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The Rhodium-Catalyzed Carbene Cyclization Cycloaddition Cascade Reaction of Vinylsulfonates

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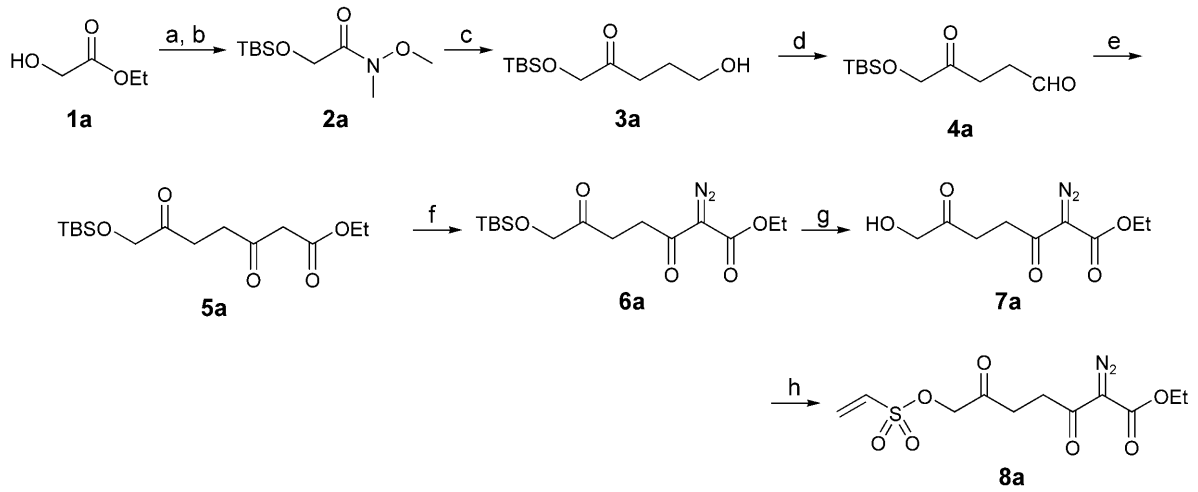
Abstract: Vinylsulfonates have proved to be excellent dipolarophiles for carbonyl ylides derived from diazoketones in rhodium-catalyzed intramolecular cycloadditions. Polyfunctional substrates, such as **8** and (+)-**15**, were readily available from hydroxy esters, e.g. **1** and the cyclopenta-1,3-dione **10**, respectively, and the resulting polycyclic sultones were formed under mild reaction conditions in high yields with very good diastereoselectivities. A ruthenium-catalyzed asymmetric transfer hydrogenation was found to desymmetrize the *meso*-cyclopenta-1,3-dione **12** efficiently.

Keywords: asymmetric reduction; cycloaddition; domino reactions; sulfur heterocycles; transition metal catalysis

The carbene cyclization cycloaddition cascade (CCCC) reaction is a powerful and atom-economical reaction to yield stereochemically defined oxapolycyclic adducts.[1] In this one-step metal-catalyzed reaction, three distinct sigma bonds are forged, resulting in the creation of up to four new stereogenic centers. The utility of this reaction in the construction of complex molecular scaffolds has been demonstrated by its application in the formal and total syntheses of challenging natural products, including (±)-aspidophytine,[2] (±)-illudin M,[3] (±)-vallesamidine,[4] (±)-lycopodine,[5] (±)-epoxysorbicillinol,[6] (±)-nemorensic acid,[7] (+)-zaragozic acids A[8] and C,[9] (−)-polygalolides A and B,[10] (−)-colchicine,[11] mappicine ketone,[12] (±)-camptothecin,[13] (−)-pseudolaric acid A,[14] (−)-indicol,[15] and (−)-platensimycin.[16]

It should be noted that the majority of these syntheses employed the carbene cyclization together with an intramolecular cycloaddition. This version of the reaction involves regioselective cycloadditions, due to the geometric constraints imposed by the tether. In contrast, the intermolecular cycloaddition is often limited to reactions with symmetrical dipolarophiles such as dimethyl acetylenedicarboxylate or strongly sterically-biased substrates such as terminal alkynes; with other dipolarophiles, poor regioselectivity and *endo*/*exo* diastereoselectivity is often encountered.[17] The development of novel catalysts with a range of electronic and steric characteristics to improve the selectivities of the intermolecular cycloaddition is ongoing,[18] but the results are not general.

