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Enantiospecific and Regioselective Rhodium-Catalyzed Allylic Alkylation: Diastereoselective Approach to Quaternary Carbon Stereogenic Centers

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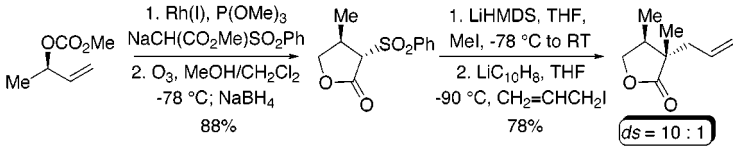
ABSTRACT



The enantiospecific and regioselective rhodium-catalyzed allylic alkylation of a series of chiral nonracemic allylic carbonates, followed by ozonolysis and reductive lactonization, provides a convenient route to optically active γ-lactones. Sequential alkylation and reductive alkylation furnished the α-quaternary-β-ternary substituted γ-lactone derivative as a $\geq$10:1 mixture of diastereoisomers.

The enantioselective construction of ternary and quaternary carbon stereogenic centers continues to be the focus of intense synthetic attention.[1] This may be attributed to the challenges associated with the design and implementation of stereoselective methods, particularly for the formation of quaternary carbon stereogenic centers. The enantiospecific metal-catalyzed allylic alkylation provides a conceptually useful method for the construction of vicinal ternary and quaternary carbon stereogenic centers. However, this approach has been restricted to symmetrical substrates to circumvent regiochemical problems, in which stoichiometric metal is utilized to minimize the erosion of enantiospecificity from metal−metal displacement reactions.[2] We recently demonstrated the first enantiospecific rhodium-catalyzed allylic substitution reactions that furnish unsymmetrical alkylation products with excellent regioselectivity.[3] The origin of the selectivity was attributed to the proposed intermediacy of a distorted π-allyl or *enyl* ($\sigma + \pi$) organorhodium intermediate.[4]

Herein, we describe the extension of this concept to a range of chiral nonracemic acyclic carbonates,[5] using the sodium salt of methyl phenylsulfonylacetate.[6] The mixed malonate derivatives were expected to allow selective functionalization of the allylic alkylation products and thus provide an expeditious entry into a variety of useful synthons for asymmetric synthesis. Furthermore, this study would also address the effect of more sterically demanding carbon-stabilized nucleophiles on the regiochemical outcome.

(1) For recent reviews on asymmetric quaternary carbon construction, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

(2) For a recent review on the transition-metal-catalyzed allylic alkylation, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed; VCH Publishers: New York, 1993; p 325. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(3) (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *39*, 1725. (b) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (c) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929. (d) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012.

(4) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(5) The enantiomerically enriched allylic alcohol precursors of **1b**−**e** and **1h** were prepared using the Sharpless asymmetric kinetic resolution of the racemates with dicyclohexyl tartrate; see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. The enantiomerically enriched allylic alcohol precursors of **1a** and **1f**/**g** were obtained from Fluka and D-mannitol, respectively.

(6) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *17*, 3477.

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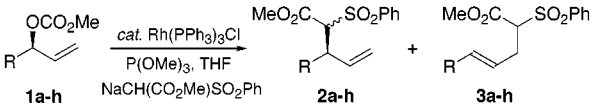
Table 1. Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Alkylation of Chiral Nonracemic Allylic Carbonates **1**

entry	allylic carbonate (R =)[a]	**1**	ee (%)[b]	ratio **2**:**3**[c,d]	ee (%)[e]	cee (%)[7]	yield (%)[f,g]
1	Me	**a**	97	36:1	95	98	86
2	CH_2=$CH(CH_2)_3$	**b**	≥99	26:1	98	98	91
3	$PhCH_2$	**c**	94	9:1	92	98	86
4	$PhCH_2CH_2$	**d**	98	22:1	95	97	87
5	$BnOCH_2$	**e**	94	≥99:1	92	98	86
6	$TBSOCH_2$	**f**	≥99	18:1	≥99	100	86
7	$TPSOCH_2$	**g**	≥99	3:1	≥99	100	78
8	Ph	**h**	98	61:1	96	98	97

[a] All of the rhodium-catalyzed allylic alkylation reactions were carried out on a 0.5 mmol reaction scale using 2−3 equiv of the nucleophile. [b] Enantiomeric excess of the allylic carbonates **1** or the allylic alcohols were determined by chiral capillary GLC and HPLC. [c] Ratios of regioisomers were determined by capillary GLC. [d] The primary products were prepared independently *via* Pd(0) catalysis.[2] [e] The phenylsulfonyl group was reductively removed, and the enantiomeric excess determined by chiral capillary GLC and HPLC.[6,9] [f] Isolated yields. [g] The allylic alkylation products were formed as a ∼1:1 mixture of diastereoisomers.

