Cyclization

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Rhodium-Catalyzed Propargylic Substitution: A Divergent Approach to Propargylic and Allenyl Sulfonamides**

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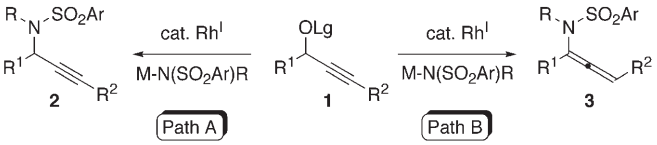
The transition-metal-mediated substitution of propargylic alcohol derivatives using a stoichiometric cobalt–alkyne complex, represents a fundamentally important synthetic transformation that is often referred to as the Nicholas reaction.[1] The catalytic version of this process, in which a number of late-transition-metal complexes have been shown to be effective catalysts, has also been described.[2,3] Nonetheless, a key and striking feature with many of the catalytic variants is the preponderance of aryl-substituted propargylic alcohols, which presumably circumvents the problem of β-hydride elimination with alkyl derivatives.

We envisioned that the rhodium-catalyzed version would prove interesting, given the unique reactivity often observed with this particular transition metal for related transformations.[4,5] Herein, we describe the first rhodium-catalyzed propargylic amination of secondary propargylic alcohol derivatives **1**, which provides a divergent approach for the preparation of propargylic sulfonamides **2** (path A: R^1 = alkyl/aryl, R^2 = H; Scheme 1) and 1,1-disubstituted allenyl sulfonamides **3** (path B: R^1 = aryl, R^2 = H).[6]



Scheme 1. General approach for the divergent construction of propargylic and allenyl sulfonamides.

Preliminary studies examined the feasibility of the rhodium-catalyzed propargylic amination of **1a** (R^1 = Ph-$(CH_2)_2$; R^2 = H) using *N*-benzyl toluenesulfonamide (Table 1). Although the attempted amination of propargylic alcohol **1a** (Lg = H; entry 1) with the Wilkinson catalyst was completely unsuccessful, the acetate **1a** (Lg = Ac; entry 2) furnished a trace amount of the desired propargylic sulfonamide **2a**. Despite the fact that the yield was not particularly encouraging, we envisioned that additional improvement would be achieved through the modification of the catalyst with trimethyl phosphite in an analogous manner to the related allylic substitution reaction.[4,5] Indeed, the trimethyl phosphite modified Wilkinson catalyst afforded **2a** with an improved yield of 27% (entry 3), albeit with significant quantities of the propargylic alcohol derived from transacylation. This result prompted the examination of alternative leaving groups (see entries 3–5). Gratifyingly, treatment of the propargylic carbonate **1a** (Lg = *t*BuOCO) with the modified Wilkinson catalyst and the lithium anion of *N*-benzyl toluenesulfonamide, furnished the propargylic sulfonamide **2a** in 82% yield (entry 5). Additional studies focused on the effect of the terminal alkyne substituent R^2. Interestingly, although a trimethylsilyl group provides the propargylic

Table 1: Optimization of the rhodium-catalyzed propargylic amination reaction.[a]

Entry	R^2	Additive (mol%)	Lg	Yield of **2a** [%][b]
1	H	–	H	0
2	H	–	COMe	trace
3	H	$P(OMe)_3$ (40)	COMe	27
4	H	$P(OMe)_3$ (40)	CO_2Me	66
5	H	$P(OMe)_3$ (40)	CO_2tBu	82
6	Me_3Si	$P(OMe)_3$ (40)	CO_2tBu	20
7	Me	$P(OMe)_3$ (40)	CO_2tBu	0
8	Ph	$P(OMe)_3$ (40)	CO_2tBu	0

[a] See Scheme 1; **1a** R^1 = Ph$(CH_2)_2$; R = $PhCH_2$, Ar = *p*-$CH_3C_6H_4$. All reactions were carried out on a 0.25-mmol scale with 10 mol% $[RhCl(PPh_3)_3]$ and 2.0 equivalents of the lithium anion of *N*-benzyl toluenesulfonamide (LiN(Ts)Bn; Ts = *p*-toluenemethanesulfonyl) at 30°C. [b] Yield of the isolated product.

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sulfonamide **2a** (entry 6), albeit in low yield, the aryl- and alkyl-substituted derivatives are completely unreactive under the analogous reaction conditions (entries 7 and 8).