One strategy by which we are attempting to address this problem is to design and investigate an intramolecular CCCC reaction to produce regioselectively and stereoselectively cycloadducts that could ultimately undergo ring cleavage to afford products which are akin to those obtained from an intermolecular cycloaddition. In this connection, we have investigated the intramolecular CCCC reaction with tethered vinylsulfonates. The vinylsulfonate is a highly reactive functional group, where the resulting sultone cycloadduct could be elaborated in various ways to eventually yield sulfur-free products.[19,20] However, while vinylsulfonates have been effectively used as Diels–Alder dienophiles,[19] they have never been investigated as dipolarophiles for carbonyl ylide cycloadditions. Herein we report the successful implementation of this CCCC strategy, which generates sultone cycloadducts with excellent yields. Moreover, the re-



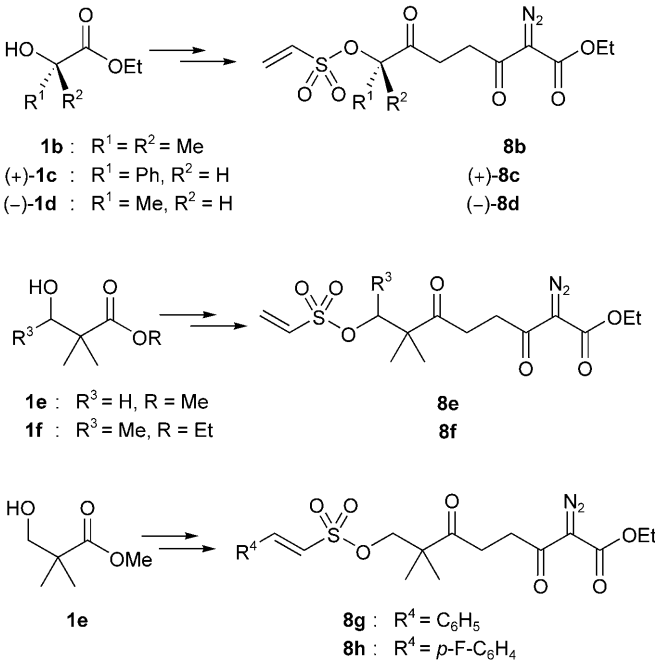
Scheme 1. Synthesis of vinylsulfonate **8a**. *Reagents and conditions*: a) TBSCl, imidazole, DMF, 0 °C to room temperature, 100%; b) HN(OMe)Me·HCl, *i*-PrMgCl, THF, −20 °C to room temperature, 93%; c) $ClMg(CH_2)_3OMgCl$, THF, 0 °C, 94%; d) Dess–Martin periodinane, CH_2Cl_2, room temperature, 82%; e) N_2CHCO_2Et, cat. $SnCl_2$, CH_2Cl_2, room temperature, 79%; f) TsN_3, Et_3N, MeCN, 0 °C, 79%; g) 40% aqueous HF/MeCN (5:95), room temperature, 98%; h) $CH_2{=}CHSO_2Cl$, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C, 67%.

action also proceeds with high diastereoselectivity and can afford optically pure cycloadducts as chiral intermediates for organic synthesis.

The first challenge was to devise a route to substrates featuring a diazoketone and a vinylsulfonate, both of which are reactive functional groups, in the presence of each other. These substrates **8** were ultimately accessed through diazoketones **6** that were deprotected and sulfonylated in the presence of the diazo functionality. The overall route is exemplified by the synthesis of **8a** (Scheme 1). α-Hydroxy ester **1a** was protected and converted to the Weinreb amide **2a**,[21] which was homologated using Normant's Grignard reagent[22] to give hydroxy ketone **3a**. Oxidation[23] to aldehyde **4a** and subsequent conversion[24] to keto ester **5a** provided the substrate for diazo transfer[25] to afford diazoketone **6a**. Cleavage of the silyl protecting group in the presence of the diazoketone was successfully achieved using HF/MeCN to give **7a**. Sulfonylation finally furnished the required substrate **8a**.

