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Synthesis of Vicinal Quaternary All-Carbon Centers via Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

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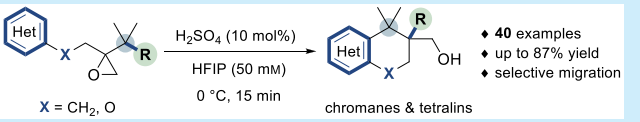
ABSTRACT: We report our studies on the development of a catalytic cycloisomerization of 2,2-disubstituted neopentylic epoxides to produce highly substituted tetralins and chromanes. Termination of the sequence occurs via Friedel–Crafts-type alkylation of the remote (hetero)arene linker. The transformation is efficiently promoted by sulfuric acid and proceeds best in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent. Variation of the substitution pattern provided detailed insights into the migration tendencies and revealed a competing disproportionation pathway of dihydronaphthalenes.



Vicinal quaternary carbon centers are present in many bioactive natural products (e.g., salimabromide (**1**),[1] lingzhiol (**2**),[2] calycanthine (**3**),[3] communesin F (**4**),[4] and koumine (**5**)[5]) and pharmaceuticals such as buprenorphine (**6**)[6] (Scheme 1A). The presence of these structural units was reported to increase the structural rigidity allowing for tighter binding to their molecular targets in many cases and greater selectivity than with more flexible congeners.[7] In nature, all-carbon quaternary centers are, for instance, accessible via reactions that proceed via carbocation intermediates.[8,9] For their construction in the chemical laboratory, a well-assorted toolbox has been established in the past.[9,10] However, synthetic challenges remain, as multistep procedures that are accompanied by low-yielding transformations are often required.

In the context of the synthesis of salimabromide (**1**), we were investigating methods to efficiently construct the fully substituted tetrahydronaphthalene core.[11] We found that ring formation and installation of the two crucial vicinal quaternary carbon centers were possible in a single step by means of a powerful cycloisomerization reaction of a 2,2-disubstituted neopentylic epoxide. This chemistry was inspired by the seminal reports by Bogert[12] and Cook[13] in 1933 (Scheme 1B). In this work, a tandem hydride migration/Friedel–Crafts-type cyclization of tertiary alcohol **7** enabled the synthesis of octahydrophenanthrene system **8**. In 2010, Khalaf extended the rearrangement–cyclization cascade by resorting to acyclic tertiary alcohols such as **9** to enable installation of two vicinal *gem*-dimethyl groups.[14]

Unfortunately, both of these reports were strictly limited to a few unfunctionalized hydrocarbon frameworks. Herein we disclose the synthesis of vicinal all-carbon quaternary centers by the consecutive 1,2-rearrangement/cyclization of 2,2-disubstituted neopentylic epoxides under mild conditions (Scheme 1C). Selective migration of various alkyl residues was achieved by exploiting ring strain, carbon–carbon bond strengths, and carbocation stabilities. This allowed for the synthesis of a library of polyfunctionalized tetralin and chromane systems.

For the initial optimization of the reaction conditions, we employed readily available electron-rich arene **11a** (Scheme 2A). We were pleased to find that the cycloisomerization proceeded most efficiently in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[15] at 0 °C with sulfuric acid (10 mol %) as catalyst, affording tetralin **12a** in 83% yield within 15 min. Alternative solvents and Brønsted or Lewis acids were found to be inferior and led to significantly reduced yields (entries 2–7).[16] Higher temperatures (23 °C, entry 9; 58 °C, entry 8) were less effective for this transformation, leading to complex mixtures of uncyclized byproducts.