Table 1 summarizes the results of the rhodium-catalyzed allylic alkylation, using the sodium anion of methyl phenylsulfonylacetate, with a series of chiral nonracemic allylic carbonates **1a**−**h** (Scheme 1). The allylic alkylation reaction

Scheme 1. Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Alkylation



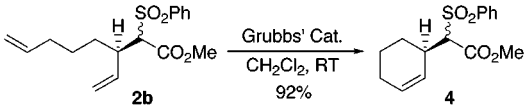
1a-h **2a-h** **3a-h**

is both regioselective and enantiospecific (≥97% cee).[7] The enantiospecificity is particularly significant for the substrates that furnish alkylation products with modest regioselectivity (entries 3 and 7). This observation presumably implies that the organorhodium intermediate is not subject to $\pi-\sigma-\pi$ isomerization or metal−metal displacement as a means of facial exchange.

Another significant aspect of this study was the tolerance to other substituents; for example, aryl, alkyl, alkenyl, and hydroxymethyl groups with various protecting groups may be utilized. The benzyloxymethyl derivative is particularly pertinent, since this functionality was expected to afford poor secondary regiochemistry as a result of the propensity of this group to competitively bind the metal-center and thus furnish the alternative regioisomer.[8]

The allylic alkylation products represent versatile synthons for asymmetric synthesis, as outlined below. Treatment of the diene **2b** with Grubbs' catalyst[10] furnished the cyclic allylic alkylation product **4** in 92% yield (Scheme 2). The

Scheme 2. RCM Approach to Enantiomerically Enriched Cyclic Allylic Alkylation Products



2b **4**

advantage of this strategy is the ability to circumvent regiochemical problems associated with the alkylation of cyclic derivatives that proceed through unsymmetrical η^3-intermediates.[11] Although stereoelectronics can often influence the regiochemical course of this type of allylic alkylation, the ability to access unsymmetrical cyclic allylic alkylation products in this manner is likely to have considerable synthetic utility.

The construction of ternary-quaternary substituted carbon stereogenic centers was also examined using a γ-lactone as a template for diastereoselective alkylation (Scheme 3). Reductive ozonolysis of the allylic alkylation product **2a** furnished the γ-lactone **5** in 92% yield, as a single diastereoisomer. Treatment of **5** with lithium hexamethyldisilazide followed by methyl iodide resulted in the installation of the α-methyl group. Reductive alkylation of the α-phenylsulfonyl γ-lactone under standard reaction conditions failed to cleanly furnish the desired product **6a**.[13] Extensive investigation demonstrated that the nature of the electrophile was crucial, in which alkyl iodides proved optimum. Hence, reductive alkylation with lithium naphthalenide and allyl iodide at −90 °C furnished the ternary-quaternary substituted γ-lactone **6a/b** in 78% overall yield, as a 10:1 mixture of diastereoisomers favoring **6a**. The ability to introduce various groups at the β-position in the lactone provides a versatile method for the construction of a variety of α-quaternary-β-ternary carbon stereogenic centers, in which the diastereoselectivity is expected to improve (≥10:1) with larger β-substituents.

In conclusion, we have demonstrated that the rhodium-catalyzed allylic alkylation may be expanded to include other stabilized carbon-nucleophiles and combined with ring-closing metathesis for the synthesis of enantiomerically

(7) The term conservation of enantiomeric excess {cee = (product ee/starting material ee) × 100} provides a convenient method of describing enantiospecificity.

(8) For an excellent review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(9) The absolute configuration of allylic alkylation product **2a** was confirmed in the following manner. Reductive desulfonylation[6] of **5** furnished (*S*)-β-methyl-γ-butyrolactone {$[\alpha]^{18}_D = -20.9$ ($c = 1.76$, MeOH); lit.[12] {$[\alpha]^{21}_D = -24.96$ ($c = 1.77$, MeOH)}.

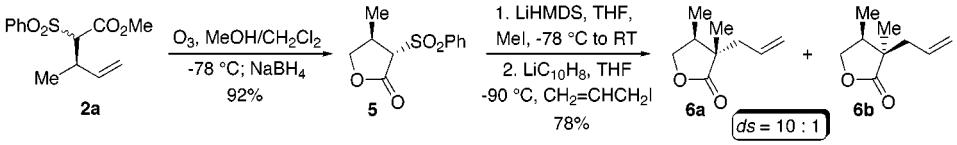
(10) For recent reviews on ring-closing metathesis, see: (a) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A Chem.* **1998**, *133*, 29. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Pandit, U. K.; Overleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, *959*, 9.

(11) Attempted rhodium-catalyzed allylic alkylation of the allylic carbonate derived from cyclohexenol furnished ***rac*-4** in 21% yield. This is consistent with our findings that alkene substitution and geometry impact the rates and selectivities.

(12) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

(13) For a related example of a reductive alkylation from an α-cyano ketone, see: Liu, H.-J.; Zhu, J.-L.; Shia, K.-S. *Tetrahedron Lett.* **1998**, *39*, 4183 and pertinent references therein.

Scheme 3. Diasteroselective Construction of Quaternary Carbon Stereogenic Centers



enriched unsymmetrical cyclic allylic alkylation products. This is anticipated to circumvent some of the regiochemical problems often encountered in unsymmetrical cyclic systems. Finally, the allylic alkylation products can be transformed into γ-lactones that serve as templates for the diastereoselective construction of α-quaternary-β-ternary carbon stereogenic centers.

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Supporting Information Available: Experimental procedures for the preparation of **6a** and copies of proton spectra for **2a**−**h**, **4**, **5**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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