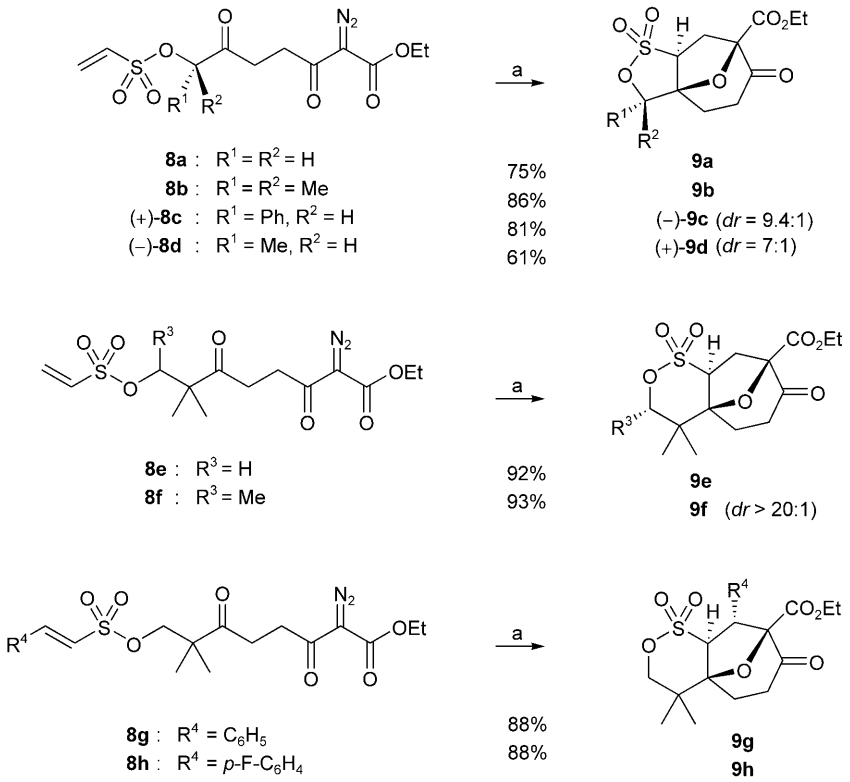
By a similar sequence of reactions, α-hydroxy esters **1b–d**, as well as β-hydroxy esters **1e**, **f** have been homologated to afford the corresponding diazoketones **8b–f** (Scheme 2). Optically pure diazoketones (+)-**8c** and (−)-**8d** were prepared from the chiral alcohols (+)-**1c** and (−)-**1d** without racemization. Analogously, diazoketones **8g** and **8h** bearing β-substituted vinylsulfonates were derived from **1e** by sulfonylation using (*E*)-styrylsulfonyl chlorides.

The results of the rhodium-catalyzed CCCC reaction of substrates **8** are shown in Scheme 3. Gratifyingly, the cycloaddition of **8a–d** and **8e–h** occurred smoothly to give the γ-sultones **9a–d** and δ-sultones



Scheme 2. Synthesis of vinylsulfonates **8b–h**.

9e–h, respectively, in high yields and with excellent stereoselectivities. Thus, the simple diastereoselectivity for prochiral substrates (**8a**, **b**, **e**, **g**, **h**) was complete, and the substrate-induced diastereoselectivity due to the presence of a stereogenic center within the tether between the reactive moieties was high (**8c**, **d**, **f**). The relative configurations of cycloadducts **9** were determined by NOE studies; moreover, the crystal structures of **9a**, **9c** and **9f** were determined by X-ray diffraction analysis.[26] In the case of the chiral sub-



Scheme 3. CCCC reaction of vinylsulfonates **8a–h**. *Reagents and conditions*: a) 3 mol% $Rh_2(oct)_4$, CH_2Cl_2, 0 °C (room temperature for **8f**).

