

New Strategic Reactions for Organic Synthesis: Catalytic Asymmetric C–H Activation α to Oxygen as a Surrogate to the Aldol Reaction

Huw M. L. Davies,* Rohan E. J. Beckwith, Evan G. Antoulinakis, and Qihui Jin

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000

hdavies@acsu.buffalo.edu

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The C–H activation of silyl ethers by means of rhodium carbenoid-induced C–H insertion represents a very direct method for the stereoselective synthesis of silyl-protected β -hydroxy esters. The reaction can proceed with very high regio-, diastereo-, and enantioselectivity and represents a surrogate to the aldol reaction. The reaction is catalyzed by the rhodium proline complex $\text{Rh}_2(\text{S-DOSP})_4$. A critical requirement for the high chemoselectivity is the use of donor/acceptor-substituted carbenoids such as those derived from methyl aryldiazoacetates. A range of silyl ethers may be used such as allyl silyl ethers, tetraalkoxysilanes, and even simple trimethylsilyl alkyl ethers. In general, C–H activation preferentially occurs at methylene sites, as the reactivity is controlled by a delicate balance between steric and electronic effects.

Practical methods for the selective functionalization of unactivated C–H bonds have the potential to revolutionize the strategies used for the synthesis of complex organic molecules. The majority of studies on C–H activation have focused on the use of highly reactive metal complexes that are capable of oxidative addition across a C–H bond.^{1,2} The major challenge with this approach has been to make the process catalytic because it is very difficult to regenerate the reactive metal complex required to complete the catalytic cycle. An alternative method for C–H activation is by means of a metal carbenoid-induced C–H insertion.³ Recently, we have demonstrated that very efficient intermolecular versions of this reaction are feasible. Furthermore, when these reactions are catalyzed by dirhodium tetraproline complexes, high asymmetric induction can be achieved.^{4–6} We have previously communicated that asymmetric C–H activation is especially favored at methylene sites adja-

cent to oxygen (eq 1).^{4c,f} This paper will give a full description of the scope of this chemistry, with particular emphasis on the remarkable chemoselectivity that can be achieved through modification of the oxygen substituent. In many instances, the reactions are highly diastereoselective, and the factors that cause this diastereocontrol will be discussed. A particularly attractive feature of this methodology is that the products are protected β -hydroxy esters, and thus the methodology may be considered as a new strategic reaction that is a surrogate to the aldol reaction.^{7,8}

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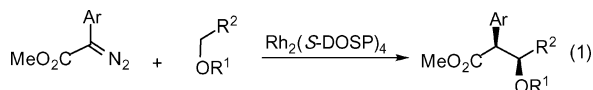
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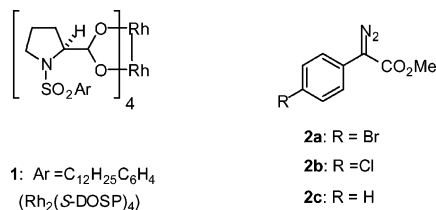
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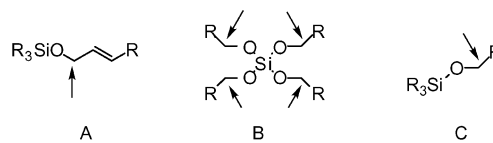
Prior to the development of our program, enantioselective C–H activation by means of carbenoid C–H insertions was limited to intramolecular examples.^{3a} Even though intermolecular C–H insertions had been demonstrated to be a feasible process in the seminal work of Teyssie and co-workers,⁹ problems of chemoselectivity and carbenoid dimerization greatly limited their synthetic utility.¹⁰ We have found, however, that diazoacetates functionalized with a donor group such as aryl or vinyl generate highly chemoselective carbenoids that are very effective at intermolecular functionalization of unactivated C–H bonds.¹¹ When these carbenoids are generated by the rhodium prolinato catalyst $\text{Rh}_2(\text{S-DOSP})_4$ (**1**),¹² highly enantioselective transformations are commonly observed.^{4,5} In this study of the scope of the C–H activation α to oxygen,¹³ the carbenoid source was limited to aryldiazoacetates **2a–c**, although it has been shown that a much wider range of donor/acceptor carbenoids are compatible with this chemistry.^{4,5}



