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Journal
Chemistry Letters, 53(11)

ISSN
0366-7022

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Publication Date
2024-11-05

DOI
10.1093/chemle/upae204

Chemistry Letters, 2024, **53**, upae204
https://doi.org/10.1093/chemle/upae204
Advance access publication 30 October 2024

Highlight Review

C–H functionalization of camphor through emerging approaches

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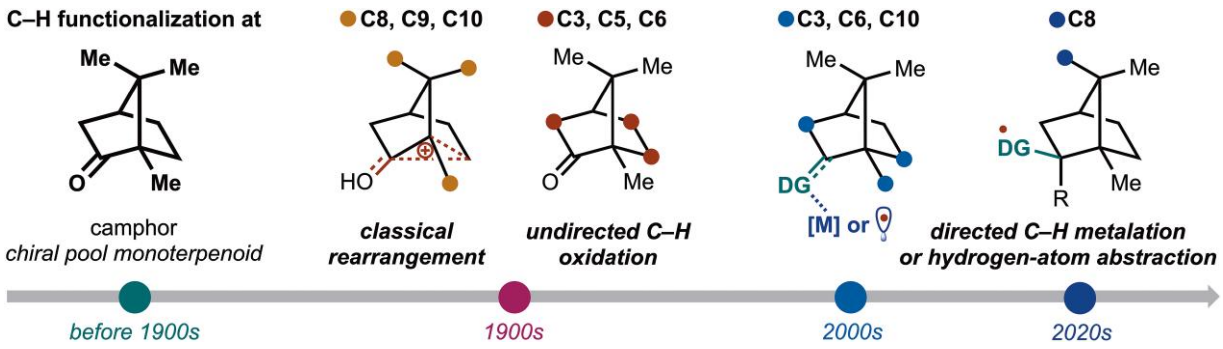
Abstract

Camphor and related monoterpenoid natural products have served as versatile "chiral pool" materials in organic chemistry for over half a century. Historically, many researchers have used a variety of transformations involving orchestrated rearrangements of the bornane skeleton to functionalize the camphor framework, expanding the utility of this chiral building block. Recent developments in C–H functionalization methodologies provide myriad opportunities to derivatize the camphor framework in a selective and predictable fashion. In this review, a short summary of the methods for functionalization of the camphor scaffold using rearrangement chemistry is provided followed by a discussion of emerging methods for directed C–H functionalizations that provide diverse new ways to derivatize the camphor framework.

Keywords: C–H metalation, hydrogen-atom abstraction.

[Received on 3 October 2024; revised on 22 October 2024; accepted on 22 October 2024; corrected and typeset on 12 November 2024]

Graphical Abstract



1. Introduction

The cyclic monoterpenoid camphor (**1**) represents one of the most readily available terpenoid chiral building blocks, featuring a bicyclo[2.2.1]heptane core (i.e. the bornane skeleton) with a carbonyl group (Fig. 1a). Because both enantiomers of **1** and the structurally related borneol (**2**) can be accessed from natural sources, these compounds have been described as a pool of chiral compounds (i.e. the "chiral pool") that are versatile starting materials for total syntheses,[1] as well as catalysts, ligands, or chiral auxiliaries in enantioselective reactions.[2,3] In addition to its ready availability, the many fascinating rearrangement processes associated with the unique structural features of **1** have led to a wide number of novel transformations.[1]

One of the most representative functionalizations using rearrangement chemistry is the synthesis of camphorsulfonic acid (CSA, **3**)[4] by treatment of **1** with sulfuric acid and acetic anhydride to effect C10 sulfonation in moderate yield (Fig. 1b).[5] The reaction proceeds through protonation of **1** (via $\mathbf{A_1}$) to generate nonclassical carbocation $\mathbf{B_1}$, which undergoes Wagner–Meerwein rearrangement and deprotonation, affording alkene $\mathbf{C_1}$. Subsequent sulfonation of the resulting double bond in $\mathbf{C_1}$ and a second Wagner–Meerwein rearrangement via $\mathbf{D_1}$ gives rise to CSA (**3**).[6] Overall, this reaction enables a net C–H functionalization of the camphor framework at C10.

On the basis of this C10 functionalization, many derivatizations of **3** have been explored over the decades,[1] adding versatility to the products of this transformation.[2,3] For example, Bartlett and Knox reported a two-step conversion of **3** into ketopinic acid (**5**),[7] which is now commercially available in enantioenriched form. In the reported procedures (Fig. 1c), treatment of **3** with phosphorus pentachloride affords sulfonyl chloride **4** quantitatively,[8] which is followed by oxidation using potassium permanganate in the presence of sodium carbonate, providing **5** in moderate yield.[9] The ketone and carboxylic acid moieties in **5** have been shown to be useful functional groups for subsequent chemical transformations.[1]

