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Catalytic Asymmetric Reactions for Organic Synthesis: The Combined C−H Activation/Siloxy-Cope Rearrangement

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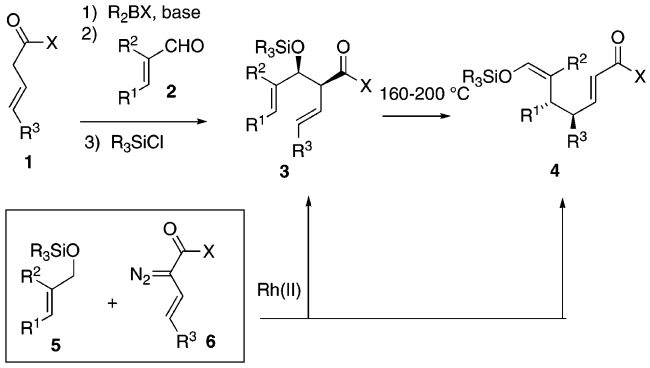
Tetrakis(*N*-[4-dodecylbenzenesulfonyl]-(L)-prolinate) dirhodium [Rh_2(*S*-DOSP)$_4$]-catalyzed decomposition of vinyldiazoacetates in the presence of allyl silyl ethers results in the formation of the direct C−H insertion product and the product derived from a combined C−H activation/siloxy-Cope rearrangement. Both products are formed with very high diastereoselectivity (>94% de) and high enantioselectvity (78−93% ee). Under thermal or microwave conditions, the direct C−H insertion product undergoes a siloxy-Cope rearrangement in a stereoselective manner.

Introduction

The ability to construct stereogenic centers with high levels of stereocontrol at positions remote from any activating functionality remains a major challenge in synthetic organic chemistry, particularly in acyclic systems.[1] A convenient approach is to establish a proximal stereogenic center through 1,2-asymmetric induction followed by chirality transfer through a sigmatropic rearrangement.[2,3] In this way the highly organized transition state of the pericyclic process ensures that the enantioinduction installed in the initial asymmetric step is maintained. A very attractive example of this strategy is the combination of the chiral auxiliary based asymmetric *syn*-aldol reaction (between the enolate of the unsaturated ester **1** and the unsaturated aldehyde **2**) to form the β-siloxyester **3** with the siloxy-Cope rearrangement of **3** to form the silyl enol ether **4** (Scheme 1).[4−7] In this paper we describe an entirely different strategy for achieving the equivalent of the tandem aldol reaction/siloxy-Cope rearrangement. The key step is a rhodium catalyzed enantioselective C−H activation between vinyldiazoacetate **6** and allyl silyl ether **5**, which leads to the formation of **4** either directly or via the β-siloxyester **3**.

SCHEME 1



Our interest in this area arose from the development of a practical intermolecular C−H activation method based on rhodium-carbenoid induced C−H insertions.[8−10] Diazoacetates **7** possessing an aryl donor group generate highly chemoselective carbenoids capable of very effective intermolecular C−H functionalization.[11] When these carbenoids are generated by the rhodium prolinate catalyst Rh_2(*S*-DOSP)$_4$ (**10**) highly enantioselective reactions are generally obtained.[8−10] A most notable example is the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **7** in the pres-

(1) For selected reviews on other methods for C−H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem.*, *Int. Ed.* **1999**, *28*, 1698. (c) Arndsten, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. (f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(2) For recent examples, see: (a) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168. (b) Allin, S. M.; Baird, R. D.; Lins, R. J. *Tetrahedron Lett.* **2002**, *43*, 4195. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9434.

(3) For a recent review of [3,3]-sigmatropic rearrangements, see: Nubbemeyer, U. *Synthesis* **2003**, 961 and references therein.

(4) For reviews on the siloxy-Cope rearrangement of chiral aldol products, see: (a) Schneider, C.; Rehfeuter, M. *Tetrahedron* **1997**, *53*, 133. (b) Schneider, C. *Synlett* **2001**, 1079.

(5) (a) Schneider, C.; Rehfeuter, M. *Synlett* **1996**, 212. (b) Schneider, C. *Synlett* **1997**, 815. (c) Schneider, C. *Eur. J. Org. Chem.* **1998**, 1661. (d) Schneider, C.; Börner, C. *Synlett* **1998**, 652. (e) Schneider, C.; Rehfeuter, M. *Tetrahedron Lett.* **1998**, *39*, 9. (f) Schneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850. (g) Schneider, C.; Börner, C.; Schuffenhauser, A. *Eur. J. Org. Chem.* **1999**, 3353. (h) Schneider, C.; Schuffenhauser, A. *Eur. J. Org. Chem.* **2000**, 73. (i) Schneider, C.; Reese, O. *Angew. Chem.*, *Int. Ed.* **2000**, *39*, 2948. (j) Schneider, C.; Reese, O. *Synthesis* **2000**, 1689. (k) Schneider, C.; Reese, O. *Chem. Eur. J.* **2002**, *8*, 2585.