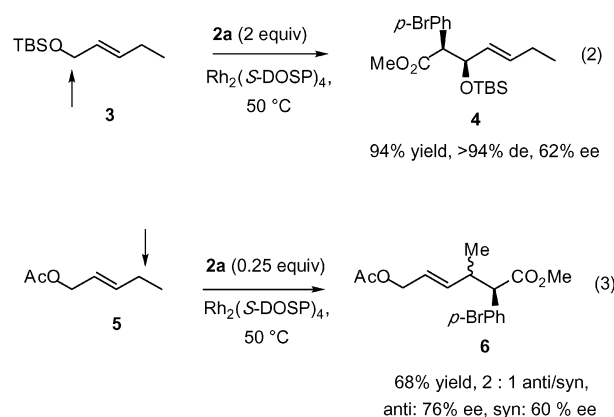
One of the main purposes of the current study is to develop general guidelines regarding the chemoselectivity that is possible in intermolecular C–H activations α to oxygen. It is well established even in intermolecular reactions with ethyl diazoacetate that a methylene site adjacent to oxygen is highly favored for C–H activation.^{10c} Intramolecular studies with diazoacetate derivatives have shown that insertion adjacent to an ether oxygen is very favorable,^{3a} while an acetoxy group behaves as a deactivating group.¹⁴ Our studies have shown that the carbenoids derived from aryldiazoacetates are very sterically demanding.^{4,5} Hence, it was hypothesized that the

chemoselectivity of the C–H activation site would be controllable by using appropriate alcohol protecting groups.

The initial exploration of the intermolecular C–H activation α to oxygen was carried out on substrates that were expected to give efficient transformations. Protected trans-substituted allyl alcohols (A) were considered to be ideal substrates because the allylic position would favor insertion, while competing cyclopropanation would be unlikely because the donor/acceptor-substituted carbenoids are ineffective at cyclopropanation of trans double bonds.¹⁵ Later sections of this paper will describe the extension of this chemistry to tetraalkoxy silanes (B) and then finally to simple silyl ethers (C). As silyl and acetyl protection were expected to lead to very different reactivity profiles, both were evaluated for many of the alcohol substrates.



$\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed decomposition of methyl *p*-bromoaryldiazoacetate (**2a**) in the presence of the pentenyl silyl ether **3** is an excellent example of the synthetic potential of this chemistry (eq 2). The exploratory reactions were conducted with 1 mol % $\text{Rh}_2(\text{S-DOSP})_4$ with respect to the aryldiazoacetate, in refluxing 2,2-dimethylbutane, which is a good inert hydrocarbon solvent for this chemistry.^{4e} When the reaction was conducted with 2 equiv of **2a**, the C–H insertion product **4** was obtained in 94% yield and 62% ee. Remarkably, this product is produced with very high diastereoselectivity (>94% de), as the second diastereomer was not observable in the NMR of the crude reaction mixture. In contrast, a low yield of C–H activation products were formed in the reaction with 2-pentenyl acetate (**5**) conducted under identical conditions. A much better reaction was achieved when 4 equiv of **5** was used, although the products **6** were derived from C–H activation at the alternate allylic site (eq 3). The diastereoselectivity in this case was moderate and consistent with our earlier results on the C–H activation of alkenes.⁴ⁱ



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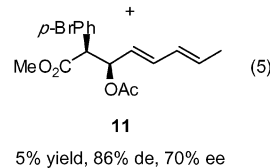
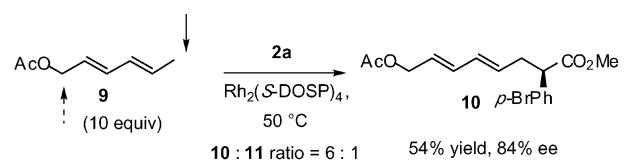
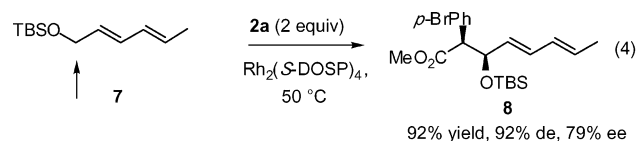
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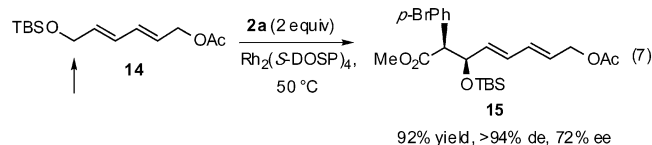
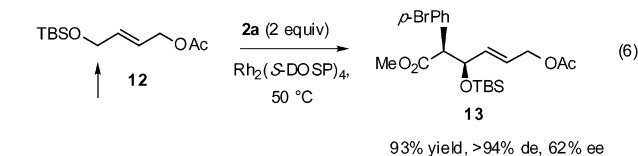
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The reaction of **2a** with hexadienyl silyl ether **7** is also a very favorable process in which **8** was formed with excellent regio- and stereocontrol (eq 4). The analogous reaction with the hexadienyl acetate **9** is more complicated and illustrates the subtleties that are associated with this chemistry. C–H activation occurred at two sites to give a mixture of **10** and **11**, where the major product **10** is derived from C–H insertion at the methyl site. We have previously shown that unless there are severe steric issues associated with the substrate, C–H activation at a methylene site is strongly preferred over a methyl site.^{4i,m} In this case, however, the reactivity of the methyl site dominates over the methylene site because of the deactivating effect of the acetoxy group at the methylene site.