2. C8 and C9 functionalization of camphor through classical rearrangement chemistry

As shown in Fig. 1b, the bridged [2.2.1]bicycle of camphor makes possible nonclassical carbocations, which lead to rearrangements under strongly acidic conditions to enable, for example, functionalization at C10. Similarly, the geminal dimethyl moiety attached to the C7 bridging carbon has been demonstrated to engage in Wagner–Meerwein rearrangement processes that functionalize the C–H bonds at C8 and C9.[1] For example, in 1951, a research group at Takeda Pharm Co. Ltd. reported C9 bromination of camphor through sequential Wagner–Meerwein rearrangements (Fig. 2a).[10] Following α-bromination of the carbonyl group in **1** at C3,[11] treatment of the resulting 3-bromocamphor (**6**) with bromine in chlorosulfonic acid effected C9 bromination to afford 3,9-dibromocamphor (**7**) in moderate yield.[12] The reaction was initiated by protonation of ketone **6** and Wagner–Meerwein rearrangement via $\mathbf{A_2}$ to form the corresponding tertiary carbocation. A [1,2]-alkyl shift from the C–C bond at C7–C8 (highlighted in blue) to the tertiary carbocation and subsequent deprotonation generated alkene $\mathbf{B_2}$. This reactive intermediate underwent bromination of the resulting double bond, followed by a [1,2]-alkyl shift of the migrated methyl group to form cation $\mathbf{C_2}$. Finally, Wagner–Meerwein rearrangement of $\mathbf{C_2}$ and deprotonation accomplished the net C–H bromination at C9. Of note, C3 bromination prior to the sequential rearrangements was crucial in suppressing racemization during the process. As a result, the overall transformation proceeded enantiospecifically.[13]

In 1975, Money and coworkers disclosed a synthesis of 8-bromocamphor using sequential rearrangements analogous to those reported for C9 bromination (Fig. 2b).[14] They found that 3,3-dibromocamphor (**8**), prepared by a second α-bromination of the carbonyl group in **6**, engaged in rearrangement events that proceeded with selectivity different from that of **6**. The process commenced with protonation of the carbonyl group in **8** and Wagner–Meerwein rearrangement via $\mathbf{A_3}$ to generate the corresponding tertiary carbocation. At this stage, they proposed that due to the steric repulsion between the C7 methyl group and the C3 bromine atom, the C7–C9 rather than C7–C8 bond migrated to the tertiary cationic carbon center, which was followed by deprotonation, providing alkene $\mathbf{B_3}$. The migrated methyl group in $\mathbf{B_3}$ then migrated again upon bromination of the resulting double bond, generating the corresponding tertiary cation. Finally, Wagner–Meerwein rearrangement via $\mathbf{C_3}$ and deprotonation furnished tribromocamphor **9** in moderate yield,[15] in which the α-*gem*-dibromo moiety at C3 could be reduced by treatment with zinc and hydrobromic acid in dichloromethane to yield 8-bromocamphor (not shown).[14]

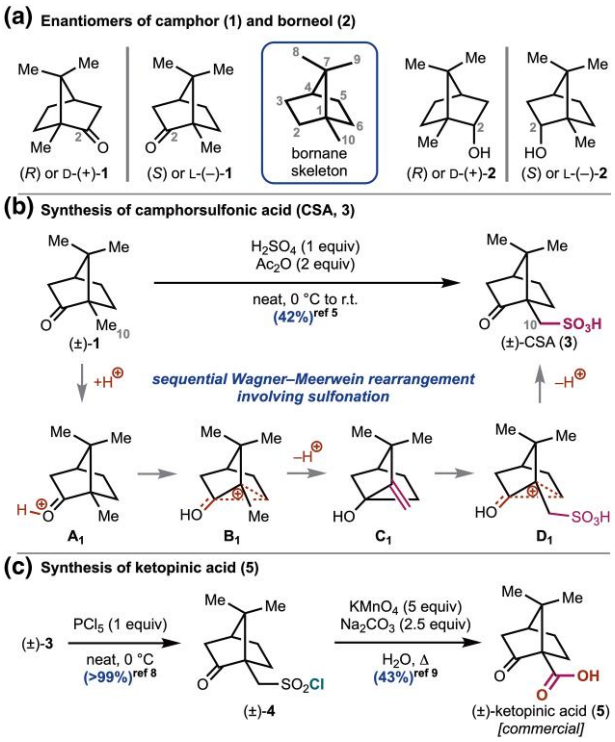


Fig. 1. a) Structures of bornane natural products. b) Formal C10 C–H functionalization through Wagner–Meerwein rearrangement. c) Conversion of CSA to ketopinic acid.

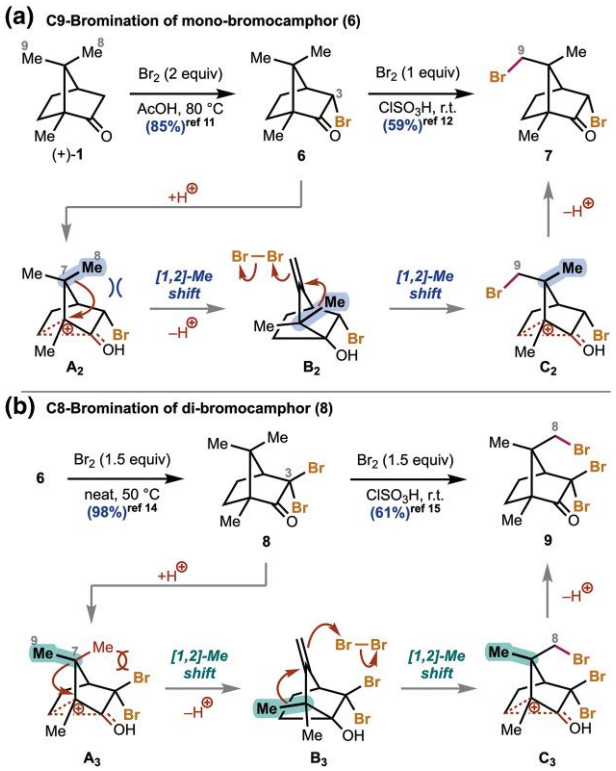


Fig. 2. a) Functionalization of the C9 C–H bond using 3-bromocamphor (**6**). b) C8 C–H functionalization using 3,3-dibromocamphor (**8**).