(6) Black, W. C.; Giroux, A.; Greidanus; G. *Tetrahedron Lett.* **1996**, *37*, 4471.

(7) (a) Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8895. (b) Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8899.

(8) For a review on the catalytic enantioselective C−H activation chemistry of diazo compounds, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(9) For a recent review on the intermolecular C−H activation chemistry of diazo compounds, see: Davies, H. M. L. *J. Mol. Catal. A: Chem.* **2002**, *189*, 125.

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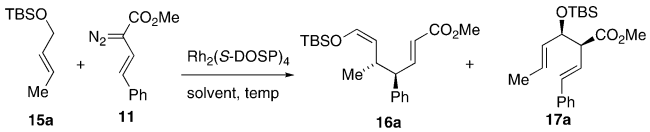
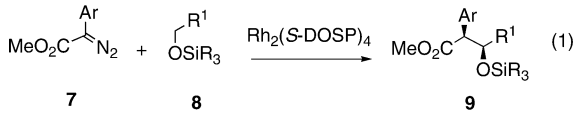
TABLE 1. Solvent and Temperature Effects



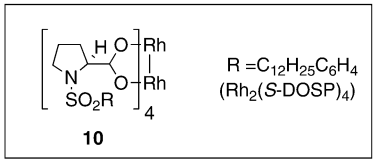
entry	solvent[a]	temp, °C	yield,[b] %	**16a**:**17a**	de for **16a**, %	ee for **16a**, %	de for **17a**, %	ee for **17a**, %
1	CH_2Cl_2	−40	35	2.8:1.0	>98	70	>98	66
2	CH_2Cl_2	23	76	1.8:1.0	>98	52	>98	48
3	toluene	−40	56	2.3:1.0	>98	92	>98	89
4	toluene	23	57	2.3:1.0	>98	78	>98	75
5	CF_3toluene	−20	61	3.2:1.0	>98	88	>98	87
6	CF_3toluene	23	68	2.3:1.0	>98	76	>98	72
7	2,2-DMB	−40	10	1.0:1.0	>98	92	>98	90
8	**2,2-DMB**	**23**	**89**	**1.0:1.0**	**>98**	**89**	**>98**	**88**

[a] 1,2-Dichloroethane failed to generate any of the desired products. [b] The combined yields of **16a** and **17a** are reported.

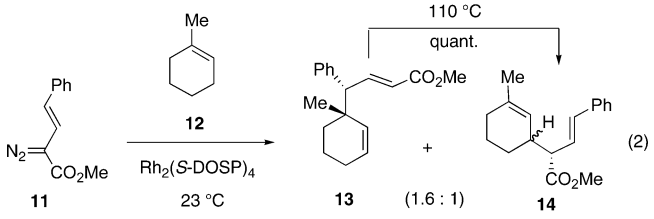
ence of silyl ethers **8**, which generates the corresponding *syn*-aldol type products **9** with up to 98% de and 96% ee (eq 1).[10d]



90-98% de, 62-96%ee



In addition, we have previously described a very unusual C−H functionalization between the vinyldiazoacetate **11** and compounds containing allylic C−H bonds (e.g. **12)** through effectively a combined C−H activation/Cope rearrangement protocol (eq 2).[12] The transformation



40%, >98% de, 99% ee

is highly diastereo- and enantioselective, offering a facile way of constructing 1,5-hexadienes **13**. The reaction, however, suffers from the competing formation of the C−H activation product **14** and this is exacerbated by the fact that in all the examples studied to date, the C−H activation product is thermodynamically favored.[12]

The effective development of this combined C−H activation/Cope rearrangement would require strategies to circumvent the current problem of the competing reactions. This led to the current study on the reaction of vinyldiazoacetates with allyl silyl ethers because the issue of competing reactions would be avoided (Scheme 1). Even though a mixture of the direct C−H activation product **3** and C−H activation/Cope rearrangement product **4** might be formed, the siloxy-Cope rearrangement of **3** could be used to drive the reaction to the desired product **4**. This catalytic approach obviates the need for a chiral auxiliary, which was used in the conventional tandem aldol reaction/siloxy-Cope rearrangement,[4−7] enhancing the practical appeal of the chemistry. Herein we describe the realization of the chemistry and outline the scope and limitations of such an approach.

