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Trifluoromethanesulfonic Acid-Catalyzed Tandem Semi-Pinacol Rearrangement/Alkyne-Aldehyde Metathesis Reaction of Arylpropagylsulfonamide-Tethered 2,3-Epoxycyclohexan-1-ols to Spiropiperidines

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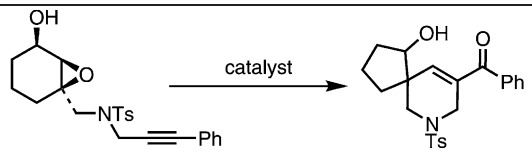
Abstract: A simple and efficient trifluoromethanesulfonic acid-catalyzed cycloisomerization of arylpropagylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols is described. The cyclization proceeds *via* tandem semi-pinacol rearrangement/alkyne-aldehyde metathesis to afford spiropiperidines under mild reaction conditions.

Keywords: alkyne/aldehyde metathesis; semi-pinacol rearrangement; spiropiperidines; tandem reactions; triflic acid

The construction of azaspirocyclic building blocks is an important synthetic goal because such ring skeletons are present in numerous natural products of biological interest.[1] Because the availability of functionalized azaspirocyclic building blocks could greatly facilitate the elaboration of more structurally complex compounds, the design of expedient and efficient synthetic routes to such intermediates has been actively pursued.[2] Many synthetic methods, as the key step, have been developed in pursuit of this structure, including the platinum(II)-catalyzed intramolecular cyclization of cyclic enesulfonamides bearing an alkyne tether;[2a] the ene-type cyclization of cyclic 1,7-enynes with tethered alkynes catalyzed by the cationic palladium complex;[2b] the samarium(II)-mediated cyclization of unsaturated ketolactams;[2c] the intramolecular radical cyclization of cyclic enamines carrying an alkyl bromide[2d] and the palladium-catalyzed transformation of 3,4-dihydro-2-pyridinones carrying a (2-bromophenyl)ethyl substituent.[2e] Although a transition metal-catalyzed process is a useful protocol to obtain azaspirocycles, most of the catalytic approaches involve addition of nucleophiles to metal-activated carbon-carbon multiple bonds. From both economical and environmental points of view, the development of metal-free catalytic processes is desirable for the synthesis of functionalized azaspirocycles. We have now demonstrated that trifluoromethanesulfonic (triflic) acid (TfOH) can be applied, in a catalytic fashion, to a series of various arylpropagylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols allowing the synthesis of functionalized spiropiperidines. In this transformation, a TfOH-induced semi-pinacol-type rearrangement[3] of the six-membered ring epoxy alcohols occurs to generate the ring contraction 2-hydroxycyclopentanecarbaldehyde derivatives. A subsequent TfOH-promoted intramolecular alkyne-aldehyde metathesis[4] then takes place to afford the spiropiperidines in good to high yields under mild reaction conditions.

The requisite arylpropagylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols **1** were prepared starting from the addition of lithiated dimethyl sulfide to 3-isobutoxycyclohex-2-en-1-one in THF at room temperature to produce 3-[(methylthio)methyl]cyclohex-2-en-1-one. Treatment of the resulting thioether with methyl iodide in CH_2Cl_2 at 40 °C afforded 3-(iodomethyl)cyclohex-2-en-1-one. Reaction of the corresponding arylpropagylsulfonamide with 3-(iodomethyl)cyclohex-2-en-1-one in acetone at room temperature followed by reduction of the resulting enones with $NaBH_4$ in MeOH at 0 °C and subsequent epoxidation with *m*CPBA in CH_2Cl_2 at room temperature provided **1** in 41–62% overall yields.[5] Due to the fact that cationic phosphine gold(I) complexes have emerged as versatile catalysts for electrophilic activation of alkynes toward a variety of nucleophiles under mild reaction conditions,[6] we first screened reaction condi-

Table 1. Optimization of the reaction conditions.