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 5) to a variety of nucleophiles and aliphatic propargylic carbonates (see below). This

Table 2: Scope of the rhodium-catalyzed propargylic amination reaction.[a]

Entry	R^1	**1**	$MN(SO_2Ar)R^2$[b]	**2**	Yield [%][c]
1	$Ph(CH_2)_2$	**a**	LiN(Ts)Bn	**a**	82
2	$Ph(CH_2)_2$	**a**	LiN(Ts)PMP	**ab**	74
3	$Ph(CH_2)_2$	**a**	LiN(Ns)Allyl	**ac**	72
4	$Ph(CH_2)_2$	**a**	LiN(Ts)N=C(Me)Ph	**ad**	83
5	$Ph(CH_2)_2$	**a**	KPhth	**ae**	71
6	$Ph(CH_2)_2$	**a**	$NaCH(CO_2Me)_2$	**af**	83
7	$PhCH_2$	**b**	LiN(Ts)Bn	**b**	85
8	CH_3	**c**	LiN(Ts)Bn	**c**	76
9	$CH_3(CH_2)_2$	**d**	LiN(Ts)Bn	**d**	74
10	$CH_2{=}CH(CH_2)_3$	**e**	LiN(Ts)Bn	**e**	78
11	$(CH_3)_2CHCH_2$	**f**	LiN(Ts)Bn	**f**	86
12	$(CH_3)_2CH$	**g**	LiN(Ts)Bn	**g**	70
13	*c*-C_6H_{11}	**h**	LiN(Ts)Bn	**h**	74
14	$(CH_3)_3C$	**i**	LiN(Ts)Bn	**i**	83
15	$BnOCH_2$	**j**	LiN(Ts)Bn	**j**	72

[a] See Scheme 1; **1** Lg = CO_2tBu, R^2 = H. All reactions were carried out on a 0.25-mmol reaction scale using 10 mol% $[RhCl(PPh_3)_3]$ modified with 40 mol% $P(OMe)_3$ in THF at 30°C. [b] 2.0 equivalents of the lithium anion of the *N*-substituted sulfonamide. [c] Yields of the isolated product. Phth = phthalimide.

transformation proved tolerant of both *N*-alkyl and aryl sulfonamides (entries 1 and 2), in which the *p*-toluenesulfonamide could be substituted for the more readily removed *p*-nitrobenzenesulfonyl group to improve the synthetic utility of this protocol (entry 3).[7,8] The *N*-sulfonyl hydrazone, phthalimide, and dimethyl malonate also provided suitable nucleophiles, thus clearly illustrating the scope of this process (entry 4–6).[9] Another impressive feature of this transformation is the range of aliphatic propargylic substituents that can be utilized. For example, linear (entries 7–10) and branched (entries 11–13) aliphatic substituents, including the *tert*-butyl (entry 14) and benzyloxymethyl (entry 15) substituents, afford the corresponding propargylic sulfonamides **2** in good yield.[10,11] Hence, the ability to accomplish the rhodium-catalyzed propargylic amination of a wide range of aliphatic propargylic alcohol derivatives represents an important addition to the area of metal-mediated propargylic substitutions.

Although the propargylic substitution of alkyl-substituted propargylic carbonates was straightforward, the aryl derivative **1m** (R^1 = Ph) furnished the 1,1-disubstituted allenyl sulfonamide **3m** as the major product under analogous conditions (Table 3, entry 5). The origin of the divergent reactivity was attributed to a base-induced isomerization of the initially formed propargylic sulfonamides **2m** to the corresponding allene **3m**.[12] We reasoned that the isomerization could be suppressed with a weaker base. Gratifyingly, the propargylic amination of **1m** with potassium carbonate as

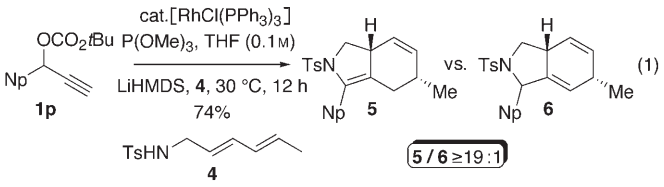
Table 3: Divergent approach to propargyl and allenyl sulfonamides through rhodium-catalyzed propargylic substitution.[a]

Entry	R^1	**1**	Base	**2**/**3**[b]	Yield [%][c]
1	*p*-$MeOC_6H_4$	**k**	LiHMDS	≥19:1	51
2	*p*-$MeOC_6H_4$	**k**	K_2CO_3	≥19:1	78
3	*p*-MeC_6H_4	**l**	LiHMDS	1:1	63
4	*p*-MeC_6H_4	**l**	K_2CO_3	≥19:1	72
5	Ph	**m**	LiHMDS	≤1:19	77
6	Ph	**m**	K_2CO_3	≥19:1	74
7	*p*-BrC_6H_4	**n**	LiHMDS	≤1:19	70
8	*p*-BrC_6H_4	**n**	K_2CO_3	≥19:1	69
9	*p*-$CF_3C_6H_4$	**o**	LiHMDS	≤1:19	48
10	*p*-$CF_3C_6H_4$	**o**	K_2CO_3	2:1	61
11	Np	**p**	LiHMDS	≤1:19	82
12	Np	**p**	K_2CO_3	≥19:1	83
13	1-furyl	**q**	LiHMDS	≤1:19	63
14	1-furyl	**q**	K_2CO_3	≥19:1	55