Results and Discussion

The first stage of the study required the determination of the general reactivity profile of the chemistry between vinyldiazoacetates and allyl silyl ethers. The Rh_2(*S*-DOSP)$_4$-catalyzed (1 mol %) decomposition of methyl phenylvinyldiazoacetate **11** (2 equiv) in the presence of TBS-protected crotyl alcohol **15a** was used as the test reaction (Table 1). We were delighted to find that the desired operation could be effected as a single pot process affording silyl enol ether **16a** with >98% de and as a single geometric isomer. The stereochemistry of the product matched the major product **4** obtained in the chiral auxiliary based stepwise approach[4−7] and was in agreement with the established model for a thermal Cope rearrangement in which the silyl ether adopts a pseudoaxial conformation in a chairlike transition state.[13] In addition to silyl enol ether product **16a**, the direct C−H insertion product **17a** was also obtained with excellent

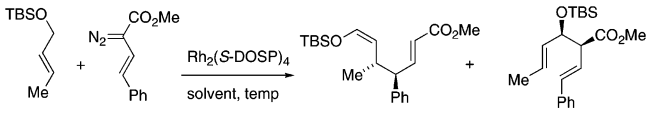
(10) For recent examples of enantioselective intermolecular C−H activation of diazo compounds, see: (a) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769. (b) Davies, H. M. L.; Hopper, D. W.; Hansen, T.; Liu, X.; Childers, S. R. *Biorg. Med. Chem. Lett.* **2004**, *14*, *1799*. (c) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462. (d) Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126. (e) Davies, H. M. L.; Yang, J. *Adv. Synth. Catal*. **2003**, *345*, 1133. (f) Davies, H. M. L.; Jin, Q. *Tetrahedron*: *Asymmetry* **2003**, *14*, 941. (g) Davies, H. M. L.; Walji, A. M. *Org. Lett*. **2003**, *5*, 479.

(11) Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. S. *Tetrahedron Lett*. **1998**, *39*, 4417.

(12) (a) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T.; Churchill, M. R.; Keil, K. M. *Tetrahedron Lett.* **2000**, *41*, 2035. (c) Davies, H. M. L.; Jin, Q. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5472. (d) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862.

(13) (a) Hill, R. K.; Gilman, N. W. *J. Chem. Soc.*, *Chem. Commun.* **1967**, 619. (b) Doering, W. von E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.

TABLE 2. Effect of Catalyst



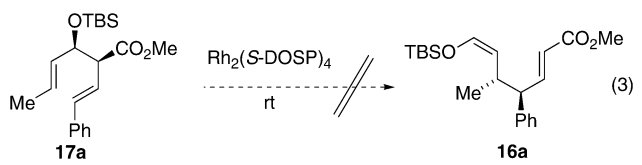
15a **11** **16a** **17a**

entry	catalyst	solvent	temp, °C	yield, %	**16a**:**17a**	ee for **16a**, %	ee for **17a**, %
1	Rh_2(OOct)$_4$	2,2-DMB	23	35	1.0:1.0		
2	**Rh_2(*S*-DOSP)$_4$**	**2,2-DMB**	**23**	**89**	**1.0:1.0**	**89**	**88**
3	Rh_2(*S*-biTISP)$_2$	2,2-DMB	23	32	1.2:1.0	3	3
4	Rh_2(*S*-PTTL)$_4$	2,2-DMB	23	12	1.0:4.0	59[a]	54[a]
5[b]	Rh_2(*R*-BNP)$_4$	CH_2Cl_2	40	0			
6	Rh_2(5*S*-MEPY)$_4$	CH_2Cl_2	40	0			
7	Rh_2(*S*-IBAZ)$_4$	CH_2Cl_2	40	0			

[a] Opposite enantiomer to that illustrated was obtained. [b] The reaction in toluene at 70 °C also failed to produce any desired products.

