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Semipinacol-Type Rearrangements of [3-(Arylsulfonyl)bicyclo[1.1.0]butan-1-yl]alkanols

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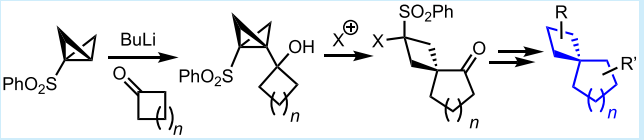
ABSTRACT: Selective lithiation of arylsulfonylbicyclo[1.1.0]-butanes at the bridgehead methine and addition to carbonyl compounds yield tertiary bicyclobutyl alcohols that form spiro[3.4]octanes and related heteroatom-containing spirocycles via an acid- or halogen-mediated semipinacol rearrangement. Further synthetic transformations at the carbonyl or arylsulfone positions, in general in high yield and good chemoselectivity, allow access to acetals, difluorides, amides, and methylenecyclobutene building blocks.



While bicyclo[1.1.0]butanes contain a relatively simple fused cyclopropane scaffold, these compact carbocycles have a unique reactivity profile that distinguishes them from cyclopropanes by virtue of more than double the ring strain (66.3 kcal/mol vs 27.0 kcal/mol for a single cyclopropane) as well as a central C(1)−C(2) bond that has significantly more π- than σ-bond character.[1] The results of NMR studies are in agreement with a calculated sp^{18} hybridization at C(1) and C(2), i.e., a significant preponderance of a p orbital-like electron distribution between the two carbon atoms.[2] Substituent effects at these bridgehead carbons are therefore more pronounced on bicyclo[1.1.0]butanes than on cyclopropanes, and arene rings or heteroatoms such as sulfur strongly modulate stereoelectronic properties at all core carbon atoms.[3] For example, introduction of a phenylsulfone at C(1) and a hydroxymethylene group at C(2) of bicyclo[1.1.0]-butane opens the interflap angle by ∼3°, lengthens the C(1)−C(2) bond distance by 0.02 Å, reduces its bond order by 35%, and introduces a significant Mulliken atomic charge differential across this core bond. The methine C(2) hydrogen also is more readily deprotonated to generate the synthetically useful 3-(phenylsulfonyl)bicyclo[1.1.0]butyl carbanion.

Previously, our group studied the preparation of (bicyclo[1.1.0]butan-1-yl)alkylamines **1** and their thermal and transition metal-catalyzed conversions to five-, six-, and seven-membered heterocycles such as **2** and **3**.[1,4,5] Other noteworthy discoveries in the field include enantioselective routes to bicyclo[1.1.0]butanes **5**, diastereoselective additions to substituted cyclobutanes **7** and **10**, and insertions to access 2,2-dihalobicyclo[1.1.1]pentanes **12** (Scheme 1).[6] Very recently, and independent of our concomitant studies, Gregson et al. disclosed strain-release semipinacol rearrangements of isoelectronic azabicyclo[1.1.0]butyl carbinols **14** toward azetidines **15**[7]

The sulfone substituent on the bicyclo[1.1.0]butane bridgehead C(1)−C(2) bond in **16** was previously found to facilitate the deprotonation of the vicinal methine C−H bond and allow additions and substitutions with a broad range of electrophiles.[13,14] We sought to combine the ease of addition of these metalated species to ketones **17** with a semipinacol-type ring enlargement of tertiary alcohols **18**, with the goal of generating a new route to spirocyclic ketones **19** (Figure 1). Arylsulfonyl-substituted cyclobutanes **19** could be further converted to scaffolds **20**, commonly encountered in natural products such as trefolane A,[15] astellatol,[16] aplydactone,[17] α-panasinsene,[18] and maoecrystal M,[19] yet still rarely used in pharmaceuticals (e.g., UCB-1184197[20]), and commercially available building blocks.

1-(Phenylsulfonyl)bicyclo[1.1.0]butane (**16**) was prepared as previously reported from sodium benzenesulfinate in 41% overall yield.[13] For the preparation of **23b** and **23c**, sulfonyl chlorides **21b** and **21c** were alkylated with 4-bromobutene and epoxidized with *in situ*-generated dimethyldioxirane to give γ,δ-epoxysulfones **22b** and **22c** (Scheme 2). Intramolecular epoxide opening, followed by mesylation of the primary alcohol and treatment with *n*-BuLi, closed the second three-membered ring and provided bicyclo[1.1.0]butanes **23b** and **23c** in moderate overall yields.[21] Treatment with *n*-butyllithium in THF at −78 °C followed by addition of cyclobutanone **24** provided tertiary alcohols **25a−c** in 65−88% yield.[14a]

