close the first catalytic cycle. In a new catalytic cycle, oxidative addition of **6** would give **15**, which could undergo an intramolecular migratory insertion into the enone moiety to provide **16** containing the bicyclo[2.2.2]octane scaffold. β-Hydride elimination would then close the second cycle to afford **7** as the desired product. We hypothesized that with an appropriate ligand—in particular, one that would provide a large steric demand—insertion at the α-carbon could be favored to position the Pd(II) complex at the less substituted β-carbon.[7] Initial studies therefore commenced with a screen of various ligands using $Pd(OAc)_2$ as the catalyst, cyclobutanol **11**, dichlorostyrene **17**, and cesium carbonate. From this screening of conditions, we identified Xantphos as the ligand that provided the highest conversion of **11** and yield of the desired bicyclo[2.2.2]octane (i.e., **19**; see the Supporting Information for details on the ligand screen). At 70 °C, **19** was obtained in 56% yield along with a small amount of vinyl chloride **18** (Figure 2B, entry 1). The loading of Xantphos relative to $Pd(OAc)_2$ proved to be critical for reliable results, with a lower ratio of bicyclo[2.2.2]octane **19** to vinyl chloride **18** observed at a higher ligand loading (entry 2). We speculate that when excess Xantphos is used relative to Pd, ligand association saturates the Pd center, leading to catalyst deactivation and diminished oxidative addition of **18**.[10] The use of excess base proved to be important, with poorer conversion to **19** observed when 2 equiv of Cs_2CO_3 were used instead of 4 equiv (entry 3). In this case, the excess base likely scavenges the HCl generated in the course of the reaction. At 100 °C, neither **18** nor **19** was detected due to decomposition of **17** at these higher temperatures (entry 4). At a lower temperature of 40 °C, only formation of **18** was observed

along with recovered cyclobutanol **11** (entry 5). Using the more reactive dibromoalkene **20** led to alkyne adduct **21** as the major product (Figure 2C)—presumably formed from the dehydrobromination of **20** to give a Pd-acetylide species prior to the coupling.[11]

Having established suitable conditions to achieve our desired C–C bond cleavage/vinylation/Mizoroki–Heck cascade reaction using styrenyl *gem*-dichloroalkene electrophiles, we next investigated the use of alkyl *gem*-dichloroalkenes that would be desired for the total syntheses of the hydroxypatchoulol congeners. Dichloroalkenes possessing an alkyl substituent (e.g., **22**, Figure 3) led to tricyclo[3.2.1.0]octanes (e.g., **23**) as the major product. We hypothesize that, with alkyl dichloroalkene coupling partners, two consecutive carbopalladations occur prior to β-H elimination, giving rise to **23** via **24**, whereas β-H elimination following a second carbopalladation event is not possible for the aryl substituted dichloroalkene electrophiles discussed earlier (see Figure 2B). A range of alkyl-substituted dichloroalkenes (**25–30**) coupled with **11** under the conditions that we have established to provide the tricyclo[3.2.1.0]octane products in moderate yields.

The vinylcyclopropane moiety of the resulting products underwent concomitant hydrogenation and hydrogenolysis when subjected to Pd/C and H_2 to give bicyclo[3.2.1]octane products (e.g., **31** → **32**). Although cleavage of the less-substituted C–C bond is usually favored in reactions of vinylcyclopropanes with metal complexes,[12] we observed preferential cleavage of the more substituted C–C bond in **31**, which we hypothesize results from nucleophilic attack of Pd onto the vinylcyclopropane moiety to give a π-allylpalladium species,[13] which is selectively protonated and hydrogenated on the more accessible convex face to give **32**.

Our observations in these initial coupling studies set the stage for a synthesis of **10**, as outlined in the retrosynthesis in Scheme 1A. We envisioned the patchoulol framework arising from **33** through an intramolecular aldol reaction, and designed a synthesis involving a key coupling step between cyclobutanol **11** and dichlorovinyl ketone **34**.[14] Notably, **34** would introduce the carbonyl group to enable the aldol reaction to close the final ring. In addition, **34** lacks any β-hydrogens that would give rise to the competing formation of a tricyclo[3.2.1.0]octane from the coupling, as observed using dichloroalkenes **25–30**. In practice, **34** polymerized under the reaction conditions. However, ketal-protected **35** proved more serviceable and provided bicyclo[2.2.2]octane **36** containing all of the requisite carbon atoms of the undecane carbon skeleton in 53% yield (Scheme 1B).