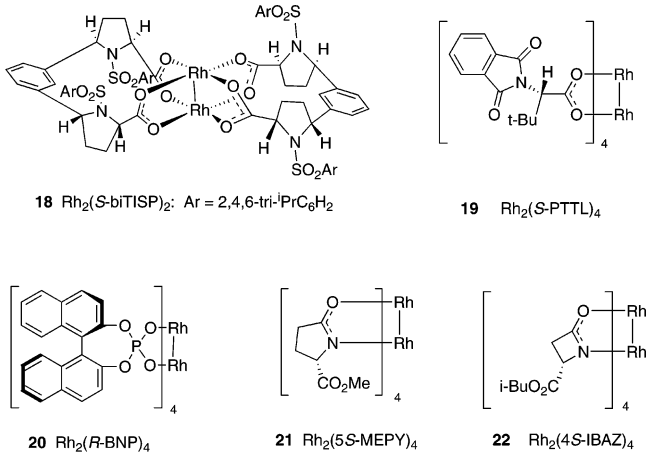
diastereoselectivity (>98% de). The stereochemistry of **17a** was assigned as syn in accord with results reported for similar systems.[10d] The formation of only **16a** and **17a** demonstrates the regioselectivity of the vinylcarbenoid chemistry as no product arose from reactions at the distal methyl site in **15a**.[12d] The ratio of **16a**:**17a** obtained was found to be influenced by solvent and temperature effects, with lower temperatures and more polar solvents favoring the formation of the combined C−H activation/siloxy-Cope product **16a**. Although not substantial, the greatest effect was observed when conducting the reaction in α,α,α-trifluorotoluene ($PhCF_3$) at −20 °C, which favored formation of **16a** by 3.2:1.0 (Table 1, entry 5). When the reaction was carried out in dichloromethane, a solvent traditionally used in rhodium-carbenoid chemistry, substantially lower levels of asymmetric induction were observed even at −40 °C (Table 1, entries 1 and 2). Less polar solvents such as 2,2-dimethylbutane (2,2-DMB) tended to generate an equal mixture of **16a**:**17a** irrespective of temperature. As expected, lower temperatures gave higher enantioinduction with levels up to 92% ee for **16a** (Table 1, entries 3 and 7). Overall, however, the optimum conditions with regard to both yield and enantioselectivity were obtained when the reaction was conducted in a nonpolar solvent such as 2,2-DMB at ambient temperatures. It is worthy to note that no products were obtained as a result of additional C−H insertion following the formation of the initial C−H activation products, despite using an excess of the vinyldiazoacetate **11**.

On initial inspection, one might assume that silyl enol ether **16a** was generated via a two-step process involving C−H insertion to generate *β*-siloxy ester **17a** followed by a [3,3]-sigmatropic rearrangement. However, exposing *β*-siloxy ester **17a** to the standard reaction conditions failed to generate any **16a** and ester **17a** was completely recovered (eq 3). It would appear that the siloxy-Cope



17a **16a**

type product **16a** was generated in a single step through a competing pathway to the direct C−H activation reaction, thereby generating effectively a mixture of C−H activation to combined C−H activation/siloxy-Cope product. Even so, the transition states for the two reactions are likely to have considerable similarity because the enantioselectivities for the two reactions are nearly the same in all cases.



18 Rh_2(*S*-biTISP)$_2$: Ar = 2,4,6-tri-^{i}PrC$_6$H$_2$ **19** Rh_2(*S*-PTTL)$_4$

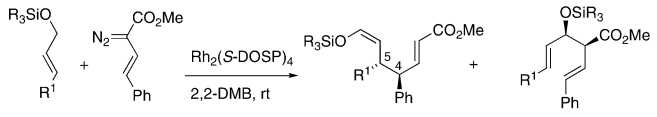
20 Rh_2(*R*-BNP)$_4$ **21** Rh_2(5*S*-MEPY)$_4$ **22** Rh_2(4*S*-IBAZ)$_4$

FIGURE 1. Structure of dirhodium catalysts.

In an attempt to install greater control over the course of the reaction such that only the C−H activation product or solely the combined C−H activation/siloxy-Cope product could be obtained, a range of rhodium(II) catalysts were investigated (Table 2). Only the rhodium(II) carboxylate catalysts proved to be effective in generating a carbenoid that was sufficiently reactive yet selective to undergo the desired C−H activation process (Table 2, entries 1−4). Pirrung's phosphate catalyst, Rh_2(*R*-BNP)$_4$ (**20**),[14] and Doyle's Rh_2(5*S*-MEPY)$_4$ (**21**)[15] and the more active Rh_2(*S*-IBAZ)$_4$ (**22**)[16] all failed to generate any of the products **16a** and **17a** (entries 5−7). The achiral catalyst Rh_2(OOct)$_4$ generates **16a**:**17a** in a similar ratio to Rh_2(*S*-DOSP)$_4$ but the yields were lower (entry 1). The tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$ is clearly the optimum catalyst with regard to yield and enantioinduction (entry 2). The bridged tetraprolinate catalyst Rh_2(*S*-biTISP)$_2$ (**18**)[17] was not very effective in this chemistry, generating **16a** and **17a** in low yield and very low

(14) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987.
(15) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968.
(16) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.