On the basis of ^{1}H NMR studies that suggested that the more electron-rich *p*-methoxy-substituted sulfonylbicyclo[1.1.0]butane **25b** rearranged more quickly

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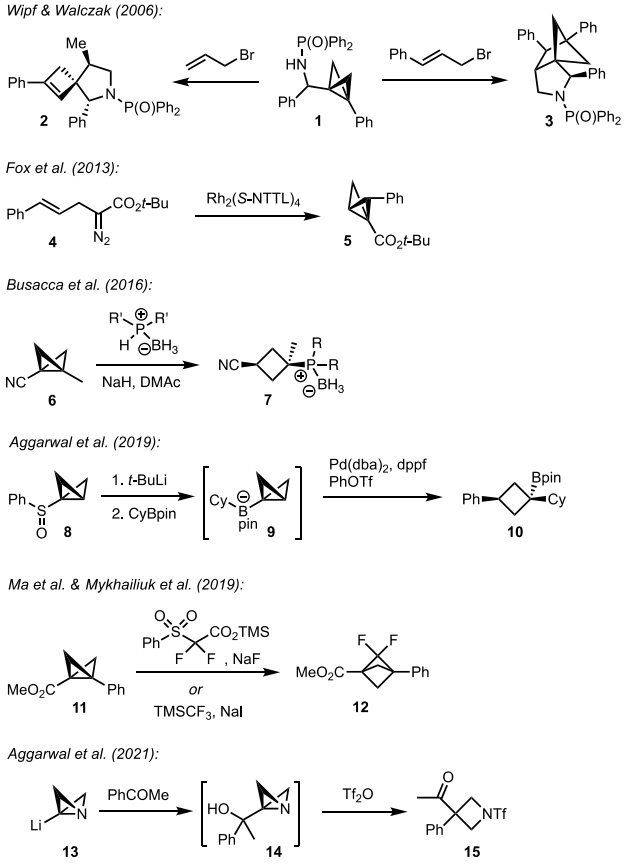
Scheme 1. Cycloadditions of Bicyclo[1.1.0]butanes to Heterocycles 2 and 3,[5] Enantioselective Preparations of 5,[8] and Syntheses of Cyclobutylphosphine Boranes 7,[9] Pinacol Boronates 10,[10] Difluorinated Bicyclo[1.1.1]pentanes 12,[11,12] and Azetidines 15[7]



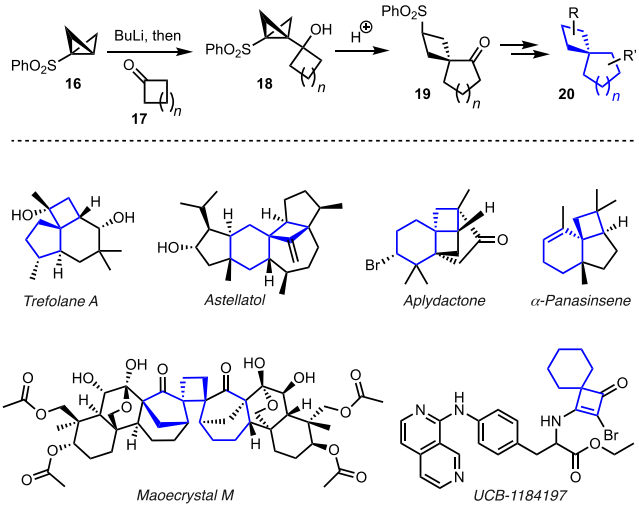


Figure 1. Semipinacol-type rearrangement of sulfonylbicyclo[1.1.0]-butane alcohols **18** to spiroalkanes **19**, and representative natural products and pharmaceuticals with spiro[3.4]octane substructures.

under acidic conditions than analogues **25a** and **25c**, we selected **25b** for a survey of acidic conditions for the semipinacol rearrangement to spiro[3.4]octan-5-one **26b** (Table 1). Carboxylic acids such as AcOH and TFA were ineffective at catalyzing this conversion at ambient temperatures (entries 1 and 2). In contrast, sulfonic acids such as camphorsulfonic acid (CSA) and methanesulfonic acid (MsOH) led to a stereoselective formation of **26b** in >90% conversion in CH_2Cl_2 even at 1 mol % loading after a 12 h reaction time (entries 2−7). We noticed a significant solvent dependence in this rearrangement, because methanol, THF, acetonitrile, and toluene suppressed the conversion (entries 8−11). Lewis acids such as BF_3 etherate could be used in place of MsOH but also led to the formation of side products that were tentatively assigned as dehydrated derivatives of **25b**. The combination of $LiNTf_2$ and Bu_4NPF_6 also led to the desired rearrangement at room temperature but was not further optimized for cost reasons.

