

Asymmetric Catalytic C–H Activation
Applied to the Synthesis of *Syn*-Aldol
Products

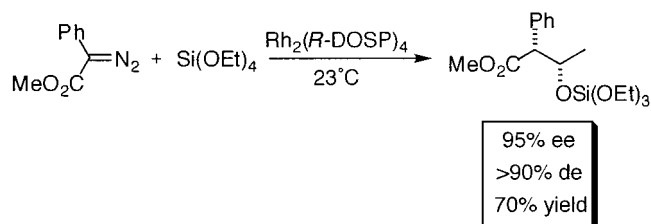
Huw M. L. Davies* and Evan G. Antoulinakis

Department of Chemistry, State University of New York at Buffalo, Box 603000,
Buffalo, New York 14260-3000

hdavies@acsu.buffalo.edu

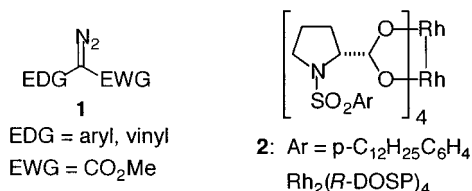
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ABSTRACT



$\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed decomposition of methyl phenyldiazoacetate in the presence of tetraalkoxysilanes results in the asymmetric synthesis of *syn*-aldol products. This catalytic asymmetric intermolecular C–H activation proceeds by means of a rhodium–carbene-induced C–H insertion.

The metal-catalyzed decomposition of diazo compounds has been extensively used in organic synthesis.¹ In recent years it has become clear that diazo compounds containing both electron-withdrawing (EWG) and electron-donating groups (EDG) (**1**) are especially useful because reactions of the



carbenoids derived from such systems are highly chemo-selective.² Highly diastereoselective cyclopropanations are routinely achieved with such systems³ even though poor diastereoselectivity is a recurring problem in diazoacetate

systems that contain only an EWG.¹ Furthermore, by using either Rh₂(R-DOSP)₄ (**2**) or Rh₂(S-DOSP)₄ as the catalyst with such systems (**1**), highly enantioselective cyclopropanations can also be achieved.^{4,5}

Recently, a new and general transformation for diazo compounds **1** has been discovered. These diazo compounds are capable of undergoing efficient asymmetric intermolecular C–H insertions.^{6,7} This reaction is used as a catalytic

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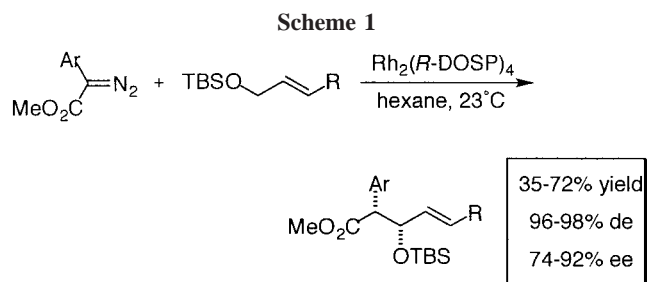
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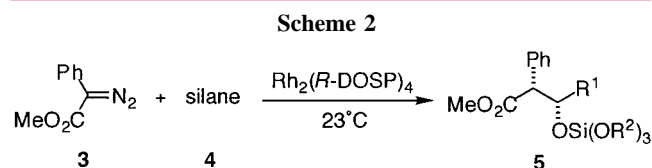
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asymmetric method for the C–H activation of alkanes.^{6a,h} One novel application of this chemistry is for the asymmetric synthesis of *syn*-aldol products⁸ by reaction of aryldiazoacetates with allyl silyl ethers (Scheme 1).^{6c} The Rh₂(R-



DOSP)₄-catalyzed reaction of *p*-chlorophenyldiazoacetate with *trans*-disubstituted allyl silyl ethers occurs with high diastereoselectivity and moderate enantioselectivity.^{6c} In this Letter we report that tetraalkoxysilanes are exceptional reactants for this type of C–H insertion, which greatly expands the synthetic utility of this novel transformation.