TABLE 3. Effect of Allyl Silyl Ether Structure

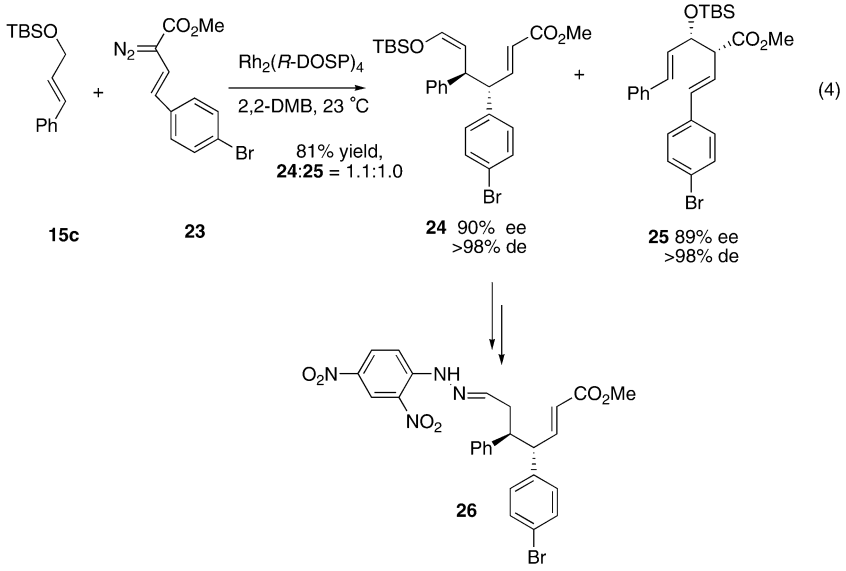


15a-f 11 16a-f 17a-f

product	SiR_3	R^1	yield, %[a]	**16**:**17**	de for **16**, %	ee for **16**, %	de for **17**, %	ee for **17**, %
a	TBS	Me	85	1.0:1.0	>98	89	>98	88
b	TBS	(*E*)CH_3CH_2═CH-	69	2.5:1.0	>98	92	>98	91
c	TBS	C_6H_5	94	1.4:1.0	>98	91	>98	91
d	TMS	Me	82	1.3:1.0	>98	91[b]	>98	90
e	TMS	(*E*)CH_3CH_2═CH-	85	4.2:1.0	>98	93[b]	>98	91
f	TMS	C_6H_5	98	1.4:1.0	>98	91[b]	>98	91

[a] Combined yield of **16** and **17**. [b] The corresponding aldehyde product was isolated and fully characterized.

SCHEME 2



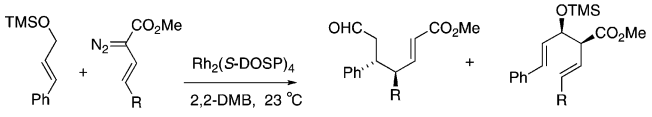
enantioinduction (entry 3). Hashimoto's C_2-symmetric phthalimido catalyst Rh_2(*S*-PTTL)$_4$ (**19**)[18] displayed a marked preference for the direct C−H activation pathway to generate **16a**:**17a** in a 1:4 ratio, but the overall yield was very low (entry 4).

The nature of the allylic silyl ether substrate also influenced the outcome of the reaction as demonstrated in Table 3. Conducting the reaction in the presence of silyl-protected (*E*,*E*)-hexadien-1-ol (**15b** or **15e**) gave much greater preference for the formation of **16** (Table 3, entries 2 and 5). Possibly the presence of an sp^2 center adjacent to the olefin of the silyl ether limits steric crowding in the transition state enabling suitable alignment of the olefin orbitals thereby favoring the pathway that generates the combined C−H activation/siloxy-Cope type product. An aryl ring, however, adjacent to the olefin has little influence on the product distribution, as observed with silyl-protected cinnamyl alcohol (**15c** or **15f**). In all cases the products were formed as single double bond geometric isomers with excellent diastereoselectivity. The use of the less bulky TMS-protecting group appears to give marginally better yields of products overall, although the level of enantioinduction is comparable between a TMS and a more bulky TBS-protecting group.

Predictions about the expected stereochemistry of the C−H activation products **17** and the combined C−H activation products **16** can be readily made by analogy to some related reactions. The Rh_2(*S*-DOSP)$_4$-catalyzed C−H activation of silyl ethers has been shown to give very predictable stereoinduction favoring the formation of the (*S*) configuration at the site of the original carbene center.[10d] The C−H activation chemistry of allyl silyl ethers with aryldiazoacetates has been shown to give strong preference for the formation of the syn diastereomer.[10d] The double bond geometries in **16** indicate that the oxy-Cope rearrangement occurs through a chair transition state and so **17c** (2*S*,3*R*) would be expected to rearrange to the **16c** (4*R*,5*S*) isomer. This stereochemical prediction for **16** is the same as was found in related combined C−H activation/Cope rearrangement products whose configuration was unambiguously assigned by X-ray crystallography.[19] To confirm that the predicted stereochemical outcome is indeed occurring in this study, the Rh_2(*R*-DOSP)$_4$ catalyzed reaction of *p*-bromostyryldiazoacetate **23** with **15c** was conducted (Scheme 2). A 1.1:1.0 ratio of Cope-type product **24** to C−H activation