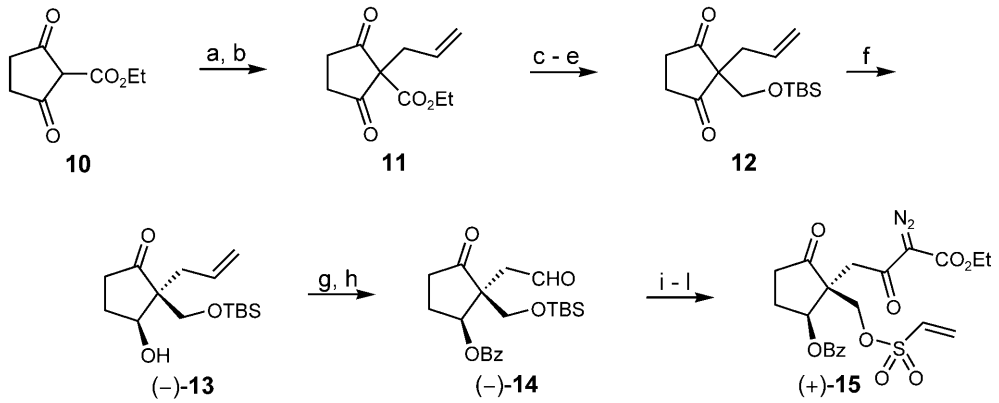
strates (+)-**8c** and (−)-**8d**, the optically active sultones (−)-**9c** and (+)-**9d** were isolated. Substitution at the vinylsulfonate moiety ($R^4 \neq H$) was tolerated, and the olefin geometry in **8g**, **h** was fully retained in the cycloaddition to give the sultones **9g**, **h** as single diastereomers. The effect of different rhodium(II) catalysts – rhodium(II) acetate [$Rh_2(OAc)_4$], rhodium(II) octanoate [$Rh_2(oct)_4$], and rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$] – on the yield and diastereoselectivity of the reaction was briefly examined. The results were rather similar for the three catalysts, producing yields varying in the range of ±5–8%. Generally, $Rh_2(oct)_4$ was found to be the best choice for substrates **8**.

The high yield, good diastereoselectivity, and ease of this CCCC reaction are not trivial, as underscored by the finding that the corresponding acrylate of **7c** (acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 85%) only gave rise to a 6% yield of diastereomeric γ-lactone analogues of **9c** ($dr = 2.6:1$), under the conditions used for the synthesis of sultone **9c**.[27]

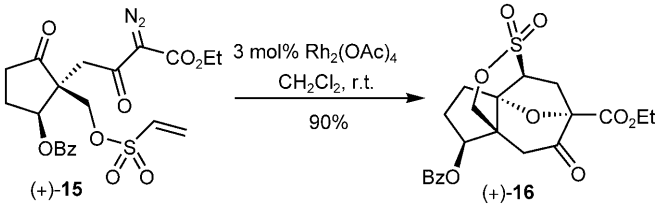
Having established the feasibility of the concept by demonstrating the first carbene cyclization cycloaddition cascade (CCCC) reactions employing vinylsulfonates, the next challenge was to apply this expertise to synthesize more complex sultones, such as the tetracyclic sultone **16** (Scheme 5) containing the hydroazulene framework.

Synthesis of **16** commenced with the known compound **10** (Scheme 4).[28] Allylation of **10** gave rise to a mixture of *C*-allylated product **11** and the corresponding *O*-allylated isomer. Claisen rearrangement of the latter also afforded tricarbonyl compound **11**, which was thus isolated in a total yield of 81% from **10**. After hydride reduction of **11** to furnish a triol and subsequent chemoselective silylation of the primary alcohol, oxidation of the remaining diol resulted in the desired *meso* 2,2-disubstituted 1,3-diketone **12**. Whereas no conversion was noted upon treatment of **12** with baker's yeast,[29] a Noyori asymmetric transfer hydrogenation catalyzed by [(*S,S*)-TsDPEN]Ru(*p*-cymene)[30] efficiently desymmetrized **12** to yield a monoreduction product with high diastereoselectivity ($dr = 12:1$) as well as enantioselectivity (93% *ee*). While its relative configuration was experimentally determined by NOE studies, its absolute configuration was tentatively assigned as depicted in (−)-**13**. Following protection and ozonolysis to afford aldehyde (−)-**14**, the remaining steps to vinylsulfonate (+)-**15** were accomplished in high yields similar to the synthesis of compounds **8**.