The dioxolane protecting group in **36** was cleaved with pyridinium *p*-toluenesulfonate (PPTS) to provide enone **37** (Scheme 2A). Global hydrogenation of **37** was accomplished with Pd/C and H_2 to give the fully saturated product (**38**) in excellent yield and diastereoselectivity. In the presence of excess lithium hexamethyldisilazide (LiHMDS), **38** cyclized to give the aldol product (not shown).[15] We found that protection of the resulting hydroxy group was necessary to avoid a retro-aldol reaction under basic conditions. In situ protection of the alkoxide resulting from aldol cyclization of **38** with TMSCl provided the corresponding silyl ether, along with a mixture of silyl enol ethers which readily hydrolyzed to give **39** upon silica gel chromatographic purification.

α-Methylation of ketone **39** was accomplished in moderate yield (49% yield) albeit with a significant amount of recovered starting material (38% rsm), favoring alkylation on the convex face of the molecule to give undesired diastereomer **40** as the major product. Thermodynamic epimerization mediated by DBU at 70 °C provided *epi*-**40** bearing the desired equatorially disposed α-methyl group (see Scheme 2B).

Removing the ketone group directly proved to be challenging. For example, attempted Wolff–Kishner reductions, including the Caglioti[16] and Myers modifications,[17] were unsuccessful. Attempts to convert the carbonyl group to a thiocarbonyl or thioketal prior to reduction were equally unsuccessful. Ultimately, reducing ketone *epi*-**40** to alcohol **41** using dissolving metal conditions, followed by Barton–McCombie deoxygenation, accomplished the desired net removal of the ketone group. A subsequent cleavage of the silyl protecting groups furnished **10**.

We found that the NMR data that we acquired for **10** did not match those described in the isolation report. As such, we unambiguously characterized **10** using X-ray crystallographic analysis. From our analysis, it appears that the compound characterized in the isolation report as **10** is actually a constitutional isomer of **10** that bears a primary hydroxy group, but does not contain the patchoulol skeleton. This latter statement is supported by the fact that all other hydroxymethyl derivatives of patchouli alcohol are known, and none have characterization data that match those attributed to the compound described as **10** in the isolation report.[9a,18] To gain further support for our conclusions, we also prepared 14-hydroxypatchoulol (**9**) in an analogous manner to our synthesis of 15-hydroxypatchoulol, beginning from diastereomeric cyclobutanol **43** obtained from the reductive cyclization of epoxycarvone **42** (Scheme 2C), which provided data that also did not match those of the compound described as **10** in the isolation report.[19]