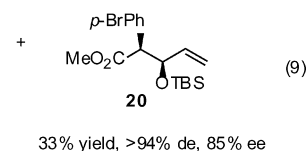
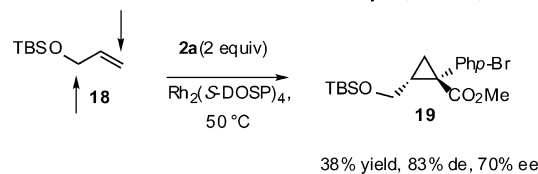
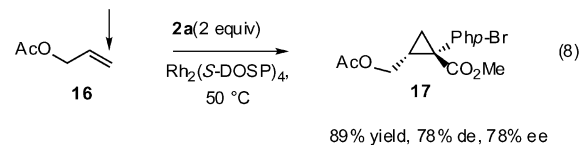


Due to the considerable difference in reactivity between the silyloxy and acetoxy groups, substrates containing differentially protected alcohols were examined (eq 6 and 7). With both the alkene derivative **12** and the diene derivative **14**, excellent regioselectivity was obtained favoring attack adjacent to the silyloxy group to form **13** and **15** in high yield. Again, the reactions proceeded with excellent diastereocontrol (>94% de) and useful enantiocontrol (62–72% ee).



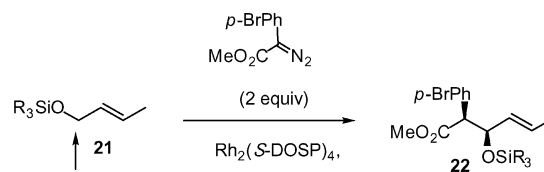
Similar reactivity differences between the silyloxy and acetoxy groups are also seen with unfunctionalized allyl alcohols. A monosubstituted alkene is generally an excellent substrate for cyclopropanation because it is sterically unencumbered.¹⁵ Indeed the reaction of allyl acetate **16** with **2a** results in the formation of the cyclopropane **17** (eq 8). As is well established for the reactions of donor/

acceptor carbenes with $\text{Rh}_2(\text{S-DOSP})_4$,^{15a} the cyclopropanation is highly diastereoselective and enantioselective. In contrast, with the silyl allyl ether **18**, a 1:1 mixture of the cyclopropane **19** and the C–H activation product **20** is obtained (eq 9). The fact that C–H activation is able to compete with the cyclopropanation of a monosubstituted double bond is a profound demonstration of the activating influence of the silyloxy group.



The C–H activation is dependent on the size of the silyl substituent as illustrated for the reaction of the butenyl silyl ethers **21** (Scheme 1). The high diastereoselectivity

SCHEME 1



	R ₃ Si	50 °C			23 °C		
		yield, %	de, %	ee, %	yield, %	de, %	ee, %
a	Me ₃ Si	93	>94	65	89	>94	85
b	<i>t</i> -BuMe ₂ Si	71	>94	68	65	>94	79
c	<i>t</i> -BuPh ₂ Si	64	>94	18	0	–	–

in the formation of the C–H activation products (**22**) is independent of the nature of the silyl group, but the highest yields are obtained with the smallest silyl group (**22a**). Indeed with the TMS ether **21a**, high yields are obtained at 23 °C, while the TBDPS ether **21c** is unable to undergo C–H activation at this temperature. As is common for the $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reactions,^{15a} higher enantioselectivities are observed at lower temperatures, and at 23 °C, **22a** is formed in 89% yield, >94% de, and 85% ee. In the case of the TBDPS ether **21c**, not only the yield but also the enantioselectivity is severely eroded, and this appears to be a common phenomenon when the site for insertion is crowded.^{4d}

The C–H activation of allyl *tert*-butyldimethylsilyl ethers has been applied to a range of substrates. The results are summarized in Table 1. Even though the