After identifying optimal conditions for the rearrangement of **25b** in CH_2Cl_2 in the presence of 5 mol % MsOH, we explored the scope of this reaction with diverse tertiary alcohol substrates (Table 2). Addition of lithiated **23b** to the corresponding ketones occurred preferentially *anti* to the substituents at position 2 or 3 of the cyclobutanone and generated alcohols **25f−n** in 60−92% yield as single diastereomers (see the Supporting Information).

In agreement with our preliminary ^{1}H NMR studies, there was a notable reaction time difference between the electron-deficient *p*-trifluoromethylphenyl sulfone **25c** (Table 2, entry 3) and the electron-rich *p*-methoxyphenyl sulfone **25b** (entry

Scheme 2. Preparations of Bicyclo[1.1.0]butanes 23b and 23c from Sulfonyl Chlorides 21b and 21c, Followed by Conversion to Cyclobutyl Alcohols 25a−c and Spirocycle 26b

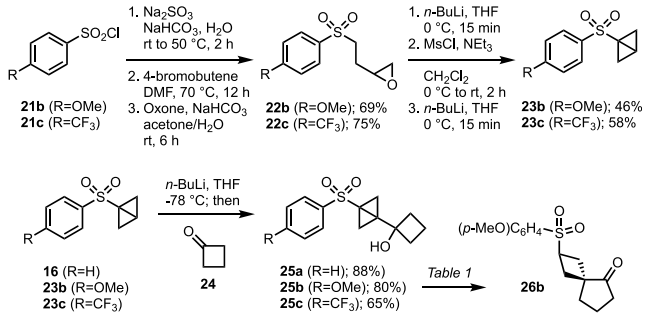


Table 1. Optimization of Semipinacol Rearrangement of 25b to Spirocycle 26b[a]

entry	acid (mol %)	solvent	time (h)	conversion (%)
1	AcOH (10)	CH_2Cl_2	12	0
2	TFA (10)	CH_2Cl_2	12	11
3	CSA (10)	CH_2Cl_2	12	83
4	MsOH (10)	CH_2Cl_2	12	100
5	MsOH (5)	CH_2Cl_2	1	100
6	MsOH (2.5)	CH_2Cl_2	1	91
7	MsOH (1)	CH_2Cl_2	12	99
8	MsOH (1)	MeOH	12	9
9	MsOH (1)	THF	12	5
10	MsOH (1)	MeCN	12	24
11	MsOH (1)	toluene	12	4
12	$BF_3{\cdot}OEt_2$ (10)	CH_2Cl_2	1	85

[a]All reactions were performed at room temperature at a concentration of 0.05 M on a 0.1 mmol scale; the conversion was determined by LC-MS using an internal standard (4-bromophenylacetic acid), and the conversion was based on both starting material and product peak integration.

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Table 2. Semipinacol Rearrangement of Tertiary Alcohols 25 to Spirocycles 26 [R = (*p*-MeO)PhSO$_2$] in the Presence of a Catalytic Acid

Entry	Tertiary Alcohol	Rearrangement Product	Reaction Time	Yield (%)[a]
1	**25a**	**(26a)**	80 min	94
			100 min	97[b]
2	**25b**	**(26b)**	80 min	94
			70 min	97[c]
3	**25c**	**(26c)**	3 h	92
4	**(25d)**	**(26d)**	12.5 h	74[d]
5	**(25e)**	**(26e)**	NR	NR
6	**(25f)**	**(26f)**	4 h	76
7	**(25g)**	**(26g)**	75 min	86
8	**(25h)**	**(26h)**	2 h	85
9	**(25i)**	**(26i)**	5.5 d	51
10	**(25j)**	**(26j)**	10 h	91[e]
11	**(25k)**	**(26k)**	10 h	95[e]
12	**(25l)**	**(26l)**	10 h	84[e]
13	**(25m)**	**(26m)**	24 h	84
14	**(25n)**	**(26n)**	5 d	50[d]

Table 2. continued

[a]All reactions were performed in CH_2Cl_2 at room temperature in the presence of 1 mol % MsOH on a 0.5 mmol scale unless indicated otherwise; yields are based on the isolated compound. [b]On a 5.0 mmol scale. [c]On a 2.0 mmol scale. [d]Two portions of 5 mol % MsOH were added. [e]On a 0.33 mmol scale. NR, no reaction.