(17) Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287.
(18) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

TABLE 4. Effect of Vinyldiazoacetate Structure

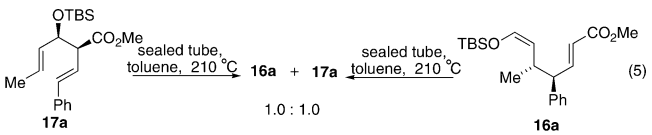


product	R	yield, %	**28**:**29**	de for **28**, %	ee for **28**, %	de for **29**, %	ee for **29**, %
a	(*E*)$PhCH_2$=CH-	73	1.6:1.0	>98	83	>98	83
b	Me	66	1.0:1.6	>98	78	>98	76
c	Et	57	1.0:2.7	>98	81	>98	80

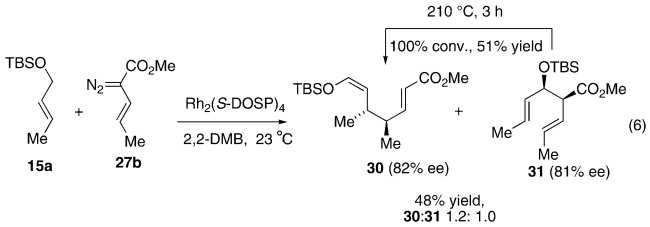
product **25** was formed again with very high diastereoselectivity and good enantioselectivity (eq 4). The silyl enol ether **24** was readily converted to the crystalline 2,4-dinitrophenylhydrazone **26**. The configuration of **26** was unambiguously assigned as (4*S*,5*R*) by X-ray crystallography (see Supporting Information).[19] Thus, the Rh_2(*S*-DOSP)$_4$ catalyzed reaction would form the (4*R*,5*S*) configuration of **24** and **16c**.

The combined C−H activation/siloxy-Cope rearrangement is applicable to various 3-substituted vinyldiazoacetate systems. The generality of the process is illustrated by the Rh_2(*S*-DOSP)$_4$ reaction of vinyldiazoacetates **27a**−**c** with TMS-protected cinnamyl alcohol substrate (**15f**) (Table 4). A mixture of the combined C−H activation/siloxy-Cope rearrangement products, isolated as the aldehydes **28a**−**c** and the direct C−H activation products **29a**−**c**, was obtained. The presence of an sp^2 center adjacent to the vinyl system as in **27a** gives greater preference for the Cope-type product **28** with sp^3 centers giving a preference for the direct C−H insertion product **29** (Table 4, cf. entry 1 with entries 2 and 3).

A potential advantage of the combined C−H activation/siloxy-Cope rearrangement over our previously published C−H activation/Cope rearrangement[12] is the opportunity to drive the reaction to completion. This in theory enables sole formation of the oxy-Cope type product to be achieved simply by heating the mixture obtained from the Rh_2(*S*-DOSP)$_4$-catalyzed reaction. Attempted thermal rearrangement of either C−H activation product **17a** or siloxy-Cope type product **16a** derived from arylvinyldiazoacetates tended toward an equilibrium mixture of products in a 1:1 ratio (eq 5). Even though it would normally be expected for the siloxy-Cope rearrangement to go to completion, in this case, the conjugated styryl group in **17a** makes the rearrangement thermodynamically balanced.



For the siloxy-Cope rearrangement to go to completion, it was proposed that systems lacking extended conjugation would be required. To test this concept, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl 3-pentenediazoacetate **27b** in the presence of TBS-protected crotyl alcohol **15a** was examined. The reaction generated a mixture of the silyl enol ether **30** and the direct C−H activation product **31** with a slight preference for the siloxy-Cope type product (eq 6). Once again **30** was formed essentially



as a single diastereomer. Even though **31** was stable under the reaction conditions, on heating at 210 °C in a sealed tube following the general procedures of Schneider,[4] **31** rearranged to **30** in 51% yield with the same relative and absolute configuration as the material formed from the rhodium-catalyzed reaction.