With the optimized conditions in hand, we investigated the scope of the cycloisomerization in more detail (Scheme 2B). As a first parameter, we studied different aromatic residues as the nucleophilic component for the Friedel–Crafts termination step. Activating methyl and *tert*-butyl substituents provided yields of up to 83% (**12c** and **12d**). Methoxy-substituted tetralins were obtained in virtually identical yields as for unsubstituted tetralin **12b**, with only a little influence of the substitution pattern (69% for **12e** and 70% for **12f**). It is noteworthy that **12e** was previously synthesized by the same cascade under nonoptimized conditions in only 43% yield.[11] Remarkably, a fully methylated pyrogallol-derived epoxide

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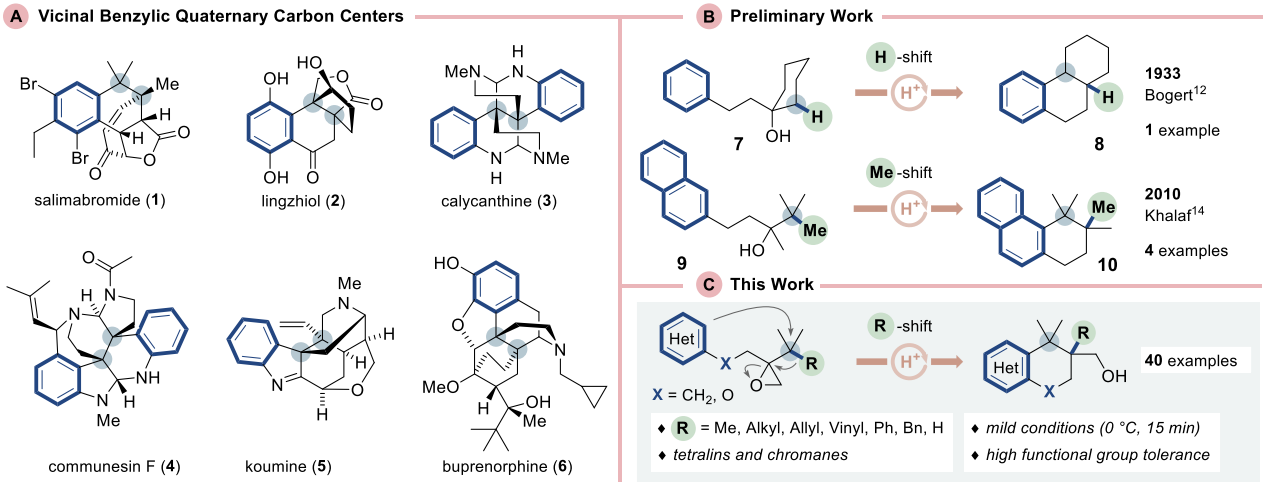
Scheme 1. Occurrence of Vicinal All-Carbon Quaternary Centers in Bioactive Molecules and Concept of this Work



formed the corresponding tetralin **12h** in only 57% yield, while benzodioxole derivative **12g** was isolated in 82%. We believe that this results from the trajectory of the approaching arene, which leads to severe steric interaction between the outer methoxy groups and the tertiary carbocation unit. As expected, substrates with deactivating substituents delivered the corresponding tetralins in only low yields or completely shut down the reaction (see Scheme 2D, limitations). Fluorinated tetralins **12i** and **12j** were formed in 35 and 41% yield, respectively. Pinacol boronate **12k**, which is a valuable building block for further derivatizations via Suzuki−Miyaura cross-coupling reactions, was formed in 29% yield. Electron-rich, nonbasic heterocycles also proved to be compatible with the reaction conditions. For a thiophene substrate, efficient alkylation took place to afford the annealed 6/5-system **12l** in 77% yield. Furans **12m** and **12n** were formed in lower yields under the reaction conditions, probably because of competing hydrolysis or polymerization.[17] We were pleased to see that the methodology is not limited only to aromatic nucleophiles: oxane **12o** was formed in 43% yield from the corresponding primary alcohol. Interestingly, even for this relatively small nucleophile no oxolane formation was observed. This underpinned our assumption that the formation of a less-strained six-membered ring must be one of the major driving forces for the cascade (vide infra). This hypothesis was also experimentally supported by product **12p**, which was formed from a distal epoxide via a formally inverse methyl migration along the alkyl chain. The non-rearranged 7/6 system was not observed under these conditions.