TABLE 1. $\text{Rh}_2(\text{S-DOSP})_4$ -Catalyzed C–H Activation of Allyl *tert*-Butyldimethylsilyl Ethers

entry	R	Ar	diazo (equiv)	temp, °C	product	yield, %	de, % ^b	ee, %
1	CH ₂ CH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	4	94	>94	62
2	CH ₂ CH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	23	4	40	>94	78
3	CH=CHCH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	8	92	92	79
4	CH=CHCH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	23	8	70	92	87
5	CH=CHCH ₃	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	23	71	98 ^c	74
6	CH ₂ OAc	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	13	93	>94	62
7	CH=CHCH ₂ OAc	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	15	92	>94	72
8	H	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	20	33	>94	85
9	H	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	24^a	36	98 ^c	90
10	H	C ₆ H ₅	2c (0.5)	23	25^a	52	>94	92
11	CH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	50	22b	71	>94	68
12	CH ₃	<i>p</i> -BrC ₆ H ₄	2a (2.0)	23	22b	65	>94	79
13	CH ₃	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	26^a	72	96 ^c	80
14	C ₆ H ₅	C ₆ H ₅	2a (2.0)	-25	27^a	94	>94	88
15	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	28^a	70	97 ^c	85
16	C ₆ H ₅	C ₆ H ₅	2c (2.0)	23	27^a	98	>94	74
17	C ₆ H ₅	C ₆ H ₅	2c (0.5)	23	27^a	73	>94	77
18	<i>p</i> -OMeC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	29^a	52 ^d	>94	78
19	<i>p</i> -BrC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	30^a	88 ^d	>94	80
20	CO ₂ CH ₃	<i>p</i> -ClC ₆ H ₄	2b (2.0)	23	31^a	93 ^d	>94	48
21	CO ₂ CH ₃	<i>p</i> -ClC ₆ H ₄	2b (0.5)	23	31	34	>94	51

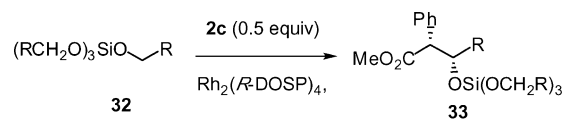
^a Reaction was conducted with $\text{Rh}_2(\text{R-DOSP})_4$ in hexane. The absolute configuration of the product is opposite to that drawn in Table 1. ^b Diastereomeric ratio was determined from the NMR of the crude reaction mixture unless noted otherwise. ^c Diastereomeric ratio was determined by GCMS. ^d Yield calculated by NMR using an internal standard.

exploratory reactions were conducted in refluxing 2,2-dimethylbutane, the reactions can be conducted at lower temperatures, and under these conditions, the enantioselectivity improves but the yield tends to decrease (entries 1 vs 2, 3 vs 4). One of the most impressive examples is the reaction of **2a** with *trans*-cinnamyl TBS ether at -25°C , as the C–H activation product is formed in 94% yield, >94% de, and 88% ee (entry 14). Due to the stabilized nature of the donor/acceptor carbenoids, the reactions can be carried out with the substrate as the limiting agent, and under these conditions, the yields are often superior to the reaction where the diazo compound is the limiting agent (entries 16 vs 17, 20 vs 21). Even though 2,2-dimethylbutane is the optimum inert solvent, the high reactivity of the allyl silyl ethers is such that hexanes can be used as a substitute solvent without any obvious detrimental effects. In the case of the reaction with the chloro derivative **2b**, the reactions were conducted with $\text{Rh}_2(\text{R-DOSP})_4$ instead of $\text{Rh}_2(\text{S-DOSP})_4$ in order to facilitate the chiral HPLC analysis. In virtually all instances (except for entries 3 and 4), the diastereoselectivity was so high that only a single diastereomer was observable in the NMR of the crude reaction mixtures. In those cases in which the diastereomeric ratio was determined by GCMS, the diastereomeric ratio was determined to be between 96 and 98%.

Having demonstrated that *trans*-allyl silyl ethers were exceptional substrates for the C–H activation chemistry, the study was expanded to a wider array of substrates. The readily available tetraalkoxysilanes were anticipated to be effective substrates because the presence of four active C–H insertion sites per molecule should enhance the C–H activation chemistry. The $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed reactions of the tetraalkoxysilanes **32** with phenyldiazoacetate **2c** were all highly stereoselective. The diastereoselectivity for the formation of the C–H

activation products **33** was >90% de, while the enantioselectivity ranged from 93 to 96% ee.