Even though the thermal rearrangement of **31** to **30** was achievable, only a modest yield of **30** was obtained under the harsh conditions. Consequently, the microwave-assisted rearrangement[20] of **31** was explored. When the reaction was conducted with an ionic liquid additive (1-ethyl-3-methyl-1*H*-imidazolium)[21] in α,α,α-trifluorotoluene ($PhCF_3$), the aldehyde **32** was formed in 92% yield without loss of stereochemistry (eq 7). In addition, when the reaction was conducted in nonpolar solvents such as hexane, in the presence of carboflon heating inserts[22] to aid heating, desilylation of the Cope product could be predominantly avoided and the silyl enol ether **30** was obtained.

The C−H functionalization/siloxy-Cope rearrangement can be further enhanced by conducting the rhodium-catalyzed and the microwave-induced reactions without purification of intermediates. This is illustrated in the reaction of **27b** with the TMS protected alcohol **15d** (eq 8). Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **27b** in the presence of 10 equiv of **15d** in 2,2-DMB at ambient temperature followed by removal of the solvent and excess silyl ether prior to microwave-assisted heating afforded aldehyde **32** in 53% yield over two steps in >98% de and 81% ee.

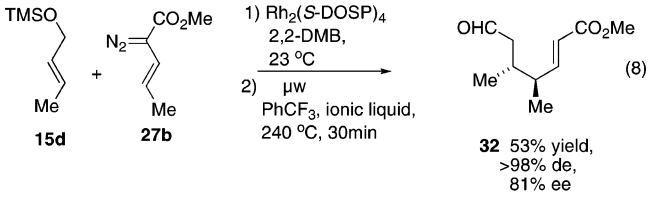
The next question to be addressed was would the relative stereochemistry be controlled by the allyl silyl ether geometry. This issue was tested by reaction of TMS-protected (*Z*)-crotyl ether **33** with vinyldiazoacetate **27b**. The Rh_2(*R*-DOSP)$_4$-catalyzed reaction followed by microwave-assisted thermal rearrangement of the intermedi-

(19) The X-ray crystallographic data have been submitted to the Cambridge Structure Database [Gerlits, O. O.; Coppens, P. Private Communication (1078), 2004], Deposition no. CCDC 237997.

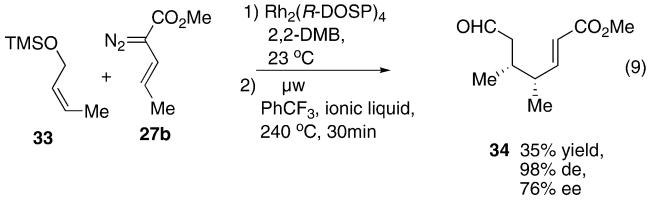
(20) For a review on microwave assisted organic synthesis see: Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(21) (a) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850. (b) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.

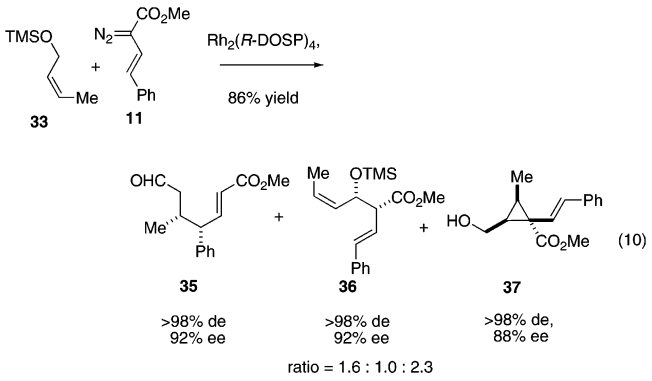
(22) Carboflon heating inserts (part number SP-1125) were obtained from CEM. For an example of the use of a similar heating additive in organic synthesis, see: Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371.



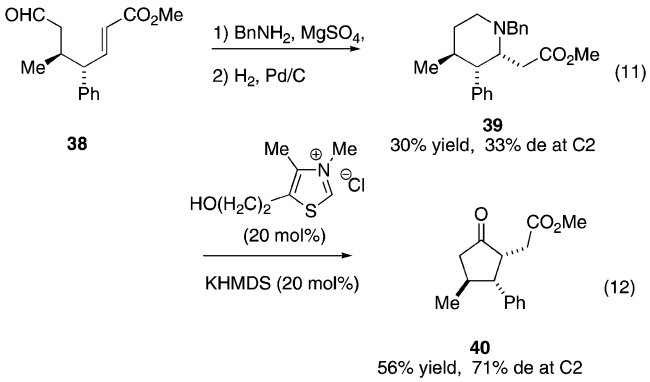
ate gave the (4*R*,5*R*)-aldehyde **34** in 35% yield as a single diastereomer with 76% ee (eq 9). The absolute stereochemistry of the product ($[\alpha]^{23}_D$ −41.8 (*c* 0.44, $CHCl_3$)) was confirmed by comparison with the literature compound ($[\alpha]^{20}_D$ −51.0 (*c* 1, $CHCl_3$)).[5c] As both enantiomers of the catalyst are available, the combined C−H activation/siloxy-Cope rearrangement can be used to prepare selectively any of the four stereoisomers of the product.