Having investigated the conversion of a panel of variously substituted (hetero)arenes to afford tetralins, we proceeded to vary the carbon chain connecting the epoxide and (hetero)-arene (Scheme 2C). By replacement of the ethylene linker with an oxymethylene unit, we envisioned being able to access heterocyclic chromane systems. We were pleased to see that a series of these readily available phenyl ethers delivered highly substituted chromanes **13a−l** in medium to good yields. For all of the substrates investigated, a competing hydride shift to form a stabilized phenoxycarbocation ion was not observed. Electron-rich phenyl and naphthyl ethers underwent the cascade reaction in up to 76% yield. Similarly substituted chromanes were generated in only slightly reduced yields compared to the corresponding tetralin analogues. An exception was methoxy derivative **13d**, which was formed in only 33% yield together with a 7% yield of its *ortho* regioisomer **13e**. Interestingly, we observed an unexpected effect of the substitution pattern of methoxyphenols, affording the highest yield (58%) for the *ortho*-substituted derivative **13f**. The *p*-fluoro- and *p*-chlorophenyl ethers delivered the corresponding chromanes **13i** and **13j** in 73% and 68% yield, respectively. For substrates carrying a (boronic) ester (CO_2Et or Bpin), only small amounts of the corresponding chromanes were isolated (23% yield for **13k** and 39% yield for **13l**). In these cases, the phenyl ether proved to be less stable, leading to the isolation of free phenols in substantial amounts. Electron-poor (hetero)-arenes turned out to be incompatible not only for the formation of tetralins but also for chromane systems (Scheme 2D). The 2,3-substituted pyridine **12q** was not observed even in the presence of excess acid and prolonged reaction times. A trifluoromethyl group (**12r**), amide (**12s**), or nitrile (**13m**) prevented the final cyclization and gave mostly complex mixtures of uncyclized elimination products. To our surprise, protected aniline derivative **13n** was not accessible either, and only a complex mixture was obtained.

To better understand the reaction sequence, we studied the migration tendencies of different alkyl residues (Scheme 3). For this purpose, we replaced the *tert*-butyl group attached to the epoxide with different aliphatic rings (ring size = 4, 5, 6). Highly strained methylcyclobutyl epoxide **14a** exclusively underwent ring expansion/alkyl migration, affording *cis*-benzohydrindane **16a** in 76% yield. The same behavior was observed for the formation of tetralin **16d** (82%) and chromane **16e** (87%). The less-strained cyclopentyl derivative **14b** afforded both *cis*-benzodecalin **16b** and spirane **15b** as an inseparable mixture (9:1 ratio), still preferring the ring-expanded product **16b** in 54% yield. Cyclohexyl derivative **14c** exclusively formed spirane **15c** (71%) with no detectable amount of the 7/6/6-expansion product **16c**.

In an effort to investigate the requirements for successful 1,2 migration, we further modified the *tert*-butyl group and replaced one of the three methyl groups with an allyl, prenyl, benzyl, or vinyl group. Epoxide **17a** afforded allyl-migrated tetralin **18a** in 38% yield as the major product. Preferential migration of the weaker allylic bond was also observed for the prenyl substrate **17b**. For this particular case, we observed protonation of the remote double bond of **18b** and subsequent spiroxane formation with the neopentylic alcohol (39% yield of **19**). Similar migration was observed for the benzyl group,