[a] See Scheme 1; **1** Lg = CO_2tBu, R^2 = H. All reactions were carried out on a 0.25-mmol reaction scale with 10 mol% $[RhCl(PPh_3)_3]$ modified with 40 mol% $P(OMe)_3$ in THF at 30°C with TsNHBn (2 equiv) and the requisite base (2 equiv). [b] Ratio of amination products was determined by NMR (400 MHz) spectroscopic analysis on the crude reaction mixture. [c] Yield of the isolated products. HMDS = hexamethyldisilazane.

the base furnished the propargylic sulfonamide **2m** in 74% yield (entry 6). A series of *para*-substituted aryl propargyl alcohol derivatives **1k–o** were examined to determine the scope of this divergent behavior. This study indicates that the isomerization may be directly related to the relative acidity of the α-proton in the propargylic sulfonamide **2**. For example, strongly electron-donating substituents suppress the isomerization (entries 1–4), whereas the strongly electron-withdrawing groups are prone to isomerization to the allene with even a weak base, albeit to a much lesser extent (entries 7 and 8 versus 9 and 10). The napthyl (Np) **1p** and furyl **1q** derivatives demonstrate analogous behavior to the phenyl and *p*-bromophenyl derivatives **1m** and **1n** and facilitate the selective formation of either derivative (entries 11–14).

We developed a sequential one-pot two-component rhodium-catalyzed propargylic amination/isomerization followed by a [4+2] carbocyclization [Eq. (1)][12–15] to highlight



the synthetic utility of the base-induced isomerization of aryl-substituted propargylic sulfonamides to the corresponding 1,1-disubstituted allenes in situ. Treatment of the aryl-substituted propargylic carbonate **1p** under the standard reaction conditions and with the lithium anion of sulfonamide derivative **4** afforded the bicyclohexadienes **5**/**6** in 74% yield with 19:1 selectivity for **5** (d.r. ≥ 19:1, as determined by ^{1}H NMR spectroscopy). The relative configuration of **5** was determined by X-ray crystallography. Although allenes have

been utilized in an array of metal-catalyzed carbocyclization reactions, the ability to utilize 1,1-disubstituted derivatives in this manner represents a novel process.[15,16]

In conclusion, we have demonstrated that rhodium-catalyzed propargylic amination provides an efficient and versatile method for the construction of aliphatic-substituted propargylic sulfonamides. This study also demonstrates that the divergent behavior in the rhodium-catalyzed variant of the propargylic substitution, in which either aryl-substituted propargylic or allenyl sulfonamides can be prepared is dependent upon the acidity of the propargylic proton. Finally, the synthetic utility of the isomerization of aryl-substituted propargylic sulfonamides in situ was demonstrated in a one-pot two-component rhodium-catalyzed propargylic amination/isomerization followed by a [4+2] carbocyclization. We anticipate the ability to prepare functionalized bicyclohexadienes in this manner will have significant synthetic utility for target-directed synthesis.

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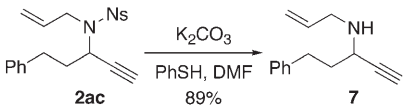

2ac 7

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[10] LiHMDS (0.5 mL, 0.5 mmol, 1.0 M in THF) was added dropwise to *N*-benzyl *p*-toluenesulfonamide (0.132 g, 0.5 mmol) in anhydrous THF (1.5 mL). The anion was allowed to form over approximately 5 min. In a separate flask, trimethyl phosphite (12 μL, 0.10 mmol) was added directly to a red solution of the Wilkinson catalyst (23.1 mg, 0.025 mmol) in anhydrous THF (1.0 mL) under an atmosphere of argon. The catalyst was allowed to form over approximately 5 min, thus resulting in a light-yellow homogeneous solution. The propargylic carbonate **1a** (65.6 mg, 0.25 mmol) was then added dropwise through a tared 250-μL syringe, and the reaction mixture was heated to 30 °C for approximately 15 h (tlc control). The reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and partitioned between diethyl ether and saturated NH_4Cl solution. The aqueous phase was washed with diethyl ether, and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (ethyl acetate/hexanes 5:95) furnished the propargylic sulfonamide **2a** (86.4 mg, 82%) as a colorless oil.
[11] Interestingly, this transformation does not allow the chirality transfer observed with the analogous allylic substitution; for example, treatment of the enantiomerically enriched propargylic carbonate (*S*)-**1a** (85% *ee*) under the optimized reaction conditions, furnished propargylic sulfonamide **2a** in 75% yield as the racemate (0% *ee*).
[12] Treatment of the propargylic sulfonamide **2m** with the lithium anion of the *N*-benzyl *p*-toluenesulfonamide furnished the 1,1-disubstituted allene **3m** in 99% yield, thus clearly demonstrating that the rhodium catalyst is not involved in the isomerization. For a similar process that involves a mixed catalyst, see: M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* **2004**, 2712 – 2713.
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[15] The excellent selectivity for the rhodium-catalyzed [4+2] cycloaddition with the allene versus the alkyne moiety to afford **5** rather than **6**, respectively, is feasible as the alkyne carbocyclization requires higher temperature (60 °C).
[16] For an example of a metal-catalyzed [4+2] carbocyclization reaction with an unactivated allene, see: P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432 – 6434.