SCHEME 2



	R	yield, %	de, %	ee, %
a	Me	70	>90	95
b	Et	52	>90	96
c	<i>n</i> -Pr	58	>90	93

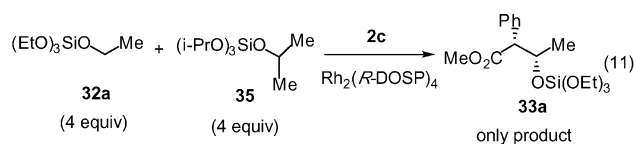
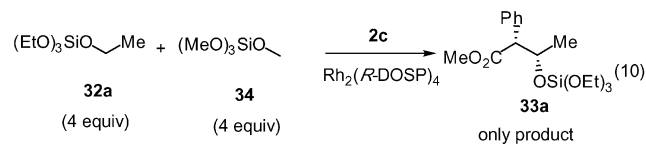
The reactions of tetraalkoxysilanes are ideally suited for exploration of the steric environment on the rate of reaction. Competition reactions between tetraethoxysilane (**32a**) with tetramethoxysilane (**34**) and tetraisopropoxysilane (**35**) were conducted, and the results are summarized in eqs 10 and 11. Tetraethoxysilane was by far the most reactive substrate as in the competition experiments no C–H insertion into the other alkoxy-silanes was observed. A similar high preference for reaction at methylene sites over methyl and methine sites was seen in benzylic systems.^{4m} The chemoselectivity effects, however, are subtle because uncrowded methine sites can be favored in C–H activation of simple alkanes and *N*-methyl is favored over *N*-methylene sites in acyclic *N*-Boc-protected amines.^{4k}

The C–H activation can also be conducted on dialkoxy-silanes as illustrated in eq 12. These reactions offer a novel approach to chiral alcohols **37** functionalized by unusual silicon protecting groups not generally obtained

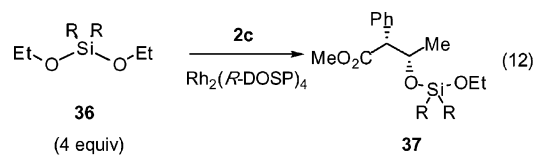
TABLE 2. C–H Activation of Alkyl Silyl Ethers

$$\text{R}_3\text{SiOCH}_2\text{R}^1 + \text{MeO}_2\text{C}-\text{CH}(\text{Ph})-\text{N}_2 \xrightarrow[\text{2,2-DMB, 23 }^\circ\text{C}]{\text{Rh}_2(\text{R-DOSP})_4} \text{MeO}_2\text{C}-\text{CH}(\text{Ph})-\text{CH}_2\text{R}^1-\text{OSiR}_3$$

entry	R ₃ Si	R ¹	product	yield, %	de, %	ee, %
1	TBS	CH ₃	38	45	>90	96
2	TMS	C ₂ H ₅	39	47	90	91
3	TBS	C ₂ H ₅	40	36	>90	93
4	TMS	C ₃ H ₇	41	45	90	87
5	TBS	C ₃ H ₇	42	24	88	81
6	TMS	C ₅ H ₁₁	43	59	90	86
7	TMS	C ₇ H ₁₅	44	40	90	84
8	TMS	C ₉ H ₁₉	45	52	88	86



by the standard approach of alcohol silylation. These reactions are also highly diastereoselective (90% de) and enantioselective (91–94% ee).

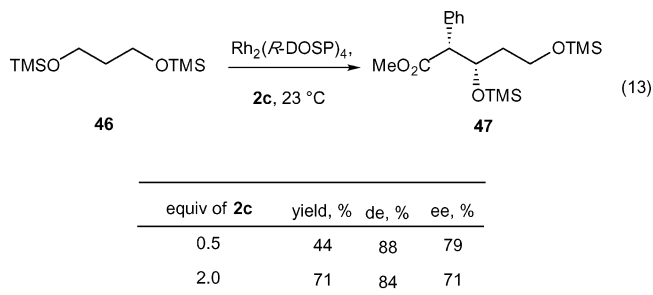


	R	yield, %	de, %	ee, %
a	Me	51	90	91
b	Ph	52	90	94

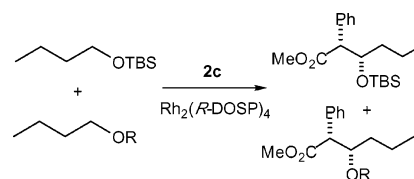
The final series of experiments were directed toward determining if the C–H activation chemistry could be extended to simple silylated alcohols. Considering the ease of silylation of alcohols and the fact that, in most instances, the role of the silyloxy group is as a protecting group, the successful C–H activation of these substrates could have wide utility. The reactions of a series of alkyl silyl ethers are summarized in Table 2. Due to the relatively low reactivity of the silyl ethers, 2,2-dimethylbutane rather than hexanes must be used as a solvent in these reactions. Even though the yields of these products are fairly moderate (24–59%), it is impressive that such readily available substrates are capable of participating in these C–H activations. In general, higher yields are obtained with TMS ethers (40–59%) compared to TBS ethers (24–45%) and this trend is presumably due to steric effects.