In conclusion, we have accomplished 12-step syntheses of both 14- and 15-hydroxypatchoulol from (*R*)-carvone. Key to this strategy was the development of a concise entry into substituted bicyclo[2.2.2]octanes using a Pd-catalyzed cyclobutanol C–C bond cleavage/cross-coupling/Mizoroki–Heck cascade coupling reaction with select *gem*-dichloroalkenes, which differs from pioneering syntheses of the patchouli sesquiterpenoids that feature cycloadditions to build the bicyclo[2.2.2]octane framework.[20] In our approach, tricyclo[3.2.1.0]octanes can also be prepared when alkyl substituted dichloroalkenes are employed as coupling partners. Given the biological[21] and organoleptic[22] properties of patchouli alcohol, we anticipate that this synthetic approach to hydroxylated patchouli alcohol congeners will set the stage for comprehensive function studies. In addition to preparing other hydroxylated patchoulol congeners for testing, our current studies are focused on gaining insight into the observed regioselectivity of the intramolecular Mizoroki–Heck portion of the cascade sequence, as well as generalizing the reaction manifold to other cycloalkanol substrates to access other unique carbon frameworks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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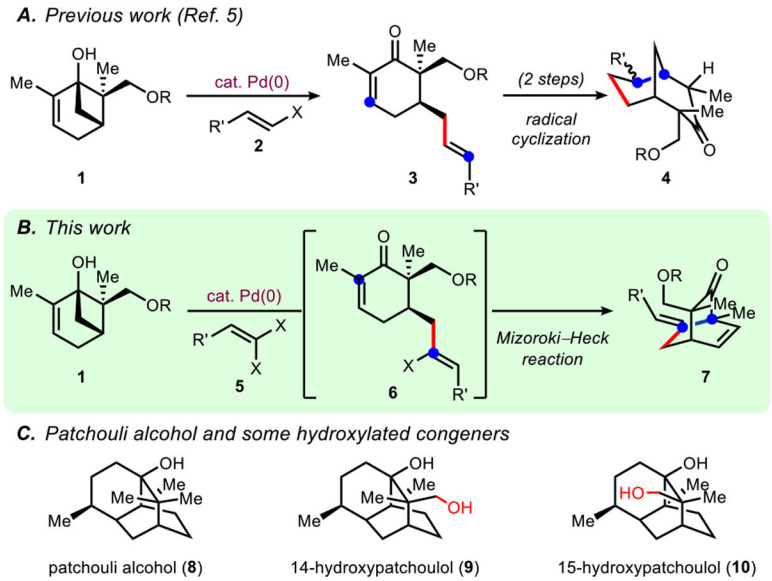
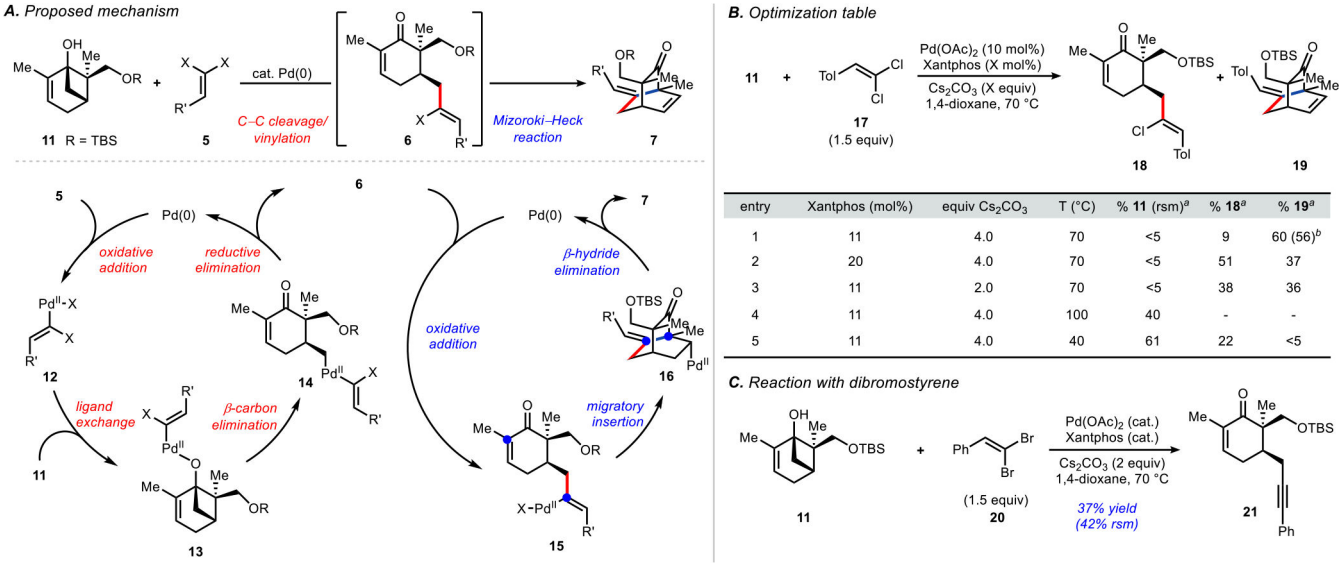


Figure 1.

(A, B) C–C bond cleavage/cross-coupling tactics to access bridged bicycles and (C) natural products containing bicyclo[2.2.2]-octane frameworks.



entry	Xantphos (mol%)	equiv Cs_2CO_3	T (°C)	% **11** (rsm)[a]	% **18**[a]	% **19**[a]
1	11	4.0	70	<5	9	60 (56)[b]
2	20	4.0	70	<5	51	37
3	11	2.0	70	<5	38	36
4	11	4.0	100	40	-	-
5	11	4.0	40	61	22	<5

Figure 2.

(A) Proposed mechanism. (B) Optimization table. [a]Determined by 1H NMR spectroscopy of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard; [b]Isolated yield. (C) Reaction with dibromostyrene.