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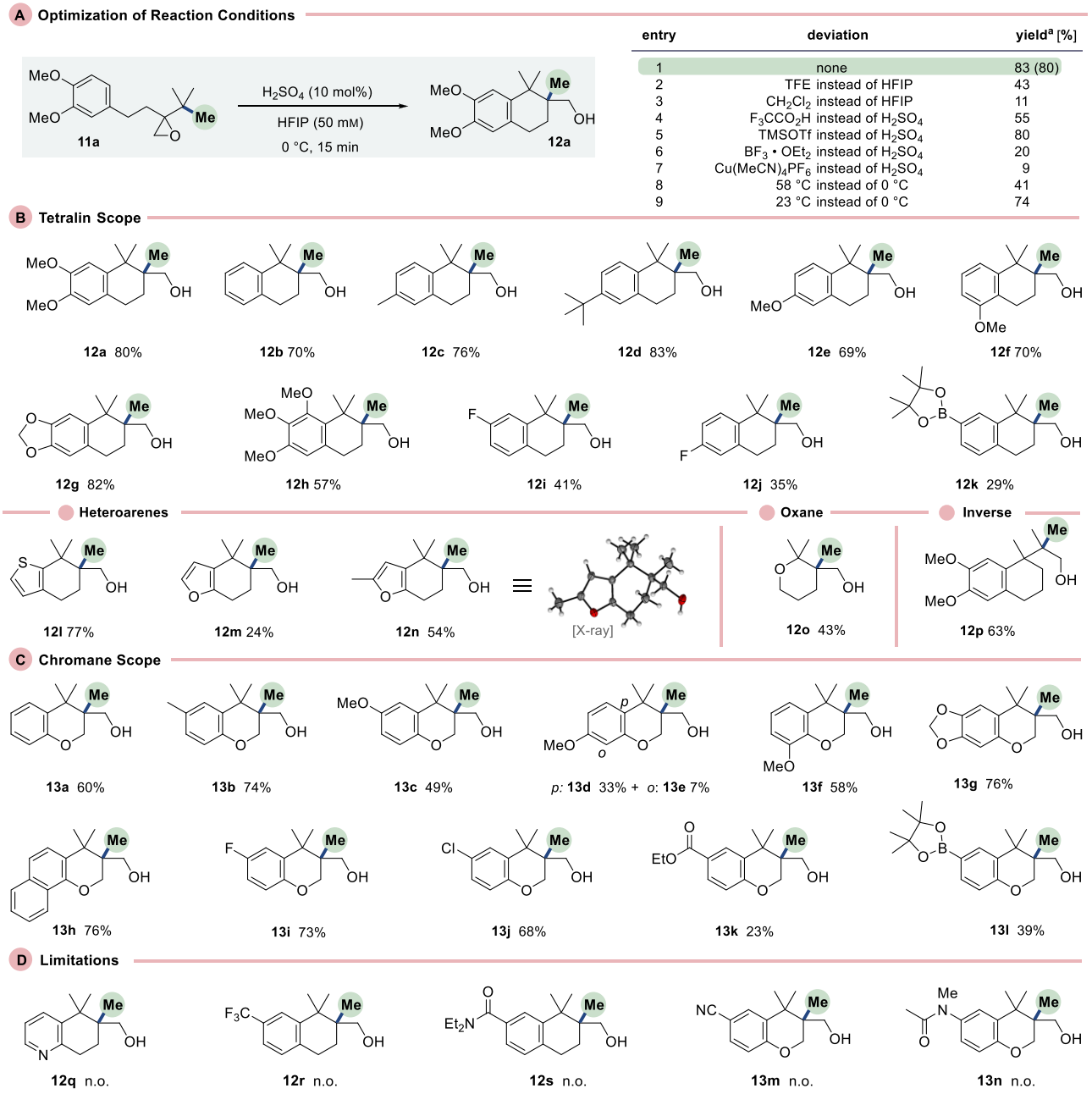
Scheme 2. Optimization and Scope of the Cycloisomerization



[a]^{1}H NMR yields with 2,3,5,6-tetrachloronitrobenzene as the internal standard are shown, with isolated yields in parentheses. n.o. = not observed.

affording **18c** in 36% yield. The competing methyl migration was also observed for this substrate, leading to the formation of **20** as a mixture of diastereomers (1.6:1 d.r.) in 19% yield. Careful analysis of the product mixture revealed the unusual 6/6/6/6-product **21** (hexahydrobenzo[*c*]phenanthrene) as the major product (41%). Despite the stronger sp^2–sp^3 bond (*t*-Bu–vinyl = 97.8 kcal mol^{-1} vs *t*-Bu–methyl = 87.5 kcal mol^{-1}),[18] the migration of a vinyl group was also observed to afford tetralin **18d** in 22% yield together with a complex product mixture. The eight-membered-ring product **22**, originating from at least two alkyl migration steps, was isolated as the only byproduct in 7% yield.[19]