Even though our original study with allyl silyl ethers resulted in effective C–H insertions, it also indicated that the reaction was of limited scope.^{6c} Highly diastereoselective C–H insertions were obtained only when *trans*-allyl silyl ethers were used as substrates. To broaden the scope of this chemistry beyond allyl silyl ethers, the reaction with tetraalkoxysilanes as substrates was explored. The presence of four active methylene sites per molecule was expected to enhance the C–H insertion chemistry. All of the reactions were carried out in 2,2-dimethylbutane as solvent, which is a good inert solvent for C–H insertion.^{6h} Rh₂(R-DOSP)₄ (1 mol %) catalyzed decomposition of phenyldiazoacetate **3** in the presence of tetraethoxysilane (**4a**) at room temperature was very promising (Scheme 2).⁹ The C–H insertion product

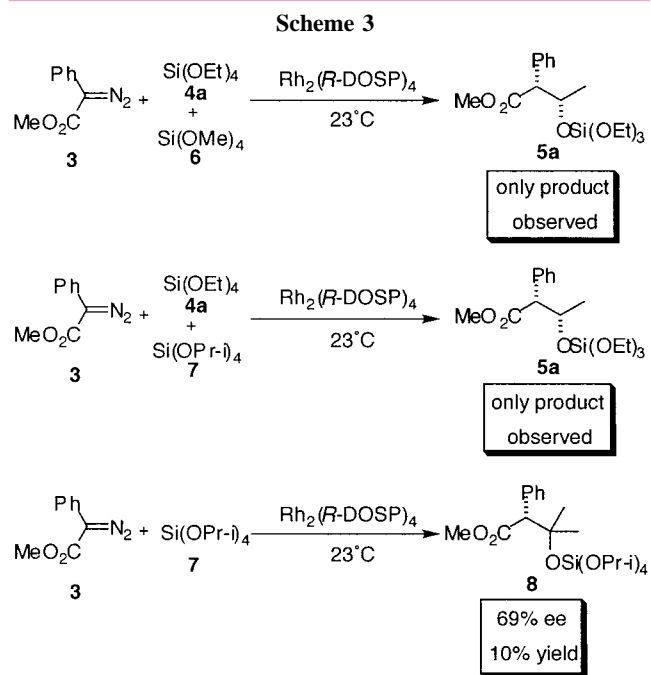


	silane	R ¹	R ²	yield, %	de, %	ee, %
a	Si(OEt) ₄	CH ₃	Et	70	>90	95
b	Si(OPr- <i>n</i>) ₄	CH ₂ CH ₃	Pr	52	>90	92
c	Si(OBu- <i>n</i>) ₄	CH ₂ CH ₂ CH ₃	Bu	58	>90	93

5a was formed in 70% yield, >90% de, and 95% ee. Similar transformations with likewise high diastereo- and enantioselectivities were also possible with tetrapropoxysilane (**4b**) and tetrabutoxysilane (**4c**). The chemoselectivity of these reactions was extremely high, with insertion occurring

exclusively at the methylene adjacent to the oxygen, and only one insertion occurring on each substrate molecule with all substrates tested.

The C–H insertion occurs preferentially at a methylene site as illustrated in Scheme 3. A competition reaction



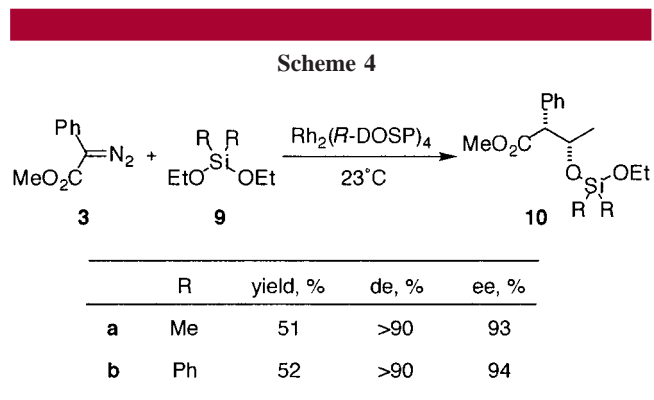
between tetramethoxysilane (**6**) and tetraethoxysilane (**4a**) leads to the formation of a single C–H insertion product, **5a**, arising from exclusive insertion into tetraethoxysilane (**4a**). The reaction with tetramethoxysilane (**6**) alone as the trapping agent does not generate any C–H insertion product. A second competition reaction between tetraethoxysilane (**4a**) and tetraisopropoxysilane (**7**) again resulted in only a single product, **5a**, arising from exclusive C–H insertion into tetraethoxysilane (**4a**). The reaction with tetraisopropoxysilane (**7**) alone as the trapping agent results in the formation of C–H insertion product **8** in only 10% yield and 69% ee.