These C8 and C9 selective syntheses of bromocamphors highlight the importance of a deep understanding of rearrangement chemistry in the bornane framework driven by substrate-controlled stereoselectivity. Overall, orchestrated rearrangement processes enabled the nonintuitive functionalization of the C–H bonds at all three methyl groups of the bornane skeleton.

Hereafter, we briefly summarize and discuss C–H oxidation of the camphor framework at methylene positions, and then discuss emerging directed C–H functionalization reactions that install various appendages at sites not easily accessed using well-established rearrangement and oxidation reactions.

3. Undirected C–H oxidation of the camphor framework

Because C–H oxidation of the camphor framework[16] and related compounds[17] is well documented in several review articles,[1,18] here, we summarize the recent improvements of previously reported conditions (Fig. 3a) as well as an emerging method that employs a photocatalyst to enable mild aerobic oxidation of the camphor framework (Fig. 3b). Representative of the site-selective C–H oxidation of camphor (**1**) at the methylene positions is the C3 Riley oxidation,[19] leading to camphorquinone (**10**).[20] In a modified procedure,[21] treatment of (+)-**1** with 2.1 equivalent of selenium dioxide in acetic anhydride at reflux gave rise to **10** quantitatively. This compound is now commercially available. In addition, acetylborneol (**11**) was shown to participate in C–H oxidation at the C5 position under classic chromium trioxide-mediated conditions.[22] In 2015, Andrus and coworkers reported that the addition rate of a solution of chromium trioxide in acetic acid was critical to increasing the yield. Upon treatment with an

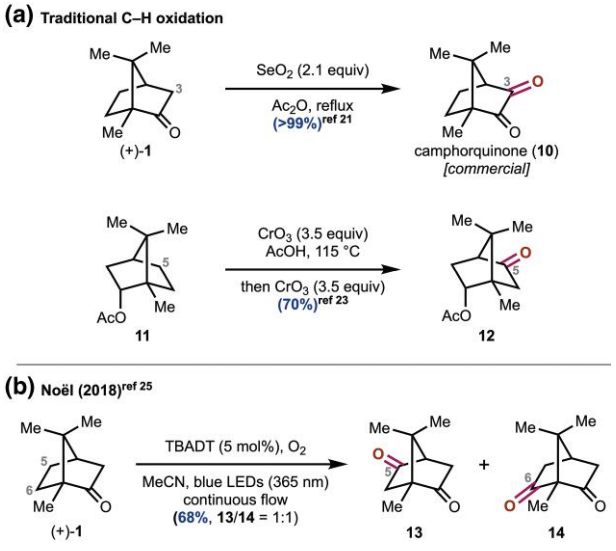


Fig. 3. a) Selective C3 and C5 oxidation of the camphor framework using stoichiometric oxidants. b) Photoinduced aerobic C–H oxidation of camphor.

additional equivalent of the oxidant, ketone **12** was obtained in good yield.[23]

In the context of the recent trend and impact of using undirected C–H functionalization,[24] Noël et al.[25] reported a mild C–H oxidation method under aerobic photoirradiation conditions in flow (Fig. 3b). They found that subjection of (+)-**1** to photoirradiation conditions with tetrabutylammonium decatungstate as a photocatalyst under ambient oxygen

atmosphere in a microflow reactor provided a 1:1 mixture of diketones **13** and **14** in good yield. Albeit modestly selective between C5 and C6, this reaction showcased effective C–H oxidation of the unactivated methylene positions in the camphor framework.

4. Directed C–H functionalization of the camphor framework using transition metals

Selective transformations of the inert but ubiquitous C–H bonds of camphor using directing groups have emerged over the past two decades as a powerful tool for installing functional groups at various positions.[26] Particularly, transition metal-mediated C–H functionalization methods have been actively developed,[27] some of which have been shown to provide valuable camphor derivatives.

One of the pioneering studies for directed C–H functionalization of the camphor framework is the C10 derivatization of camphor-derived oxime **15**, which was reported by Sanford et al.[28] in 2004. This reaction provided acetate **16** in good yield using a palladium catalyst and an oxidant (Fig. 4a). The key mechanistic insights involve coordination of the palladium catalyst to the nitrogen lone pair of O-methyl oxime **15** to form $\mathbf{A_4}$, followed by selective C–H palladation at the adjacent C10 position through a concerted metalation deprotonation process (see $\mathbf{B_4}$) to generate 5-membered palladacycle $\mathbf{C_4}$. Oxidation of $\mathbf{C_4}$ by iodobenzene diacetate and subsequent reductive elimination of the generated Pd(IV) species afforded **16**. On the basis of this work, various modifications of the reaction conditions were extensively explored, enabling the use of potassium persulfate, a polymer-immobilized iodine(III) reagent, a sodium nitrate/oxygen system, and peracetic acid as alternatives to the expensive oxidant.[29] Later, the groups of Che,[30] Chang,[31] and Li[32] demonstrated that camphor oxime **15** was amenable to C10 C–H amination under a variety of conditions using transition metal catalysts (Pd, Ir, or Rh) to afford the corresponding products (**17**–**19**, Fig. 4b). These reports demonstrate the utility of the methyl oxime directing group for selective C10 functionalization under the transition metal-catalyzed conditions.