To investigate the requirements for successful migratory cycloisomerization, we varied the degree of substitution of the terminal alkyl carbon starting with a methyl group (**23a**, R^1 = R^2 = R^3 = H). As expected, no cycloisomerization was observed for this epoxide, but disproportionated naphthalene **27a** (47%) and tetralin **28a** (49%) were obtained in nearly quantitative combined yield. The same results were observed for substrates carrying an ethyl (**23b**) or benzyl (**23c**) group. When an isopropyl group was present, naphthalene **27d** (29%) and tetralin **28d** (34%) still prevailed. However, a 1,2-hydride shift was also observed to afford cycloisomerized tetralin **24d** in 28% yield. Diphenylmethyl derivative **23e** afforded the corresponding products in similar yields. Surprisingly, in this case only phenyl migration with low diastereoselective control (**23e**, 36% yield, 1.9:1 d.r.) was observed. Epoxide **11a**, which was used for the optimization, delivered disproportionated naphthalene **27f** (8%) and tetralin **28f** (9%) under the reaction conditions. For the methoxymethyl group in substrate **23g**, we

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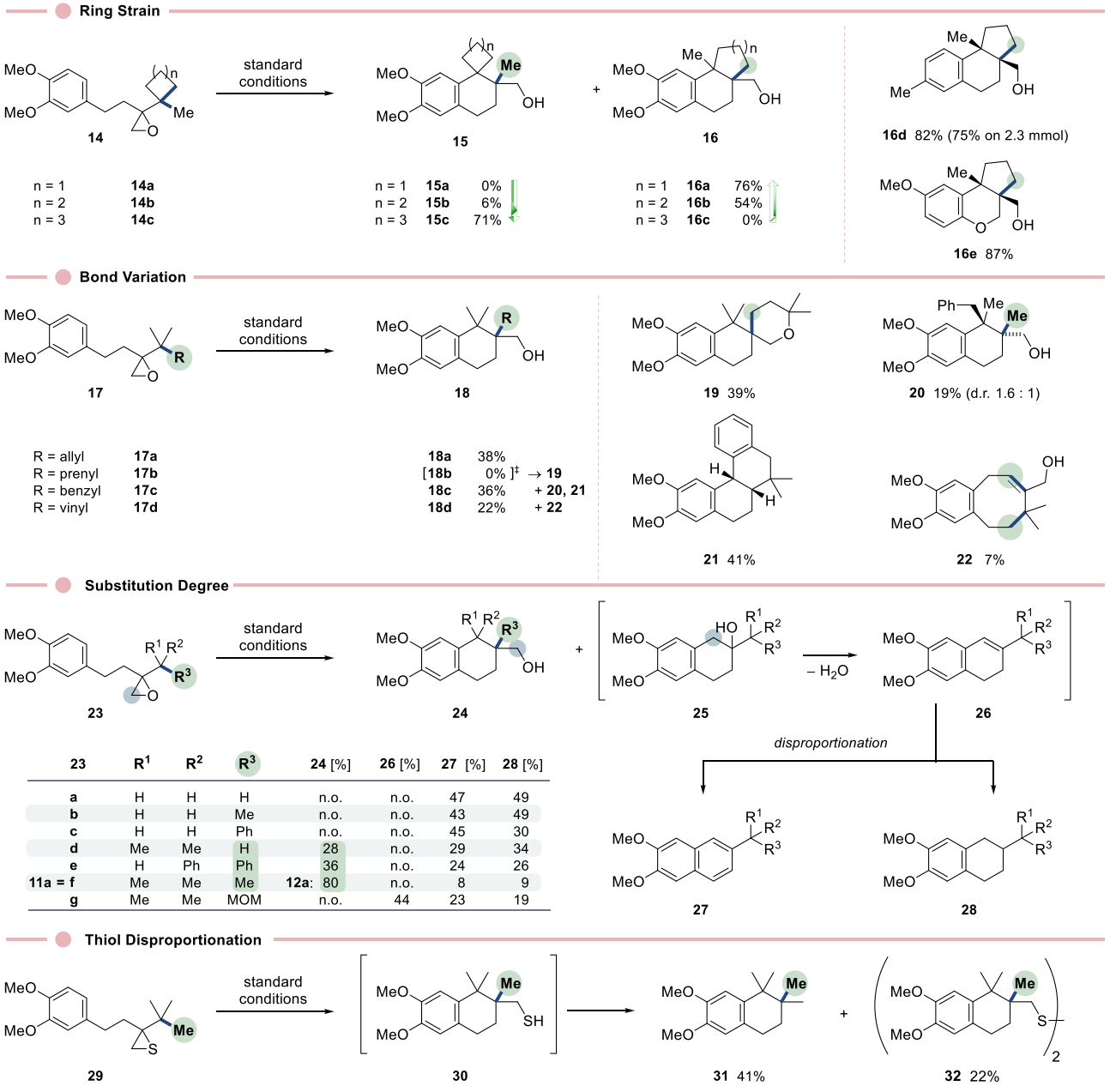
Scheme 3. Investigation of the Migration Tendencies of Substituents