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(9) **General Procedure for C–H Insertion Reactions:** A flame dried 50 mL round-bottom flask equipped with a magnetic stir bar and a rubber septum was charged with silane (3.0 mmol), Rh₂(R-DOSP)₄ (14 mg, 7.5 × 10^{−3} mmol), and degassed 2,2-dimethylbutane (0.5 mL) and stirred under argon at room temperature to give a green solution. A 10 mL gastight syringe was charged with the diazo compound (0.75 mmol) in degassed 2,2-dimethylbutane (7.5 mL) to give a 0.10 M diazo solution. Addition via syringe pump was initiated at a rate of 3.75 mL/h (2 h addition time). After the diazo addition was complete the reaction mixture was allowed to stir for an additional hour and then the solvent and excess silyl ether were removed in vacuo. Purification by flash chromatography on silica gel (petroleum ether:ether, 9:1) gave the product as a clear oil. Diastereomeric ratios were determined by 500 MHz ¹H NMR of the crude reaction mixtures. Diastereomeric ratios of >90% de could not be determined accurately from the ¹H NMR of the crude reaction mixtures and the products were not sufficiently stable for analysis by GCMS. Enantiomeric excess (ee) was determined by HPLC using a Chiralcel OD column and 2-propanol (0.8% or 1.0%) in hexane as the eluent.

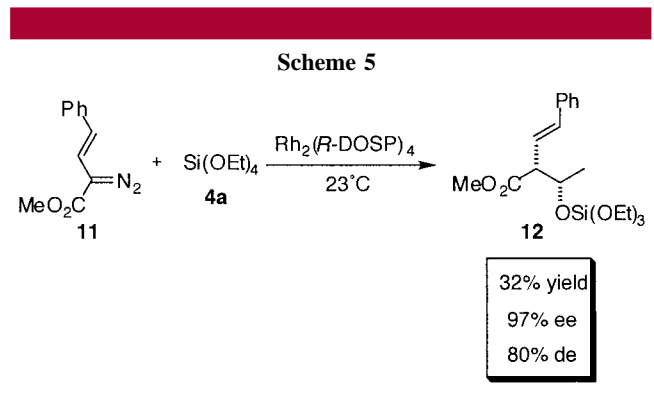
These reactions are excellent examples of the general trend in these C–H insertions where there is a delicate balance between steric and electronic effects.^{6,7} The C–H insertions at sites (3°) that would most stabilize a buildup of positive charge in the transition state are favored electronically, but the carbenoid is unable to successfully approach these sterically crowded sites. On the other hand, primary sites are very sterically accessible; however, they are unreactive toward C–H insertion, presumably because C–H bonds at primary sites are stronger than those at secondary or tertiary sites.

An interesting opportunity that is available with this chemistry is the formation of novel siloxy protecting groups that are not generally obtained by the standard approach to alcohol silylation. Two further examples are shown in Scheme 4. Reaction of phenyldiazoacetate **3** with dimethyl-



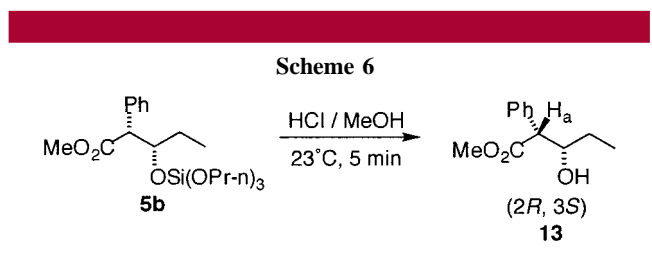
dimethoxysilane (**9a**) generated the C–H insertion product **10a** in 93% ee. Similarly, reaction of **3** with diphenyldimethoxysilane (**9b**) generated the C–H insertion product **10b** in 94% ee.