Smoliakova et al.[33] reported C–H arylation and benzylation of five-membered palladacycle **20** prepared from oxime (+)-**15** using arylboronic acids or a benzylboronic ester to provide the corresponding products (**21** and **22**, Fig. 5a).[34] They also showed that instead of the O-methyl oxime group, a similar palladacycle (compare **20** and **23**) could be isolated from a benzyl imine, demonstrating the range of directing groups for C–H palladation at the C10 position.[35] In addition, camphor-derived hydrazone **24** was shown to effect selective C–H palladation at the C3 position, yielding palladacycle **25** as a 1:1 mixture of diastereomers (Fig. 5b).[36] Compound **25** reacted with an 4-nitrophenylboronic acid to produce C3-*endo*-arylated product **26**, presumably through epimerization.[34] These results underscore how the subtle modification of directing groups can influence the site selectivity of the C–H palladation process.

Instead of the ketone-derived monodentate-type directing groups as described above, Schönecker et al.[37] reported in 2004 that camphor-derived imine **27** bearing a 2-pyridyl-imine bidentate auxiliary facilitated copper-mediated C–H oxygenation at the C10 position. On the basis of this discovery, the Baran group extensively investigated the reaction

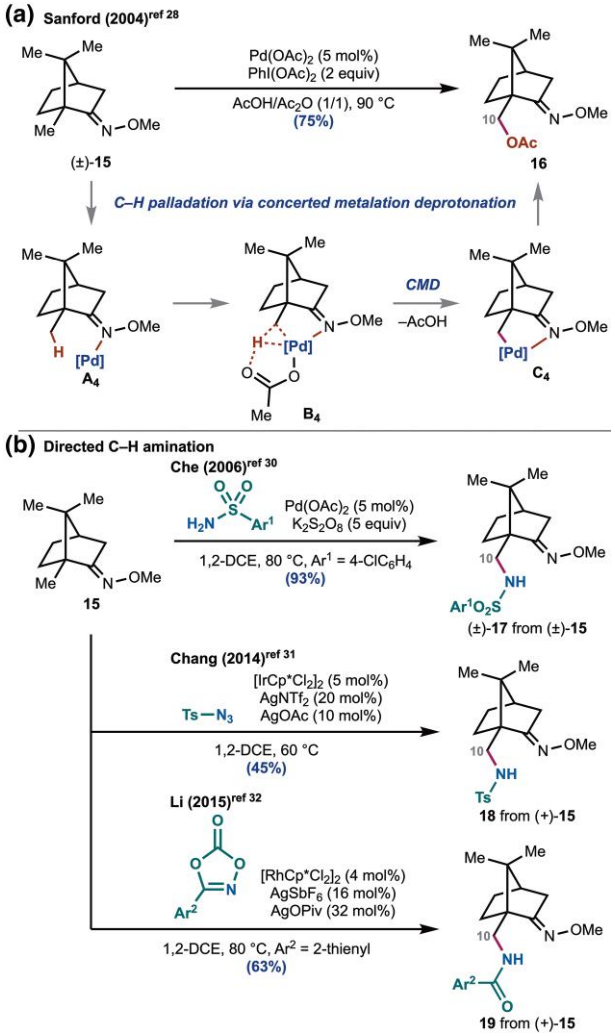


Fig. 4. a) Palladium-catalyzed directed C–H acetoxylation. b) C–H amination of camphor oxime at C10.

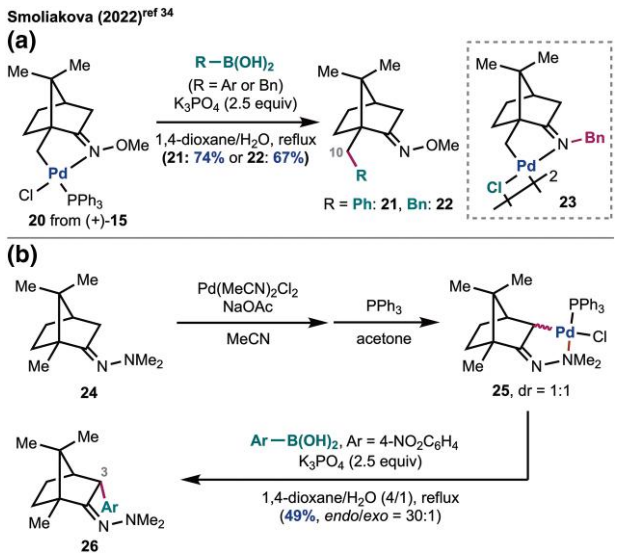


Fig. 5. a) C10 arylation and benzylation of oxime-derived palladacycles. b) C3 arylation using a hydrazone directing group.

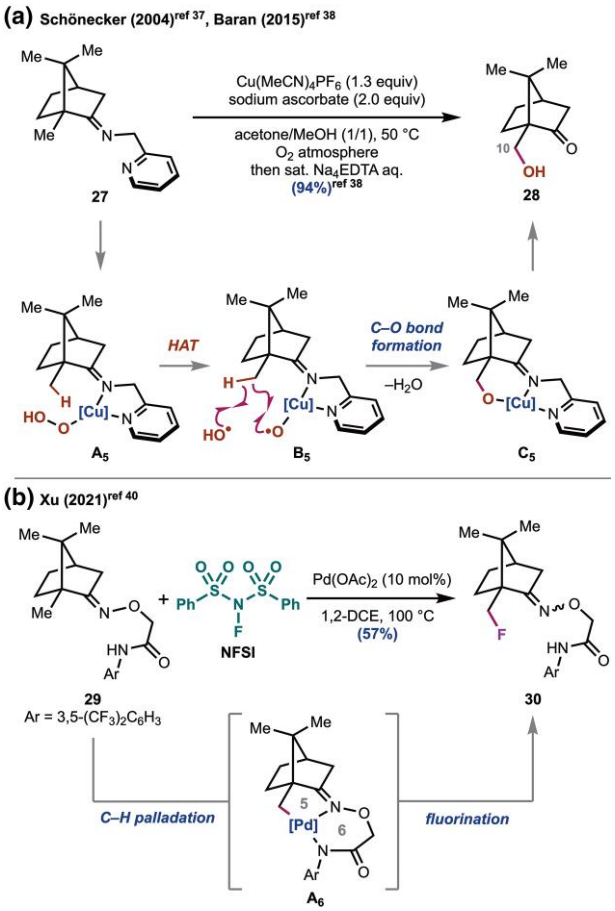


Fig. 6. a) Copper-mediated pyridyl-imine-directed C–H hydroxylation at C10. b) Bidentate oxime-directed C10 fluorination.