23	R^1	R^2	R^3	24 [%]	26 [%]	27 [%]	28 [%]
a	H	H	H	n.o.	n.o.	47	49
b	H	H	Me	n.o.	n.o.	43	49
c	H	H	Ph	n.o.	n.o.	45	30
d	Me	Me	H	28	n.o.	29	34
e	H	Ph	Ph	36	n.o.	24	26
11a = f	Me	Me	Me	12a: 80	n.o.	8	9
g	Me	Me	MOM	n.o.	44	23	19

exclusively observed direct alkylation leading to a mixture of dihydronaphthalene **26g** and its disproportionation products, the corresponding naphthalene **27g** and tetralin **28g**.[19] Fast disproportionation was observed not only for dihydronaphthalenes but also for cycloisomerized neopentylic thiol **30**. The use of thiirane **29** directly gave a mixture of desulfurized tetralin **31** (41%) and the corresponding disulfide **32** (22%).[20] While the disproportionation of thiols to disulfides and hydrogen is a common reaction,[21] the formation of a hydrocarbon and a disulfide is unprecedented to the best of our knowledge.

Finally, we also screened a panel of chiral Lewis and Brønsted acid catalysts employing substrates **11a** and **17d**. Unfortunately, we did not observe any asymmetric induction (see the Supporting Information for screening).[22] It is noteworthy that for all of the substrates investigated, no five- or seven-membered-ring systems were observed.[23]

In conclusion, we have reported a powerful cycloisomerization reaction of 2,2-disubstituted neopentylic epoxides. The reaction does not require transition metal catalysts and proceeds under mild conditions in HFIP as the solvent. Variation of the terminating nucleophile enabled rapid access to functionalized chromanes and tetralins featuring vicinal all-carbon quaternary centers. The use of cycloalkyl moieties allowed for the formation of tricyclic ring systems in one step. Analysis of the byproducts revealed fast disproportionation of dihydronaphthalenes to form naphthalenes and tetralins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02296.

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Experimental procedures, optimization screens, compound characterization, X-ray crystal structure data, computational studies, and spectral data (PDF)

Accession Codes

CCDC 2010932 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, U.K.; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(16) For a full optimization table, see the Supporting Information.

(17) In the case of **12n**, the corresponding hydrolyzed diketone was isolated in 11% yield.

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(19) For a proposed reaction mechanism, see the Supporting Information.

(20) The combined yield increased to 92% when trimethylsilyl trifluoromethanesulfonate was used instead of sulfuric acid.
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(22) The use of an enantiomerically enriched epoxide (82% ee) provided tetralin **12e** with 70% ee (see ref 11).
(23) This result was also supported by computational studies at the ωB97X-D/6-311G(d,p)/ SMD(F_3CCH_2OH) level employing **11e** (see the Supporting Information for details).

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