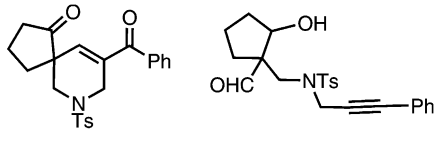


1a **2a**

Entry	Catalyst	Solvent	T [°C]	t	Yield [%] (dr)[a]
1	5% $PPh_3Au/AgOTf$	DCM	24	10 h	33 (58:42)
2	10% BF_3•OEt_2	THF	24	2.0 h	46 (52:48)
3	10% $AgSbF_6$	DCE	24	3.0 h	60 (48:52)
4	10% $NHTf_2$	DCE	24	0.5 h	83 (67:33)
5	10% TfOH	DCE	24	3.5 h	86 (49:51)
6	10% TfOH	DCE	50	40 min	91 (76:24)
7	10% TfOH	DCM	50	2.0 h	64 (73:23)
8	10% TfOH	THF	50	2.5 h	52 (63:37)
9	10% TfOH	toluene	50	2.0 h	57 (37:63)
10	10% TfOH	MeCN	50	4.0 h	33 (69:31)

[a] Diastereoisomeric ratio.

tions for the cycloisomerization of **1a** using the two-component catalytic system [$PPh_3AuCl/AgOTf$]. Thus, treatment of **1a** with 5 mol% of $PPh_3AuCl/AgOTf$ in CH_2Cl_2 at 24 °C for 10 h gave a 33% yield of spiropiperidine **2a** as a mixture of two diastereomers (Table 1, entry 1). The parent compound **1a** was then subjected to a series of Lewis and Brønsted acids and various solvents (Table 1). While boron trifluoride etherate in THF and $AgSbF_6$ in dichloroethane (DCE) could not catalyze the process efficiently (Table 1, entries 2 and 3), $NHTf_2$ (10 mol%) exhibited high catalytic activity in DCE at 24 °C and provided **2a** in 83% isolated yield after 30 min reaction time (Table 1, entry 4). The use of TfOH (10 mol%) in DCE at 24 °C for 30 min gave the desired spiropiperidine **2a** (18%) and an additional product identified as phenylpropagylsulfonamide-tethered 2-hydroxycyclopentanecarbaldehyde **4** (21%) together with recovery of the starting substrate **1a** (47%). Delightfully, the full conversion of **1a** into **2a** was accomplished after 3.5 h at 24 °C (86% yield, Table 1, entry 5). Due to the isolation of the semi-pinacol rearrangement product, compound **4** (Figure 1) is likely to be the key intermediate for the following cycloisomerization leading to the spiropiperidine **2a**.



3a **4**

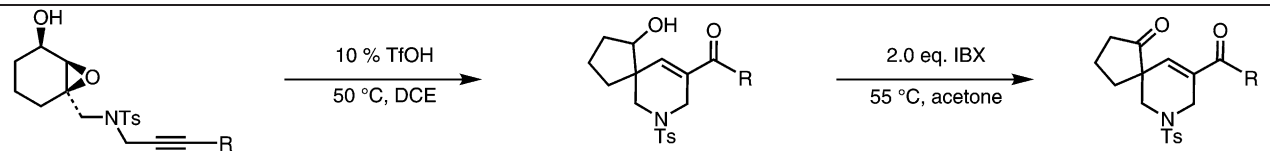
Figure 1. Structures of **3a** and **4**.

In order to facilitate analysis and shorten reaction times, the reaction temperature was increased to 50 °C. The parent compound **1a** did cycloisomerize smoothly at 50 °C and a 91% isolated yield of the expected spiropiperidine **2a** was obtained after 40 min at 50 °C (Table 1, entry 6). The investigation of various solvents in the presence of the TfOH catalyst revealed that dichloromethane, THF, toluene and CH_3CN were less effective and afforded **2a** in moderate yields (33–64%, Table 1, entries 7–10). Thus, the use of TfOH (10 mol%) in DCE at 50 °C was found to be the most efficient and was chosen as the standard reaction conditions. A similar catalytic condensation reaction of electron-rich arenes with aldehydes using various Lewis acids, for example, $AuCl_3$, $Hg(ClO_4)_2$, $Tl(ClO_4)_3$ and Brønsted acids has been reported.[7]

