Diastereoselective Cobalt-mediated Acylation-Cyclization of Allenes

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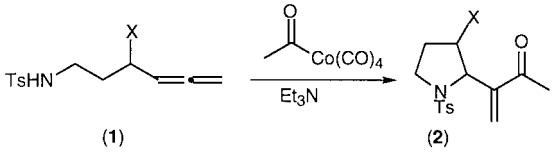
Abstract: Allenes with α-oxygen and γ-sulfonamide substituents were synthesized and cyclized to pyrrolidines using an acyl cobalt reagent. The reactions proceeded with very high *trans* selectivity.

Key words: allene, cobalt, cyclization, pyrrolidine, diastereoselectivity

The acylation-cyclization reaction of allenes (**1**, X = H) using acyl cobalt reagents was recently reported to be an efficient route to pyrrolidines (**2**, X = H) and other cyclic compounds (Equation 1).[2] We were interested in the possibility of diastereoselectivity in the cyclization if there was a substituent on the tether between the sulfonamide nucleophile and the allene. Due to our interest in the synthesis of hydroxylated pyrrolizidines, we chose to examine the effect of a protected alcohol group α to the allene (X = OPG).



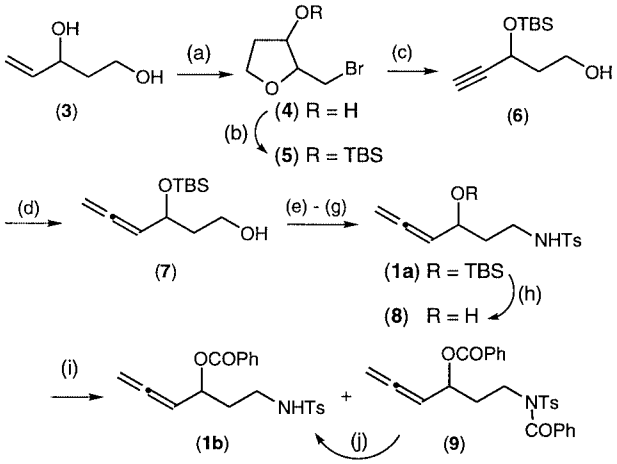
(**1**) (**2**)

Equation 1

Related cyclizations have been reported using other metals, especially palladium catalysts, although the exact mechanism is not always clear[3] (both η^2 and η^3 intermediates have been proposed). Modest to excellent diastereoselectivity has been observed.[4] Recently, it has been shown that lanthanide complexes can catalyze highly stereoselective amino allene cyclizations.[4b,5]

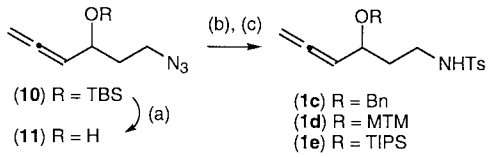
The required substituted allenes **1** (X ≠ H) were prepared from the known diol[6] (**3**) (Scheme 1). Treatment with NBS resulted in cyclization. The remaining hydroxyl group was protected by conversion to TBS ether (**5**). Elimination with ring opening was achieved by treatment with an excess of LDA[7] to give alkyne (**6**) which was further converted to allene (**7**) using the method of Searles and Crabbé.[8] The allene (**7**) was converted to the desired sulfonamide (**1a**) via its unstable azide.[9]

To obtain ester derivative **1b**, the TBS group was removed to give the alcohol **8**. On treatment with benzoyl chloride, some selectivity for O-benzoylation was achieved, but, generally, mixtures of the desired O-benzoyl product (**1b**) and O,N-dibenzoylated product (**9**) were obtained. The O,N-dibenzoylated product (**9**) could be converted to the desired O-benzoyl product (**1b**) by treatment with methanolic triethylamine.



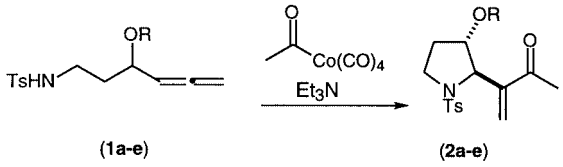
Scheme 1 (a) NBS, CH_3CN (97%); (b) TBSCl, imidazole, THF (70%); (c) LDA (4 equiv). THF, -78 °C (51%); (d) *i*-Pr_2NH, CuI, $(CH_2O)_n$, dioxane, Δ (89%); (e) MsCl, Et_3N; (f) NaN_3, DMF; (g) Zn, AcOH, THF; filter then TsCl, Na_2CO_3, H_2O, CH_2Cl_2 (from (**7**): 55%); (h) KF, Bu_4NHSO_4, CH_3CN (73%); (i) BzCl, Et_3N; (j) MeOH, Et_3N (from (**8**): overall 49%).