conditions and mechanism, resulting in improvements of the yield of alcohol **28** in up to 94% using a stoichiometric copper salt and sodium ascorbate under an oxygen atmosphere (Fig. 6a).[38] As a result of their extensive studies,[39] they proposed that homolytic O–O bond cleavage of copper(II) hydroperoxide $\mathbf{A_5}$ after coordination of the copper complex with the pyridyl-imine moiety leads to the formation of a radical pair ($\mathbf{B_5}$). Hydrogen-atom abstraction (HAT) and radical rebound processes from $\mathbf{B_5}$ then yielded oxygenated product $\mathbf{C_5}$, which was converted to 10-hydroxycamphor (**28**) in the aqueous work-up. Xu and coworkers have shown that a related ketone-derived bidentate-type directing group, camphor oxime derivative **29**, bearing an O-acetic amide moiety, was effective in promoting palladium-catalyzed C–H fluorination via 5-6 fused palladacycle $\mathbf{A_6}$ using N-fluorobenzenesulfonimide to provide **30** in moderate yield (Fig. 6b).[40]

While ketone-derived directing groups are effective in converting a C–H bond at C10 in camphor to other groups, the C3 hydroxy group in borneol and isoborneol can be also employed as functional groups for selective C–H functionalization reactions through installation of directing groups to the oxygen atom. In 2012, Hartwig and coworkers reported an iridium-catalyzed C–H silylation at C10 of isoborneol-derived oxysilane **31**, which was followed by Tamao-Flemming oxidation and acetylation to afford diacetate **32** in good yield over four steps from (+)-**1** (Fig. 7).[41] In this reaction, they proposed that oxidative addition of the iridium catalyst into the Si–H bond in **31** formed intermediate $\mathbf{A_7}$, effecting intramolecular

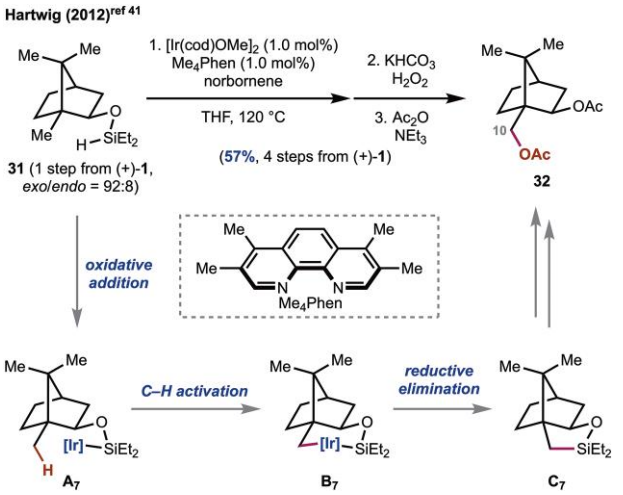


Fig. 7. Iridium-catalyzed C–H silylation at C10.

C–H activation to provide the six-membered iridacycle $\mathbf{B_7}$. Subsequent reductive elimination provided five-membered silacycle $\mathbf{C_7}$, which was converted to diol derivative **32**.

In 2015, White et al. demonstrated the manganese-catalyzed intramolecular C–H amination of borneol-derived sulfamate ester **33** to provide six-membered cyclic sulfamate **34** as a major product, along with the formation of five-membered cyclic sulfamate **35** (Fig. 8a).[42] In the proposed mechanism, C–H bond cleavage of metallonitrene $\mathbf{A_8}$, which was generated from **33** with the aid of the iodine(III) reagent, yielded carbon-centered radical $\mathbf{B_8}$ at the adjacent C10 position selectively over the secondary C3 position. Rapid radical rebound from the base metal catalyst led to cyclized sulfamate **34**. Similarly, Novikov and coworkers demonstrated that borneol-derived diazosulfonate **36** could be engaged in metal-carbenoid C–H insertion chemistry using a rhodium catalyst to provide a 9:1 mixture (C10/C6) of δ-sultones **37** and **38** in good yield (Fig. 8b).[43]

Camphor derivatives with strongly coordinating bidentate directing groups have been shown to facilitate highly selective C–H arylation reactions. In 2018, the Sheppard group showcased aminobornane-derived picolinamide **39** as a directing group for C–H arylation at the C6 methylene position to yield **40** via a 5-5 fused palladacycle $\mathbf{A_9}$ (Fig. 9a).[44] Interestingly, in a subsequent study,[45] they demonstrated that a substituent on the pyridine ring was critical in suppressing competitive double arylation at C10 (not shown). In contrast, Yu et al. reported that palladium-catalyzed C–H arylation of *exo*-oxime **41** bearing a pyruvic acid motif in the presence of a pyridone ligand occurred at C10 (Fig. 9b).[46] Arylation product **42** was obtained as a major product over **43** through a formation of 5-6 fused palladacycle $\mathbf{A_{10}}$.