It must be mentioned that attempts to separate the mixture of two diastereomeric isomers of **2a** using flash column chromatography on silica gel failed. Oxidation of the mixture with 2-iodoxybenzoic acid (IBX) in refluxing acetone for 6 h gave 9-benzoyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-one (**3a**) in nearly quantitative yield from **2a** (Figure 1). The structure elucidation of **3a** was achieved by X-ray crystallography.[8]

With the optimal reaction conditions, we next examined the substrate scope of the TfOH-catalyzed transformation. The results of the TfOH-catalyzed cycloisomerization reaction of the arylpropagylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols **1a–l** to produce spiropiperidines **2a–l** are listed in Table 2. Electron-neutral and electron-rich arenes at the alkyne terminus were proven to be good substrates, as the yields of desired spiropiperidines **2a–f** as a mixture of diastereomers ranged from 66% to 91% (entries 1–6, Table 2). The crude mixture of diastereomeric isomers of **2c** was separated in a ratio of 2:1 using flash column chromatography on silica gel. The ^{1}H NMR spectrum of the major isomer exhibited a singlet at $\delta = 6.33$ assigned to the vinyl H, a broad singlet at $\delta = 4.18$ assigned to the H at the carbinol carbon, and two doublets, centered at $\delta = 4.26$ and 3.73, assigned to the two diastereotopic methylene protons at the allylic carbon. The ^{1}H NMR spectrum of the minor isomer exhibited a singlet at $\delta = 6.58$ assigned to the vinyl H, a broad singlet at $\delta = 4.21$ assigned to the H at the carbinol carbon, and two doublets, centered at $\delta = 4.11$ and 3.69, assigned to the two diastereotopic methylene protons at the allylic carbon. However, substrates with a bromine atom at the phenyl ring, for example, **1g**, **1h**, or an electron-withdrawing group, such as an ester or nitro group at the phenyl ring, for example, **1i–k**, were less effective and required prolonged reaction times to provide spiropiperidines **2g–k** in 14% to 56% isolated yields (Table 2, entries 7–11). Moreover, substrate **1l** having a methyl group at

Table 2. Synthesis of spiropiperidines **2**.

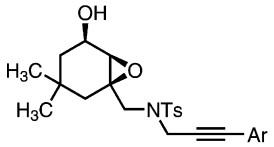


1 **2** **3**

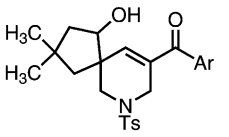
Entry	Substrate	R	*t*	Product[a]	Yield [%] of **2** (*dr*)	Yield of **3** [%][b]
1	**1a**	phenyl	40 min	**2a**	91 (76:24)	87
2	**1b**	4-methoxyphenyl	10 min	**2b**	84 (54:46)	79
3	**1c**	4-methylphenyl	30 min	**2c**	76 (67:33)	72
4	**1d**	4-phenylphenyl	15 min	**2d**	81 (58:42)	76
5	**1e**	1-naphthyl	10 min	**2e**	86 (57:43)	81
6	**1f**	9-phenanthryl	15 min	**2f**	66 (50:50)	61
7	**1g**	4-bromophenyl	4 h	**2g**	56 (38:62)	53
8	**1h**	2-bromophenyl	3 h	**2h**	48 (44:56)	43
9	**1i**	2-ethoxycarbonylphenyl	2 h	**2i**	28 (52:48)	26
10	**1j**	3-ethoxycarbonylphenyl	2 h	**2j**	51 (52:48)	48
11	**1k**	4-nitrophenyl	8 h	**2k**	14 (44:56)	13
12	**1l**	CH_3	30 h	**2l**	21 (29:71)	20
13	**1m**	H	1 h	**2m**	0 -	0

[a] All products **2** were subjected to IBX oxidation and characterized as 9-aroyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-ones **3**.