An efficient reaction was also observed with α,ω -disiloxyalkanes as illustrated for **46**. $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed decomposition of **2c** in the presence of 4 equiv of the silane **46** gave the C–H activation product **47** in 44% yield (eq 13). Once again, repeating the reaction with

an excess of the diazo compound gave considerably improved yield (from 44 to 71%), although under these conditions there was a drop in enantioselectivity (from 79 to 71% ee).



To further evaluate the possibility of using different silyl groups to control the site of C–H activation, competition experiments were conducted using a series of silylated butanol derivatives (Scheme 3). The rate of

SCHEME 3

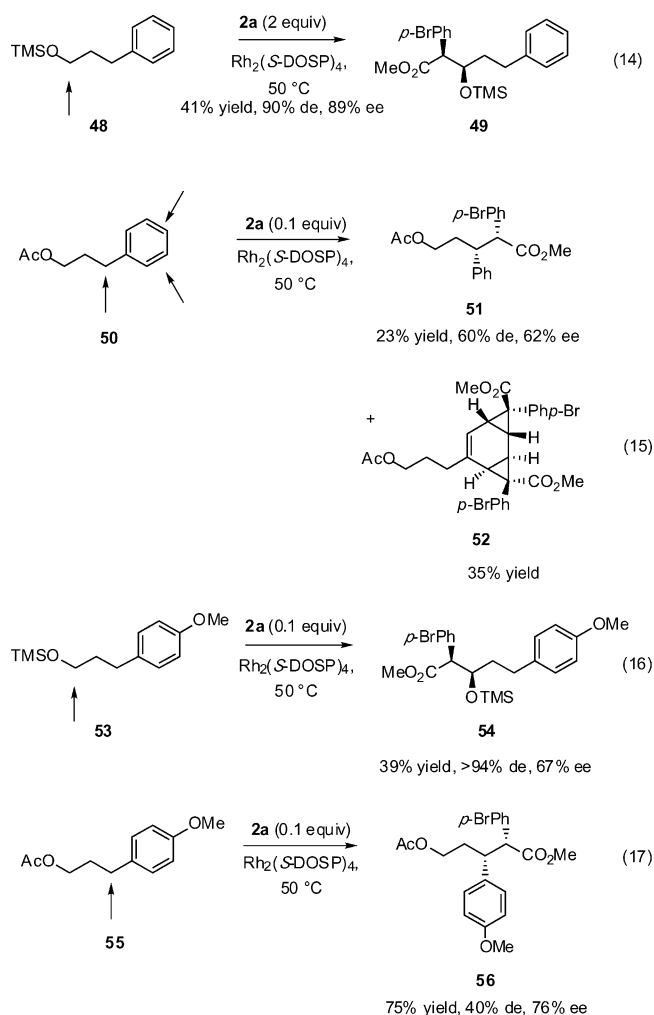
R	Relative rate
TMS	102
TES	39
TBS	14
TIPS	1.7
TBDPS	1

reaction varies by a factor of 100 with the TMS derivative being the most reactive. Thus, the opportunity exists for selective C–H activation at different *O*-silyl sites to be effectively controlled by using appropriate silyl protecting groups.

Selective deactivation is also possible by using an acetoxy group as illustrated in eqs 14 and 15. Reaction with the TMS analogue **48** results in C–H activation α to the silyloxy group to form **49**. In contrast, the acetoxy analogue **50** is protected from C–H activation α to oxygen and instead a mixture of two products is obtained, **51** derived from C–H activation at the benzylic position and the double-cyclopropanation product **52**.

By using *p*-methoxyphenyl derivatives, the benzene ring is sterically protected and site-selective C–H activation can be obtained. With the TMS analogue **53**, the C–H activation occurs exclusively α to the siloxy group to form **54** (eq 16), while with the acetoxy analogue **55**, the C–H activation occurs at the benzylic position to form **56** (eq 17). The total elimination of the cyclopropanation of the aromatic ring demonstrates the importance of steric effects in donor/acceptor carbenoid chemistry, because the aromatic rings in **53** and **55** are very electron rich.

To complete the reactivity profile studies, a few competition studies were conducted between different substrates. The relative rates of C–H activation at an allylic methylene site and a methylene site α to OTMS were



shown to be roughly equivalent from the competition reaction between **5** and butyltrimethylsilyl ether. The relative rates of C–H activation at a methoxybenzyl site and a methylbutadienyl site were also shown to be roughly equivalent from the competition reactions between **9** and **55**. The complete details of these and other competition studies are given in Supporting Information.