In contrast to C–H functionalizations that rely on the C2 ketone or hydroxy groups of camphor or the borneols, the Costas group reported a carboxylic acid-directed C–H lactonization at several positions on the camphor skeleton.[47] They disclosed that (–)-*cis*-isoketopinic acid (**44**) underwent selective C–H lactonization at C5 using (S,S)-[**Mn**]-**1** to yield γ-lactone **45** in 90% yield along with its isomer (**46**; 86:1 GC analysis), whereas the conditions using (R,R)-[**Mn**]-**1** gave a 1.7:1 mixture of γ-lactones **45** and **46** representing mismatched selectivity (Fig. 10a). (+)-Ketopinic acid (**5**) was also diastereoselectively converted to γ-lactone **47** in 80% yield

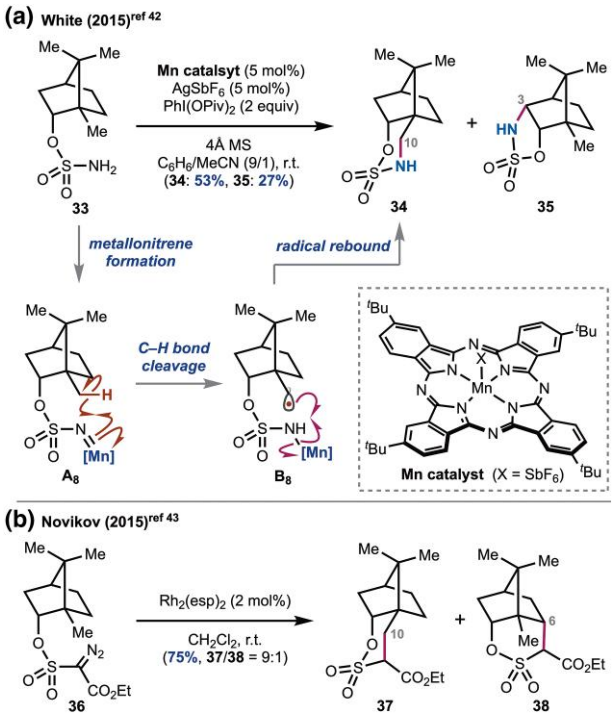


Fig. 8. a) Manganese-catalyzed C10 amination. b) Rhodium-catalyzed C–C bond formation.

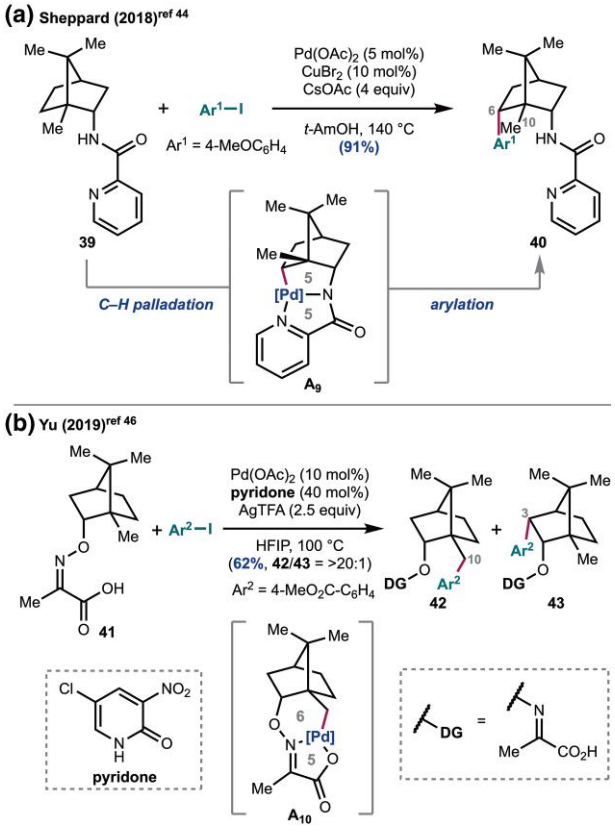


Fig. 9. a) Picolinamide-directed C6 arylation. b) C10 arylation directed by the bidentate-type exo-oxime.

using (S,S)-[**Mn**]-**2** via C–H cleavage at the primary C8 position (Fig. 10b). The mismatched case using (R,R)-**Mn-2** provided a 1:12 mixture of **47** and **48** (GC analysis). The reaction

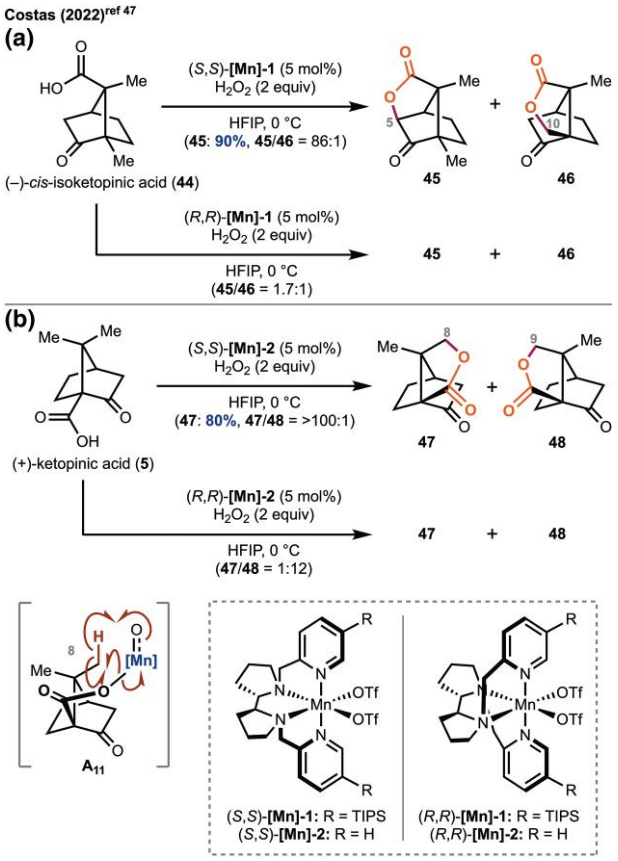


Fig. 10. a) Manganese-catalyzed C–H lactonization of isoketopinic acid. b) C8 and C9 lactonization of ketopinic acid.