A drawback with this chemistry is the low yield of the reaction of the *cis*-allyl ether **33** compared to its trans counterpart **15d**. To further define the reaction of vinyldiazoacetates with *cis*-allyl ethers, the reaction of **33** with the phenylvinyldiazoacetate **11** was examined. The Rh_2(*R*-DOSP)$_4$-catalyzed reaction gave a mixture of three products: the desired siloxy-Cope rearrangement product **35**, the direct C−H activation product **36**, and the cyclopropane **37** in a 1.6:1.0:2.3 ratio (eq 10). All three products were formed with very high diastereoselectivity. This is a useful example illustrating the boundaries in the competition between cyclopropanation and C−H insertion. The rhodium vinylcarbenoids act as sterically demanding intermediates and effectively cyclopropanate 1-substituted, 1,1-disubstituted, and cis 1,2-disubstituted alkenes.[23] Thus with *trans*-allyl silyl ethers cyclopropanation does not occur but with *cis*-allyl silyl ethers competition between cyclopropanation and C−H insertion is much more balanced.



The combined C−H activation/siloxy-Cope rearrangement offers a direct stereoselective route to the construction of a variety of γ,δ-substituted α,β-unsaturated carbonic acid derivatives in a practical and catalytic manner. Such systems have the potential to be useful building blocks for organic synthesis owing to the established stereocenters and the versatile enoate and aldehyde (or silyl enol ether) functionality. For instance, conversion of the silyl enol ether **16d** to the corresponding aldehyde **38** and then treatment with benzylamine followed by reduction of the resultant enamine gave the piperidine system **39** as a 2:1 mixture, epimeric at C-2 (eq 11).[4b] The configuration of the major diastereomer of **39** was readily confirmed by proton NMR coupling values and nOe experiments. Aldehyde **38** was also readily converted to cyclopentanone **40** in 56% yield by means of an intramolecular Stetter reaction (eq 12).[24]



The stereochemistry of the combined C−H activation/siloxy-Cope rearrangement can be rationalized by the predictive model shown in Figure 2.[14d] The catalyst is considered to adopt a D_2-symmetric arrangement and can be simply viewed as a catalyst surface with a blocking group in the front and a blocking group in the back.[12d] In this model, the carbenoid initiates the insertion into the C−H bond, but before the process is complete the two vinyl groups enter into the Cope rearrangement. The exact trajectory of approach of the allyl silyl ether is not known, but the orientation shown in structure **41** predicts the stereochemical outcome of the combined C−H activation/Cope rearrangement for both the two newly generated stereocenters and the two alkenes in **42**. In this model, the allyl silyl ether approaches from the front,

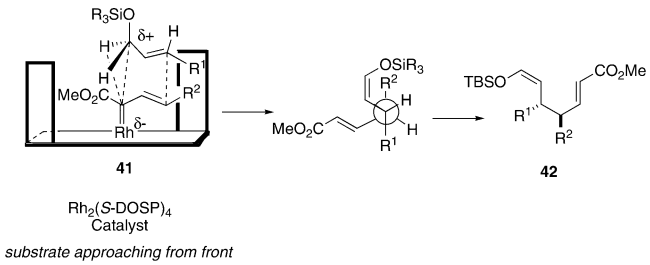


FIGURE 2. Predictive model for the stereochemistry of the Rh_2(*S*-DOSP)$_4$-catalyzed combined C−H activation/siloxy-Cope rearrangement.

(23) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(24) (a) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, p 407. (b) Ciganek, E. *Synthesis* **1995**, 1311. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

avoiding the blocking group in the back,[12d] and this leads to the observed absolute stereochemistry of the reaction.

In summary, a novel reaction has been identified involving a combined C−H activation/siloxy-Cope rearrangement. This offers a practical, catalytic approach for the controlled generation of stereocenters at positions remote from activating functionality. Furthermore, products lacking aryl functionality can be readily generated, which contrasts with our extensive studies on the intermolecular C−H activation chemistry of aryldiazoacetates.[9,10] The thermodynamically favored product in this system is the siloxy-Cope type product, which distinguishes this work from our earlier studies on the combined C−H activation/Cope rearrangement.[12] The resulting γ,δ-substituted α,β-unsaturated carbonic acid derivatives are well functionalized for use as chiral building blocks in synthesis and future work will explore this potential.

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Supporting Information Available: Full experimental data for the compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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