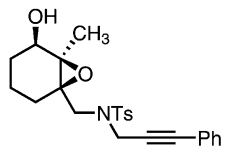
the alkynyl terminus lowered the catalytic activity of TfOH and the yield of **2l** was diminished to 21% (Table 2, entry 12). Unfortunately, the reaction of the substrate with a terminal alkyne, for example, **1m**, resulted in decomposition of the starting substrate (Table 2, entry 13). It is worthy of mention that substrates bearing a geminal dimethyl group at C-5 of the ring, for example, **1n**, **1o**, do not interfere with the catalytic activity of TfOH as shown by the fact that the yields of their corresponding spiropiperidines **2n** and **2o** were 86% and 93%, respectively. However, the reaction was sluggish with the substrate bearing an methyl group at the C-2 position of the ring, for example, **1p**, and the cyclization produced spiropiperidine **2p** in only 43% yield (Figure 2).[9]



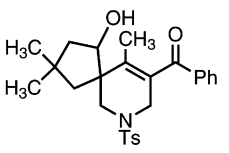
1n : Ar = Ph
1o : Ar = 4-methoxyphenyl



2n : Ar = Ph
2o : Ar = 4-methoxyphenyl



1p

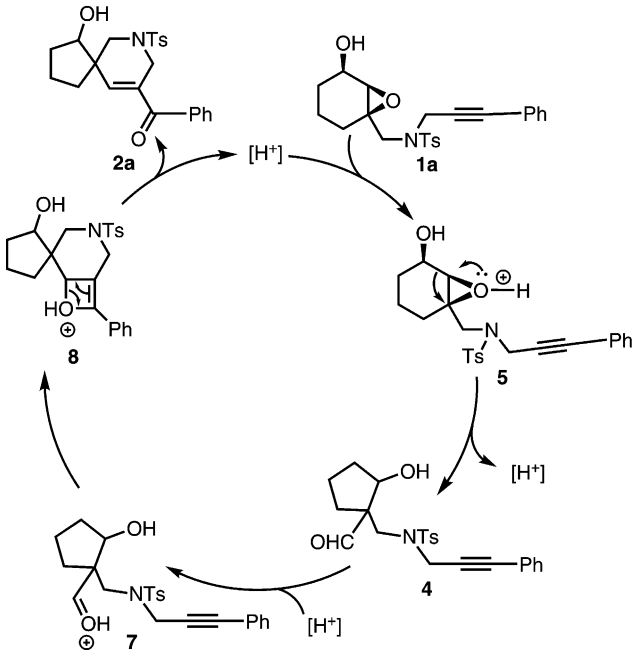


2p

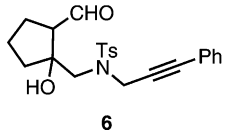
Figure 2. Structures of **1n–p** and **2n–p**.

On the basis of the experiment results, a possible reaction pathway for the observed TfOH-catalyzed cycloisomerization of **1a** to provide **2a** is suggested in Scheme 1. Protonation of the epoxide of **1a** with TfOH led to the oxiranium ion **5**, which promoted a semi-pinacol rearrangement to give the phenylpropagylsulfonamide-tethered 2-hydroxycyclopentanecarbaldehyde **4** as a mixture of diastereomers. It must be mentioned that the usual semi-pinacol rearrangement of 2,3-epoxycyclohexan-1-ols gives 2-hydroxycyclopentanecarbaldehyde **6** (Figure 3), which led to the formation of cyclopentene-1-carbaldehyde derivatives after dehydration.[3a] The formation of 2-hydroxycyclopentanecarbaldehyde **4** demonstrated that the preferred reaction pathway for the semi-pinacol rearrangement of **5** proceeded *via* migration of the hydroxyalkyl group to the tertiary carbocation. The similar unusual semi-pinacol rearrangement had previously been observed with an α-silyloxymethyl epoxide having both allylic and tertiary centers.[3c] The following TfOH-catalyzed intramolecular alkyne-aldehyde metathesis started with protonation of the formyl group of **4** to give the oxonium species **7**, which produced oxete **8** *via* [2+2]cycloaddition. The intermediate **8** then underwent [2+2]cycloreversion to afford spiropiperidine **2a** and regenerated the acid in the catalytic cycle.