Attempts to O-alkylate **8** selectively were disappointing, therefore, for ether derivatives, we returned to the intermediate azide (**10**) (Scheme 2). This was deprotected and the resulting azidoalcohol (**11**) was O-alkylated to give the benzyl, MTM and TIPS ethers. These were converted to the sulfonamides (**1c**, **1d**, **1e**) as before. It may be noted that the PTC method[10] is effective for the MTM group, proceeding in 77% yield, although it has been reported that formation of secondary MTM ethers in a Williamson fashion is inefficient.[11]

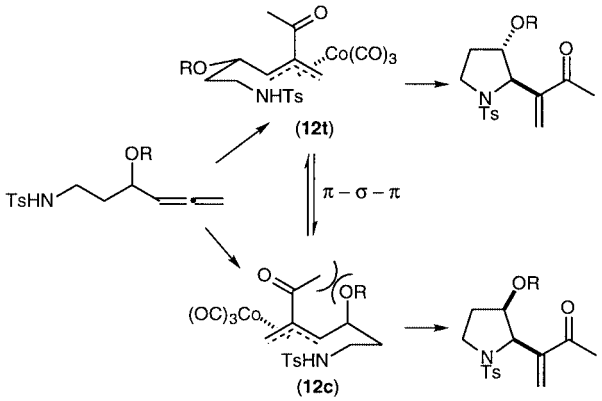


Scheme 2 (a) KF, Bu_4NHSO_4 (73%); (b) BnBr or MTMCl, KOH, Bu_4NHSO_4, toluene; or TIPSCl, imidazole, DMAP; (c) Zn, AcOH, THF; filter then TsCl, Na_2CO_3, H_2O, CH_2Cl_2 (from (**11**): 54, 59 and 26% yields respectively).

The sulfonamides (**1a-e**) were treated with acetyl tetracarbonyl cobalt and triethylamine according to our previous procedure (Equation 2).[2] In all cases the *trans*-isomer of the pyrrolidine (**2**) was the major product, in some cases the exclusive pyrrolidine product (Table).



Equation 2



Scheme 3

Table Acylation-Cyclization Diastereoselectivity[a]

substrate	R	combined yield (%)	ratio trans/cis
1a	TBS	77	26:1
1e	TIPS	61[c]	-[b]
1b	Bz	28	-[b]
1c	Bn	37	26:1
1d	MTM	31	3.6:1

[a] reaction conditions: $AcCo(CO)_4$ (1.1 equiv), THF, r.t., 10 min, then Et_3N (1.2 equiv), overnight; [b] only one isomer obtained; [c] 71% after recovered starting material

The stereochemistry could be unambiguously determined by observation of the H2-H3 coupling constants.[12] For the *trans*-isomers these coupling constants are always about 0 Hz. Molecular models confirmed a dihedral angle of about 90°. Curiously, H3 was observed as a doublet, implying that one of the H3-H4 coupling constants is also 0 Hz. Once again, observation of molecular models confirmed the feasibility of one of the H3-C-C-H4 dihedral angles being close to 90°. For the *cis*-isomers, where isolated, the H2-H3 coupling constant was larger: about 4.5 Hz. In related pyrrolidines, Carretero et al. have observed that the *cis*-isomers have a distinctly larger H2-H3 coupling constant than the *trans*-isomers.[13]

The predominance of the *trans*-isomer can be explained by appeal to a simple conformational argument (Scheme 3). The conformation of the η^3-cobalt intermediate (**12t**) that leads to the *trans*-isomer places the oxygen substituent in a pseudo equatorial position. On the other hand, the conformation (**12c**) leading to the *cis*-isomer results in a pseudo-axial position for this substituent with a distinct interaction with the acetyl substituent on the η^3-allyl moiety.[14]

It may be noted that, although the TBS ether (**1a**) gives a very high ratio, the somewhat bulkier TIPS ether (**1e**) gives exclusively the *trans*-isomer, reflecting the greater size of the TIPS group. In contrast, the MTM ether (**1d**) gives a very low ratio. We believe that coordination of the cobalt atom by the sulfur disrupts the conformations. The effect of S-Co coordination in the Pauson-Khand reaction has been noted.[15]

The consistantly high diastereoselectivity of this cyclization and the synthetic value of the products[16] makes this a useful reaction for organic synthesis. Applications to alkaloid synthesis are in hand.

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(12) data for *trans*-(**2a**): mp 93-94 °C, ^{1}H NMR δ -0.10 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), 0.62 (9H, s, *t*-Bu), 1.70 (1H, m, H4), 1.82 (1H, m, H4'), 2.42 (3H, s, $ArCH_3$), 2.44 (3H, s, $COCH_3$), 3.29 (1H, ddd, *J* = 2.6, 3.5, 6 Hz, H5), 3.70 (1H, t, *J* = 3.5 Hz, H5'), 3.92 (1H, d, *J* = 1.7 Hz, H3), 4.4 (1H, s, H2), 6.34 (1H, s, =CH), 6.41 (1H, s, =CH), 7.25 (2H, d, *J* = 8 Hz, Ar), 7.75 (2H, d, J = 8 Hz, Ar); ^{13}C δ 199.4, 147.3, 143.3, 133.4, 129.6, 128.4, 127.8, 76.1, 68.3, 45.9, 31.7, 26.4, 25.7, 21.4, 17.5, -4.9, -5.5; ν/cm^{-1}: 2928, 1687, 1599, 1 101, 834; m/z: 366 (100, M$^+$-*t*-Bu), 291 (8), 210 (32); Found C 59.53%, H 7.88, N 3.32; Calcd. for $C_{21}H_{33}NSO_4Si$: C 59.54, H 7.85, N 3.31.
cis-(**2a**) ^{1}H NMR δ -0.14 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.75 (9H, s, *t*-Bu), 1.25 (2H, m, H4), 2.34 (3H, s, $COCH_3$), 2.42 (3H, s, $ArCH_3$), 3.42-3.60 (2H, m, H5), 4.18 (1H, app. q, J = 4.5 Hz, H3), 4.64 (1H, d, J = 4.5 Hz, H2), 6.28 (1H, s, =CH), 6.31 (1H, s, =CH), 7.30 (2H, d, J = 8 Hz, Ar), 7.69 (2H, d, J = 8 Hz, Ar).
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