After experimenting with several dirhodium compounds, $Rh_2(OAc)_4$ was found to be the optimum catalyst for the CCCC reaction of (+)-**15**, giving tetracyclic sultone (+)-**16** in 90% yield as the only diastereomer observed (Scheme 5).



Scheme 4. Synthesis of vinylsulfonate (+)-**15**. *Reagents and conditions*: a) allyl bromide, K_2CO_3, DMF, microwaves, 60 °C; b) DMF, toluene, microwaves, 180 °C, 81% from **10**; c) $LiAlH_4$, THF, room temperature, 85%; d) TBSCl, cat. DMAP, Et_3N, CH_2Cl_2, room temperature, 75%; e) Dess–Martin periodinane, CH_2Cl_2, room temperature, 100%; f) 11 mol% [(*S,S*)-TsDPEN]Ru(*p*-cymene), isopropyl alcohol, room temperature, 81%, 93% *ee*; g) benzoyl chloride, DMAP, CH_2Cl_2, room temperature, 100%; h) O_3, CH_2Cl_2, MeOH, −78 °C, then Ph_3P, room temperature, 100%; i) N_2CHCO_2Et, cat. $SnCl_2$, CH_2Cl_2, room temperature, 83%; j) TsN_3, Et_3N, MeCN, 0 °C, 82%; k) 40% aqueous HF/MeCN (5/95), −15 °C, 83%; l) CH_2=$CHSO_2Cl$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, −10 °C, 79%.



Scheme 5. CCCC reaction yields sultone-bridged hydroazulene (+)-**16**.

Further synthetic elaboration of the cycloadducts **9** and (+)-**16** is ongoing, and desulfurization is being explored to provide an access to sulfur-free functionalized seven-membered carbocycles.

Experimental Section

Typical Procedure for the CCCC Reaction of Vinylsulfonates

To a solution of **8a** (179 mg, 0.56 mmol) in dichloromethane (25 mL) at 0 °C was added 3 mol% $Rh_2(oct)_4$ (13.0 mg, 16.8 μmol). The reaction mixture was stirred at 0 °C for 2 h. Then the solvent was removed. The residue was purified by flash chromatography on silica gel to afford **9a** as a white solid; yield: 118 mg (75%); R_f = 0.29 (dichloromethane/diethyl ether = 2/1); mp 180–181 °C; IR (ATR): ν = 2996, 2948, 1750 (C=O), 1731 (CO_2Et), 1448, 1372, 1339, 1283, 1169, 1082, 1068, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.61 (d, J = 10.9 Hz, 1H), 4.35–4.28 (m, 2H), 4.30 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 6.0 Hz, 1H), 3.09 (dd, J = 15.2, 6.0 Hz, 1H), 2.82 (dd, J = 15.2, 9.5 Hz, 1H), 2.81 (ddd, J = 17.7, 2.8, 8.3 Hz, 1H), 2.57–2.64 (m, 1H), 2.47–2.40 (m, 1H), 2.21 (ddd, J = 13.6, 8.6, 2.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.32, 164.79, 91.50, 90.92, 70.55, 62.75, 61.77, 36.25, 32.99, 29.80, 14.03; LR-MS (ESI): m/z = 291.0 $[M+H]^+$, 340.0 $[M+CH_3OH+NH_4]^+$; anal. calcd for $C_{11}H_{14}O_7S$: C 45.51, H 4.86, S 11.05; found: C 45.54, H 4.86, S 10.94.

Acknowledgements

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