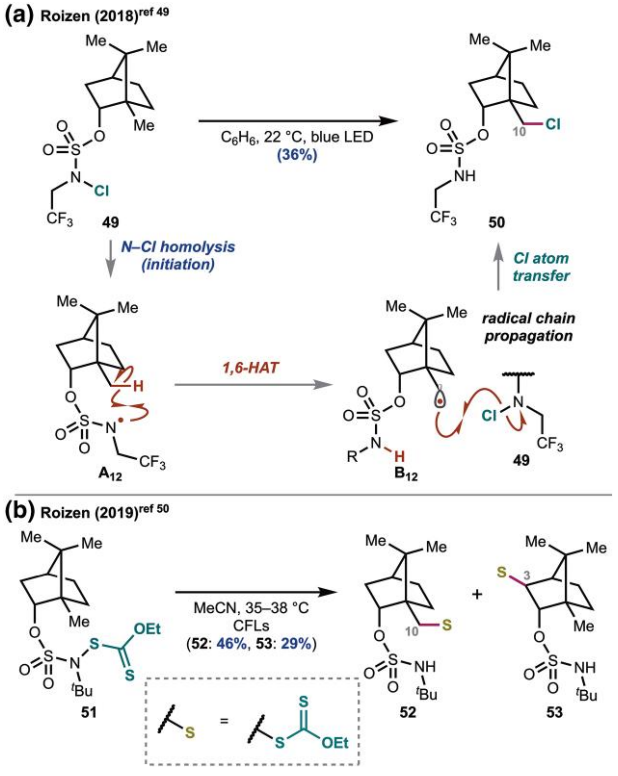


Fig. 11. a) C10 chlorination via 1,6-HAT using the sulfamate directing group. b) C3 and C10 xanthylation.

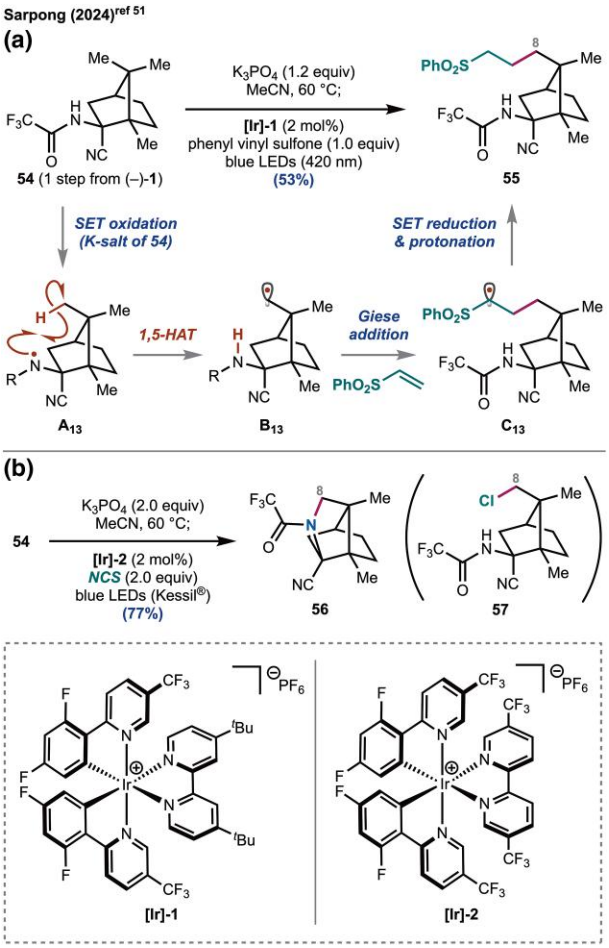


Fig. 12. a) Aminonitrile-directed C8 alkylation. b) C–H amination at C8 to form the pyrrolidine ring.