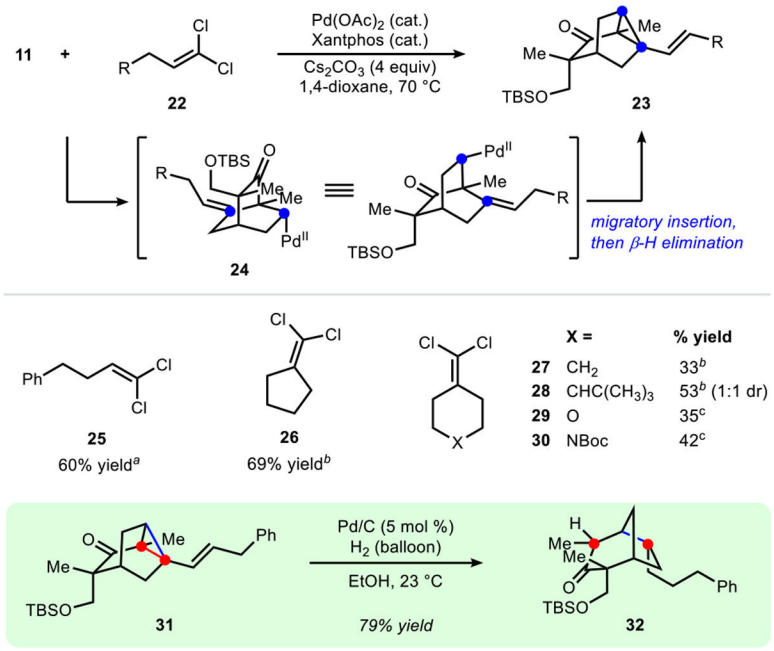
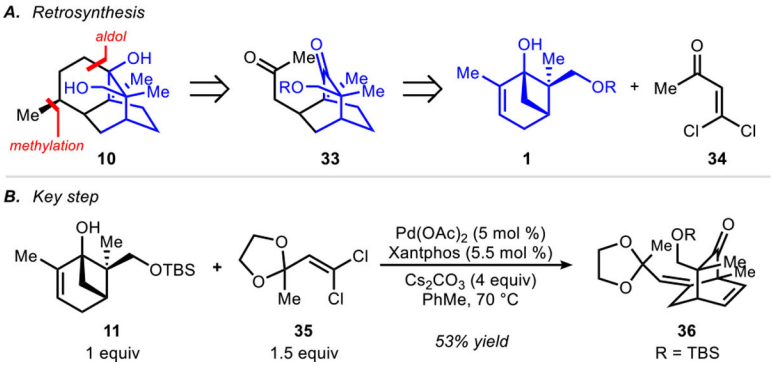


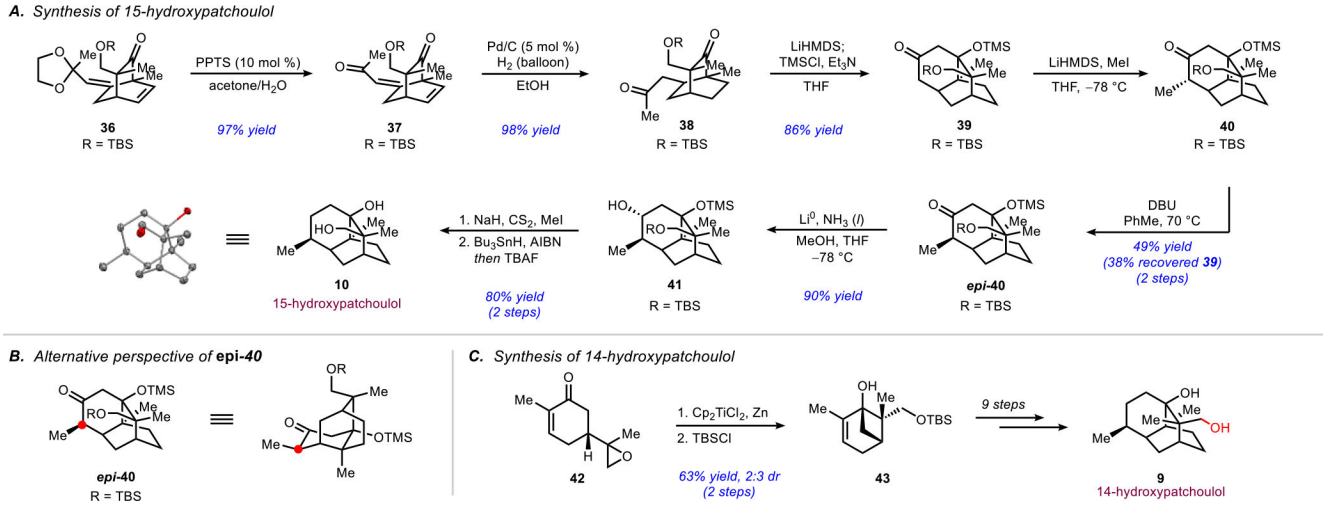
Figure 3.

Reactions with alkyl-substituted dichloroalkenes and further elaboration to the [3.2.1] framework. [a]Detailed reaction conditions: 1.5 equiv of electrophile, 10 mol % $Pd(OAc)_2$, 11 mol % Xantphos, 4 equiv of Cs_2CO_3, 1,4-dioxane (0.2 M), 70 °C, 24 h. [b]100 °C instead of 70 °C. [c]100 °C instead of 70 °C, 20 mol % instead of 11 mol % Xantphos.



Scheme 1. Retrosynthesis and Key Step[a]

[a](A) Retrosynthesis and (B) key step for the synthesis of **10**.



Scheme 2. Synthesis of 15-Hydroxypatchoulol (10) and 14-Hydroxypatchoulol (9)[a]

[a](A) Synthesis of 15-hydroxypatchoulol (**10**). (B) Alternative perspective drawing of *epi*-**40**. (C) Synthesis of 14-hydroxypatchoulol (**9**).