The C–H activation reactions of protected alcohols emphatically demonstrate the remarkable regioselectivity displayed by this chemistry. A delicate balance exists between steric and electronic effects. In particular, silyloxy groups are very activating, while acetoxy groups are deactivating. On the basis of the reactions conducted in this study, it is now possible to describe general reactivity

trends (Figure 1), which will be useful for predicting which substrates would be amenable to selective C–H activation chemistry. A silyl allyl ether is highly activated toward C–H functionalization, which generally occurs with very high diastereoselectivity (>94% de) and moderate to high enantioselectivity (62–89% ee). Methylene sites adjacent to a TMSO or an allyl group are equally reactive and more reactive than a benzylic methylene site, while an acetoxy group is highly deactivating. The deactivating effect of the acetoxy group is presumably because this group acts as an electron-withdrawing group.¹⁴ Further differentiation between competing reactive sites would be possible by modifying the size of the silyl group.

The absolute stereochemistry of this reaction is in agreement with the predictive model we have developed for this chemistry. $\text{Rh}_2(\text{S-DOSP})_4$ is considered to behave as a D_2 symmetric complex and can be simply considered as having two blocking groups on either rhodium face.¹² Although the exact trajectory of approach of the substrate to the carbenoid is not known, it is proposed that the C–H activation is a concerted nonsynchronous process and that the substrate approaches over the carbenoid electron-withdrawing group with the arrangement of the large (L), medium (M), and small (S) groups as drawn (Figure 2a).^{4d,5} The arrangement of the groups may be governed simply by steric effects, but it may also be due to stereoelectronic effects. In the reaction described herein, the silyloxy group is acting as the large group leading to the observed stereochemistry (Figure 2b).

In summary, the C–H activation of silyl ethers demonstrates that the donor/acceptor-substituted carbenoids display remarkable chemoselectivity, which allows for highly regio-, diastereo-, and enantioselective reactions to be achieved. Due to the high stereoselectivity exhibited by this transformation, it represents an intriguing complement to the classic aldol reaction. Further studies are in progress to expand the range of this chemistry with particular emphasis on diversifying the types of donor and acceptor groups than can be attached to the carbenoid.

Experimental Section

General Procedures for the Decomposition of Aryldiazoacetates **2 in the Presence of Siloxy or Acetoxy Substrates: Procedure A.** Methyl *p*-bromophenyldiazoacetate **2a** (0.79 mmol) in 2,2-dimethylbutane (7.9 mL) was added dropwise over 45 min via a syringe pump to a rapidly stirred solution of allylic silyl ether (0.39 mmol) and $\text{Rh}_2(\text{S-DOSP})_4$ (15 mg, 7.9×10^{-3} mmol) in 2,2-dimethylbutane (1.0

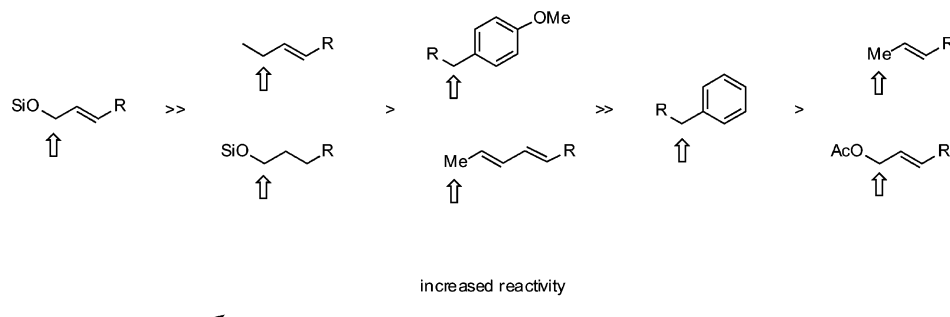


FIGURE 1. Relative rates of substrates toward C–H activation.