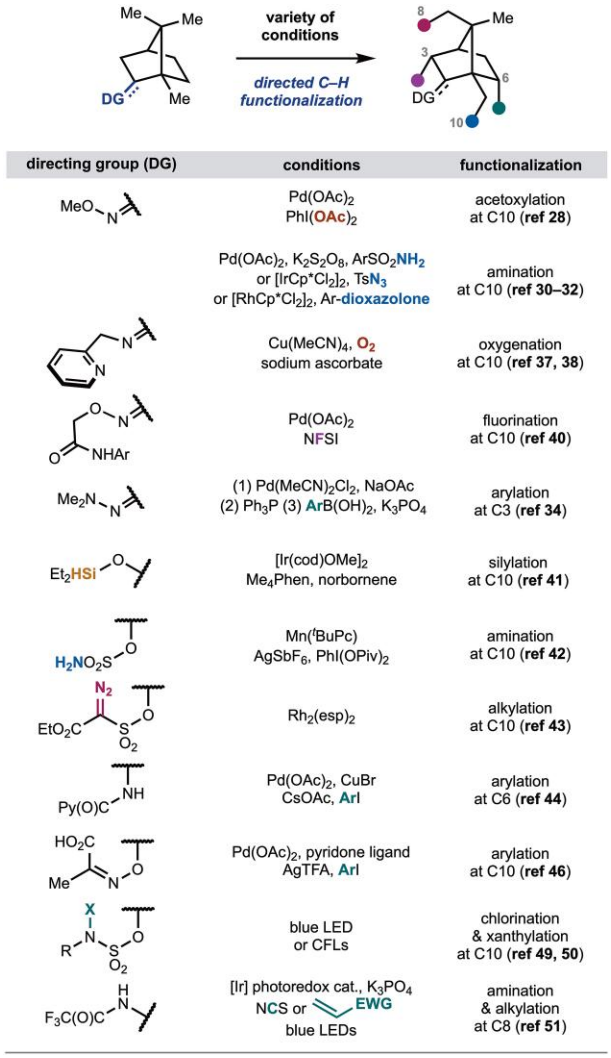


Fig. 13. Summary of camphor C2 directing group enabled C–H functionalizations.

mechanism is believed to involve complexation of the carboxylic acid moiety with the manganese catalyst to generate Mn(IV)-oxyl $\mathbf{A_{11}}$, which directs HAT and subsequent radical rebound to provide the corresponding γ-lactone. These reactions employing the carboxylic acid directing group at different positions achieve catalyst-controlled, site-selective C–H functionalization of the camphor framework.

5. Photoinduced directed C–H functionalization of camphor derivatives

In recent years, with increasing reports of photomediated reactions, HAT mediated by heteroatom-centered radicals arising through photoirradiation has emerged as a promising strategy for the functionalization of C–H bonds. Because photomediated reactions can facilitate the generation of heteroatom-centered radicals under mild conditions, distinct reaction mechanisms compared to transition metal-mediated processes are now broadly accessible.[48] Photomediated HAT reactions typically show reactivity that is complementary to transition metal-mediated C–H functionalization methods. Photomediated C–H functionalization methods have been successfully applied to camphor derivatives, providing a range of products. Roizen and coworkers reported C–H chlorination of borneol-derived N-chlorosulfamate **49** at C10 under blue LED irradiation conditions to provide chloride **50** in moderate yield (Fig. 11a).[49] In the proposed reaction mechanism, amidyl radical $\mathbf{A_{12}}$ generated through photomediated homolytic N–Cl bond cleavage was the key intermediate that effected 1,6-HAT from the C10 position, followed by trapping of carbon-centered radical $\mathbf{B_{12}}$ with a chlorine atom, affording **50**. Overall, net chlorine atom transfer from N-chloride **49** to C-chloride **50** was achieved in this simple reaction. A year later, the same group disclosed a photomediated C–H xanthylation of sulfamate ester **51** to yield xanthates **52** and **53** at both the C3 and C10 positions (Fig. 11b).[50]

In 2024, Sarpong et al. reported photoredox-catalyzed C–H functionalization reactions of camphor-derived aminonitrile **54**, which enabled the selective introduction of alkyl groups at the C8 position using electron-deficient alkenes (e.g. phenyl vinyl sulfone) as SOMOphiles (Fig. 12a).[51] Aminonitrile **54** was prepared from (−)-camphor (**1**) using a Strecker reaction and subsequent protection of the nitrogen with a trifluoroacetyl group. The proposed reaction mechanism for alkylation involves single-electron transfer (SET) oxidation of the corresponding potassium salt by deprotonation of amide **54** and 1,5-HAT mediated by the nitrogen-centered radical $\mathbf{A_{13}}$, generating the carbon-centered radical $\mathbf{B_{13}}$. This radical ($\mathbf{B_{13}}$) reacts with phenyl vinyl sulfone to form carbon-centered

radical C_{13}, which subsequently undergoes SET reduction and protonation to give product **55**. In addition, the employment of *N*-chlorosuccinimide as a SOMOphile was shown to convert **54** to pyrrolidine **56**, rather than chlorinated product **57** at the C8 methyl group (Fig. 12b). These photomediated examples involving the HAT process highlight the potential to install various functional groups at several positions via unique reactivities intrinsic to the camphor framework.

6. Conclusion

This review summarizes methodologies to functionalize C–H bonds in the bornane skeleton. Because of its wide availability in both enantioenriched forms and the inherent topological complexity of the bornane skeleton, which maps on several natural products, there has remained a significant need for selective functionalization of camphor for over the century. While classic functionalizations of camphor rely on rearrangement processes, emerging directed C–H functionalization chemistry is now providing predictable site-selective and practical functionalization of camphor and related compounds (see Fig. 13). These new developments have added profitably to the existing transformation for functionalization of these useful chiral pool materials. Specifically, a variety of C–H functionalizations of camphor at C10 are now possible, whereas methods for functionalizations at other positions continue to emerge. It is our hope that this review will spur the development of even more methods for the site-selective functionalization of the bornane framework and the application of these reactions in the preparation of complex molecules and materials.

Funding

This work was supported by the National Institutes of Health (NIGMSMIRA R35 GM130345), NSF (U.S. National Science Foundation) under the Center for Selective C–H functionalization (CHE-1700982), a Grant-in-Aid for Transformative Research Areas (A) "Latent Chemical Space" (JP24H01789) for G.S. from the Ministry of Education, Culture, Sports, Science and Technology, Japan, Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Nos. 24K18256 (G.S.), and JSPS and the Astellas Foundation for Research on Metabolic Disorders for postdoctoral fellowships (H.Y.).

Conflict of interest statement. None declared.

Data Availability

This is a Review Article and so there is no data to share.

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