The success of the intermolecular C–H insertion depends on the unique characteristics of rhodium carbenoids containing both electron donor and acceptor groups.^{6g,h,7,10} The major future challenge facing this chemistry will be to broaden the range of carbenoids that have this donor/acceptor characteristic in order to diversify the synthetic opportunities. Vinyldiazoacetate **11** is also effective in this chemistry, resulting in the formation of C–H insertion product **12** with high enantioselectivity (97% ee) but moderate yield (32%) (Scheme 5). Thus, it is possible to obtain *syn*-aldol products



lacking the aryl ring, and this allows for broader possible applications of this unusual reaction in synthesis.

The relative and absolute stereochemistry of the C–H insertion product **5b** was readily determined by hydrolysis of the silyl group of **5b** to give the alcohol **13**, whose enantiomer is known in the literature (Scheme 6).¹¹ *Syn*



stereochemistry was assigned by comparison of *J* values for H_a , which was observed to be 6.2 Hz, to that reported in the literature for the *syn*-isomer, 6.3 Hz. Absolute stereochemistry was determined to be (2*R*,3*S*), when using $Rh_2(R-DOSP)_4$ (**2**), by comparison of the sign of optical rotation of **13** ($[\alpha]_D^{24} +86.9$, $c = 0.70$, $CHCl_3$, 92% ee), which was found to be opposite that of the literature value ($[\alpha]_D^{20} -84.2$, $c = 0.87$, $CHCl_3$, 88% ee) for the (2*S*,3*R*) isomer. Similar absolute and relative¹² stereochemistries were assigned to the other C–H insertion products, assuming a similar mode of C–H insertion for all the substrates.

The predictive model^{6h} that has been used to determine the stereoselectivity of these C–H insertions is illustrated in Figure 1 using insertion into tetraethoxysilane with the

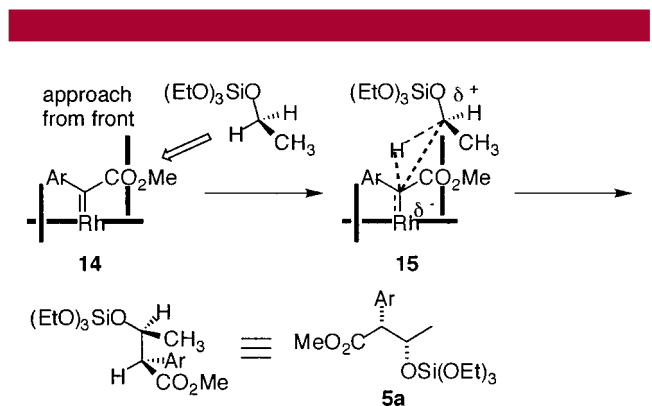


Figure 1. Predictive model for C–H insertion.

$Rh_2(R-DOSP)_4$ catalyst as an example. The catalyst is considered to behave as if it is D_2 -symmetric with two blocking groups on each face of the catalyst.^{4a,5} The approach of the substrate occurs over the EWG (CO_2Me) of the rhodium carbenoid. While the hydrogen undergoing the

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(12) Hydrolysis of products **5a–c**, **10a**, **10b**, and **12** gave their corresponding alcohols which all gave similar *J* values (4.8–6.7 Hz) for H_a , indicating a *syn* relative stereochemistry for all the insertion products.

insertion is thought to approach side-on (**14**), the large (OSi(OEt)₃) group has been postulated to be pointing up, away from the catalyst, in the least sterically demanding position. The medium-sized (Me) group would then be pointing out, away from the carbenoid, while the smallest group (H) would face in toward the catalyst. The C–H insertion is thought to occur in a concerted, nonsynchronous mode, with buildup of positive charge on the carbon which bears the hydrogen undergoing insertion (**15**).^{5b,6h} When this model is applied to the alkoxysilanes, it correctly predicts the observed stereochemistry (Scheme 2).

In summary, these studies considerably enhance the utility of the intermolecular C–H insertions of aryldiazoacetates. β -Hydroxy esters are formed with high diastereoselectivity and enantioselectivity. A major future challenge will be to broaden the range of carbenoids that exhibit this exceptional chemoselectivity.

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