2), with **25c** requiring 3 h to produce 92% product **26c** compared to 70−80 min for **26b**. There was a less significant rate difference between phenylsulfone **25a** (entry 1) and **25b**.

The introduction of a heteroatom in cyclic carbinol **25** decreased the reactivity of the substrate. Oxetanol **25d** generated 74% of furanone **26d** after reaction for 12.5 h (entry 4). In contrast, Boc-protected azetidine **25e** was inert under the standard conditions with MsOH (entry 5). Alternatively, aryl-substituted cyclobutanes **25f** and **25g** rearranged smoothly to spirocycles **26f** and **26g** in 76% and 86% yield, respectively (entries 6 and 7, respectively). Alkyl substituents at various positions on the cyclobutane also led to semipinacol products **26h** and **26j−26l** in 84−95% yield (entries 8 and 10−12, respectively). Amide and nitrile substituents in **25i** and **25n**, however, showed significantly slower conversions and lower yields to spirocycles **26i** and **26n** (entries 9 and 14, respectively). In addition to the electron-withdrawing effect of these substituents, we speculate that these groups also provide additional sites for protonation, thus preventing the acid from efficiently catalyzing the semipinacol rearrangement. In support of this hypothesis, benzyl ether **25m** was spontaneously eliminated to give enone **26m** in 84% yield after 24 h (entry 13).

The configuration of spirocycle **26b** and rearrangement products **26c−n** was assigned on the basis of an X-ray analysis of phenylsulfone **26a** (Figure 2). The carbonyl group of the

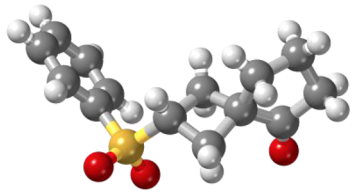

Figure 2. X-ray analysis of semipinacol rearrangement product **26a** (CCDC 2071902).

cyclopentanone and the sulfone moiety were found to be in a *syn* position across the cyclobutane ring, suggesting that the 1,2-shift in the ring expansion occurs suprafacially across the bicyclo[1.1.0]butane, placing the tertiary alcohol into an *endo* position and into the vicinity of the sulfone (Figure 3). The rearrangement-initiating proton transfer from the catalytic acid would thus occur from the large solvent-exposed *exo* hemisphere of the bicyclobutane, in agreement with related intermolecular, kinetically controlled additions.[9,10]

While (bicyclo[1.1.0]butan-1-yl)cyclopentan-1-ol **27a** and larger cycloalkanols such as **27b** and **27c** failed to undergo the semipinacol rearrangement in the presence of MsOH, these substrates were converted in 80−84% yield to cyclohexanone **28a**, cycloheptanone **28b**, and cyclononanone **28c** with 1.1−2.3 equiv of NBS (Scheme 3). While side products were not isolated in all cases, LC-MS and ^{1}H NMR analyses of some of these reactions suggested the formation of dehydrated (alkene) byproducts with >4-membered cycloalkanols and MsOH or

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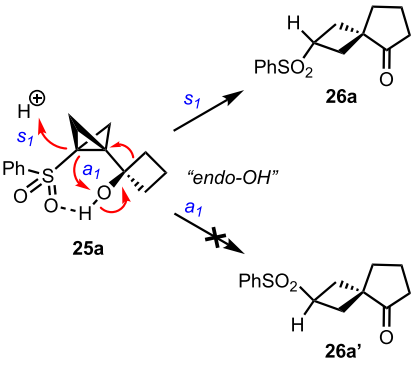
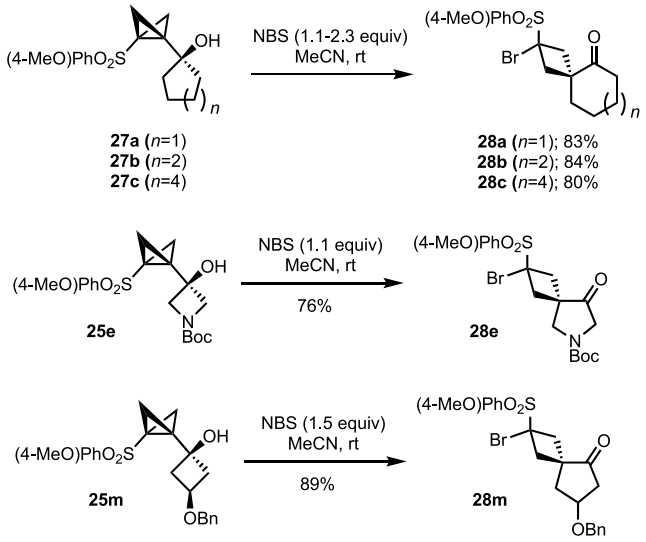


Figure 3. Mechanistic overview for supra- and antarafacial semipinacol rearrangements of bicyclo[1.1.0]butane **25a**. The exclusive formation of *syn* product **26a** eliminates the antarafacial (a_1) pathway in favor of a suprafacial (s_1) shift, possibly with a concomitant intramolecular proton transfer from the alcohol to the sulfone oxygen.