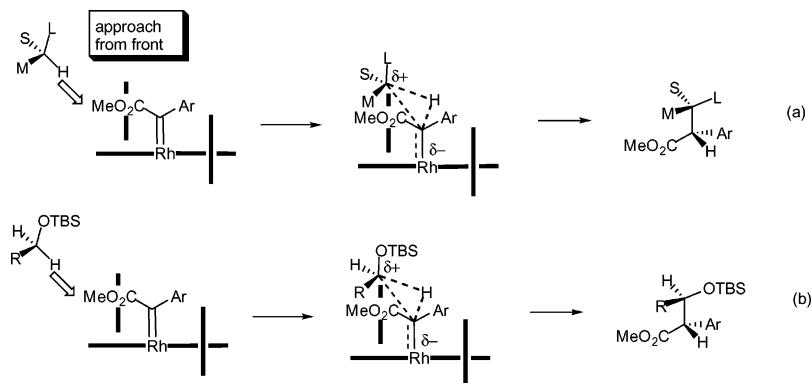


FIGURE 2. Predictive model for C–H activation stereoselectivity with (a) a generic alkane and (b) a silyl ether.

mL) at 50 °C. On completion of the methyl *p*-bromophenyldiazoacetate addition, the reaction mixture was allowed to stir for an additional 15 min prior to cooling and concentration in vacuo. Purification by flash chromatography on silica gel afforded the product(s).

Procedure B. Methyl *p*-bromophenyldiazoacetate **2a** (0.50 mmol) in 2,2-dimethylbutane (5.0 mL) was added dropwise over 45 min via a syringe pump to a rapidly stirred solution of acetyl ester (5.00 mmol) and $\text{Rh}_2(\text{S-DOSP})_4$ (9.5 mg, 0.005 mmol) in 2,2-dimethylbutane (1.0 mL) at 50 °C. On completion of the methyl *p*-bromophenyldiazoacetate addition, the reaction mixture was allowed to stir for an additional 15 min prior to cooling and concentration in vacuo. Purification by flash chromatography on silica gel afforded the product(s).

Procedure C. Aryldiazoacetate **2** (0.75 mmol) in hexane (7.5 mL) was added dropwise over 1 h via a syringe pump to a rapidly stirred solution of allylic silyl ether (1.50 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (14 mg, 7.5×10^{-3} mmol) in hexane (0.5 mL) at room temperature (23 °C). On completion of the aryldiazoacetate addition, the reaction mixture was allowed to stir for an additional 1 h prior to concentration in vacuo. Purification by flash chromatography on silica gel afforded the product(s).

Procedure D. Phenyldiazoacetate **2c** (0.75 mmol) in hexane (7.5 mL) was added dropwise over 2 h via a syringe pump to a rapidly stirred solution of alkyl silyl ether (3.00 mmol) and $\text{Rh}_2(\text{R-DOSP})_4$ (14 mg, 7.5×10^{-3} mmol) in hexane (0.5 mL) at room temperature (23 °C). On completion of the aryldiazoacetate addition, the reaction mixture was allowed to stir for an additional 1 h prior to concentration in vacuo. Purification by flash chromatography on silica gel afforded the product(s).

(2*S*,3*R*)-(E)-Methyl 2-(4-Bromophenyl)-3-(*tert*-butyldimethylsilyloxy)hept-4-enoate (4): Procedure A. Diastereo-

selectivity of >94% was obtained (as determined by ^1H NMR of the crude reaction mixture). Flash chromatography (SiO_2 ; 1:4 dichloromethane–petrol, and then 1:49 diethyl ether–petrol) afforded the title compound (157 mg, 94%) as a colorless oil: $[\alpha]_D^{25} -13.9$ (*c* 1.25, CHCl_3); IR (film) 2957, 2929, 2894, 2856, 1738, 1488, 1255, 1074, 838 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 5.68 (app. dt, $J = 15.5, 6.5$ Hz, 1H), 5.34 (dd, $J = 15.5, 7.5$ Hz, 1H), 4.53 (app. t, $J = 8.0$ Hz, 1H), 3.64 (s, 3H), 3.56 (d, $J = 8.0$ Hz, 1H), 2.01 (app. quintet, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.5$ Hz, 3H), 0.72 (s, 9H), -0.10 (s, 3H), -0.24 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 135.4, 135.1, 131.4, 131.2, 129.9, 121.4, 75.9, 59.2, 51.9, 25.7, 25.2, 18.0, 13.5, -4.2 , -5.3 ; LRMS (FAB) m/z 449 ($\text{M} + \text{Na}$, 94%), 301 (18); HRMS ($\text{M} + \text{Na}$) calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3\text{BrNaSi}$ 449.1118, found 449.1133. HPLC analysis: ee 62% (Chiralcel-OD, 0.2% *i*-PrOH in hexane, 0.8 mL/min, $\lambda = 254$ nm, $t_R = 6.0$ min, major; $t_R = 7.2$ min, minor). The reaction at 23 °C gave **4** in 40% yield and 78% ee.

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Supporting Information Available: Complete Experimental Section and details regarding stereochemical assignments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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