In summary, we have developed an efficient synthesis of 9-benzoyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-ols



Scheme 1. Plausible reaction mechanism for the TfOH-catalyzed cycloisomerization of **1** to **2**.



6

Figure 3. Structure of **6**.

via TfOH-catalyzed tandem semi-pinacol rearrangement/alkyne-aldehyde metathesis reaction from 2,3-epoxycyclohexan-1-ols tethered an arylpropagylsulfonamide. The advantages of this procedure are the mild reaction condition and the environmentally friendly catalyst. Further studies on synthetic applications of these reactions are currently in progress.

Experimental Section

General Procedure for Synthesis of 9-Benzoyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-one (3) *via* TfOH-Catalyzed Tandem Semi-Pinacol Rearrangement/Alkyne-Aldehyde Metathesis

To an oven-dried, 10-mL round-bottom flask equipped with a stirrer bar and capped with a rubber septum was added **1a** (103 mg, 0.25 mmol), TfOH (2.18 μL, 0.025 mmol) and DCE (1.25 mL) under nitrogen. The reaction mixture was stirred at 50 °C for 40 min. The mixture was allowed to cool to room temperature and was treated with 5 mL of saturated aqueous Na_2CO_3 solution. The resulting mixture was extracted with dichloromethane (10 × 3 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure to afford the crude product **2a** as a yellow oil; yield: 93 mg. The crude **2a** was used for the next oxidation step without further purification.

To an oven-dried, 10-mL round-bottom flask equipped with a stirrer bar and capped with a rubber septum was added **2a** (93 mg, 0.23 mmol), 2-iodoxybenzoic acid (0.14 g, 0.5 mmol) and acetone (2.5 mL) under nitrogen. The reaction mixture was stirred at 55 °C for 6 h. The reaction mixture was allowed to cool to room temperature and was filtered through a bed of Celite. The filtrate was concentrated under vacuum, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 10:1) to give **3a** as a colorless solid; yield: 89 mg (0.21 mmol, 87%); mp 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.0$ Hz, 2H), 7.61 (d, $J = 7.3$ Hz, 2H), 7.53 (t, $J = 7.3$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 6.28 (s, 1H), 4.43 (d, $J = 16.6$ Hz, 1H), 3.62 (d, $J = 11.6$ Hz, 1H), 3.48 (dd, $J = 16.6$, 2.0 Hz, 1H), 2.63 (d, $J = 11.6$ Hz, 1H), 2.44 (s, 3H), 2.41–2.28 (m, 3H), 2.12–2.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 216.8$, 194.5, 144.1, 141.3, 137.0, 135.8, 133.0, 132.3, 129.9 (2C), 129.3 (2C), 128.4 (2C), 127.6 (2C), 53.2, 47.6, 44.4, 38.1, 34.8, 21.5, 19.3; IR (CH_2Cl_2): $\nu = 3062$, 2966, 1738, 1645 cm^{-1}; HR-MS (EI): $m/z = 432.1252$, calcd. for $C_{23}H_{23}NO_4NaS$ ($M + Na^+$): 432.1246. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

Supporting Information

Spectroscopic characterization and copies of ^{1}H/^{13}C NMR spectra of two diastereomersi of **2c**; ^{1}H/^{13}C NMR spectra of compounds **3a–l** and X-ray crystallographic information files for compounds **3a** and **3o** are available as Supporting Information.

Acknowledgements

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[8] Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 835096 (**3a**) and CCDC 835097 (**3o**).These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+ 44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

[9] All compounds **2** were subjected to IBX oxidation and fully characterized as 9-aroyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-ones **3**.