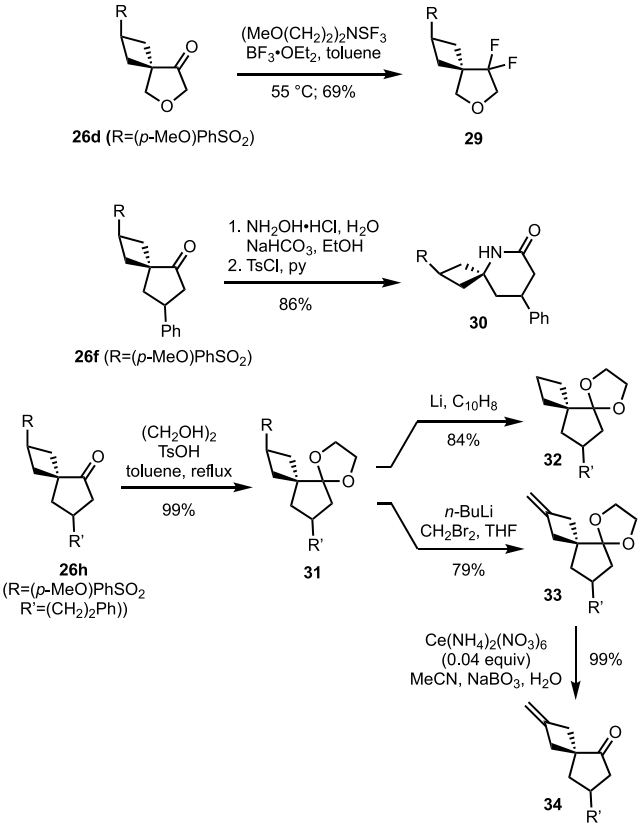
Scheme 3. Semipinacol-Type Rearrangements of Bicyclo[1.1.0]butanes 27a–c, 26e,and 26m with NBS



other acids, such as Amberlyst 15. Presumably, the tertiary alcohol may be protonated by MsOH, leading to an essentially irreversible elimination instead of undergoing the desired semipinacol ring expansion. Gratifyingly, the NBS conditions also allowed the preparation of rearrangement products **28e** and **28m** from Boc-azetidine **25e** and benzyl ether **25m**, which is remarkable because these substrates had previously remained inert or, in the case of **25m**, had led to elimination product **26m** under acidic conditions.

The spirocyclic ketone products could be further converted in high yields to difluoroalkanes and lactams (Scheme 4). Treatment of **26d** with Deoxo-fluor[22] provided difluoride **29** in 69% yield. Lactam **30** was obtained in 86% overall yield from **26f** after Beckman rearrangement of the intermediate oxime. Most significantly, after acetalization of ketone **26h**, removal of the sulfone in **31** was feasible by lithium in naphthalene reduction[23] to give cyclobutene **32**. Alternatively, methylenation[24] of sulfone **31** generated methylenecyclobutane **33**, which was converted to ketone **34** in 99% yield by acetal hydrolysis with catalytic amounts of CAN in a sodium borate buffer.[25]

Scheme 4. Selective Fluorination, Beckman Rearrangement, Acetalization, Reduction, and Methenylations of Spirocycles 26d, 26f, and 26h



In conclusion, we were able to extend the use of sulfonylbicyclo[1.1.0]butanes to the formation of spiro[3.4]-octanes and related heteroatom-containing spirocycles via the acid- and halogen-mediated semipinacol rearrangement of intermediate (bicyclo[1.1.0]butan-1-yl)alkanols. The resulting products could be synthetically manipulated at the carbonyl or arylsulfone positions, in general with high yield and in good chemoselectivity.

Beyond showcasing a novel synthetic strategy, this approach should readily lend itself to the preparation of new spiro[3.4]-octanes for future use as synthetic building blocks, as well as investigations of their biological properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01004.

Experimental details and ^{1}H and ^{13}C NMR spectra for new synthetic intermediates and products (PDF)

Accession Codes

CCDC 2071902 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.

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Notes

The authors declare no competing financial interest.

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