# Catalytic Asymmetric C−H Activation of Silyl Enol Ethers as an Equivalent of an Asymmetric Michael Reaction

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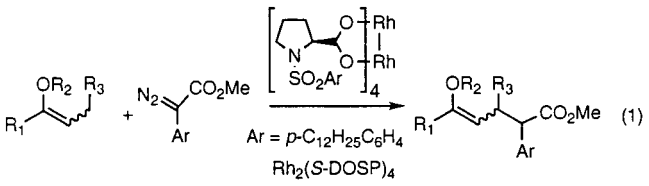
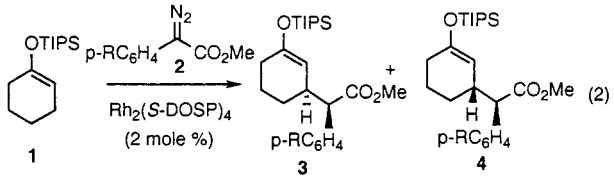
The development of chemoselective methods for C−H activation would broaden the range of strategies that could be used for the synthesis of complex molecules.[1,2] A very attractive method for catalytic asymmetric C−H activation is the C−H insertion chemistry of metal-carbenes.[3] The enantioselective intramolecular version of the metal-carbene C−H insertion is well established.[4] Recently, we demonstrated that the enantioselective intermolecular version of this reaction is also very effective with rhodium-carbenes containing both electron-withdrawing and electron-donating groups.[5] [$Rh_2$(*S*-DOSP)$_4$] is an exceptional chiral catalyst for this transformation.[6] Since then, highly enantioselective C−H activation of alkanes,[7] alkenes,[8] polyenes,[9] tetrahydrofuran,[7] N-BOC protected cyclic amines,[10] and allyl silyl ethers[11] have been reported.[12] In this paper we describe the application of the asymmetric C−H activation to the synthesis of products that would be more typically derived from an asymmetric Michael reaction.[13] The key step is the $Rh_2$(*S*-DOSP)$_4$-catalyzed decomposition of methyl aryldiazoacetates in the presence of silyl enol ethers (eq 1).




The C−H activation of vinyl ethers is an intriguing proposition, because the double bond is very electron rich, which makes it prone to cyclopropanation. Indeed, the cyclopropanation of vinyl ethers with ethyl diazoacetate has been extensively applied in organic synthesis.[14] However, the rhodium-carbenes derived from vinyldiazoacetates and aryldiazoacetates are much more chemoselective, both electronically[15] and sterically,[16] than the traditional rhodium-carbenes derived from ethyl diazoacetate. No examples are known of intermolecular cyclopropanation of *trans*-alkenes or more highly substituted alkenes by these carbenes. Consequently, even though the double bond in vinyl ethers is electron rich, we anticipated that effective C−H insertion would occur. As the C−H insertion is considered to involve a transition state with build-up of positive charge on carbon,[12] good regiocontrol between the two allylic positions was expected. Furthermore, by modifying the size of the functionality around the C−H insertion site good diastereocontrol should also be feasible.

The initial evaluation of this reaction was carried out with TIPS enol ether **1**. $Rh_2$(*S*-DOSP)$_4$-catalyzed decomposition of methyl *p*-bromophenyldiazoacetate (**2a**) at 23 °C in the presence of 4 equiv of **1** in 2,2-dimethylbutane as solvent resulted in the formation of the desired C−H insertion products **3a** and **4a** in a 2:1 ratio with a combined yield of 80% (eq 2). The diastereomers




| | R | equiv. of **2** | temp, °C | yield, **3** + **4**, % | ratio, **3** : **4** | ee, **3**, % | ee, **4**, % |
|---|---|---|---|---|---|---|---|
| **a** | Br | 0.25 | 23 | 80 | 65 : 35 | 90 | 78 |
| **a** | Br | 0.25 | 0 | 54 | 66 : 34 | 92 | 82 |
| **a** | Br | 0.25 | -30 | 44 | 60 : 40 | 95 | 85 |
| **a** | Br | 2 | -30 | 86 | 65 : 35 | 94 | 84 |
| **b** | H | 2 | -30 | 90 | 70 : 30 | 96 | 86 |

were readily separated by chromatography, and the major diastereomer **3a** was formed in 90% ee while the minor diastereomer **4a** was formed in 78% ee. On lowering the reaction temperature to −30 °C, the enantioselectivity for **3a** and **4a** was improved to 95% ee and 85% ee, respectively, but the yield was decreased (44% yield). By using **1**, however, as the limiting agent (2 equiv of **2a**) an excellent yield (86%) of **3a** and **4a** was obtained. Methyl phenyldiazoacetate (**2b**) undergoes similar C−H insertions to **2a**.

To confirm that the structure of the carbene was the critical factor that caused the C−H insertion to be the dominant reaction pathway, the reaction catalyzed by $Rh_2$(*S*-DOSP)$_4$ was repeated with ethyl diazoacetate instead of **2a**. This resulted in the formation of a 76:24 mixture of cyclopropane diastereomers **5** and the C−H insertion product **6**. $Rh_2$(*S*-DOSP)$_4$ enhances the C−H insertion because the same reaction catalyzed by $Rh_2$(OOct)$_4$ gave a 96:4 ratio of **5** to **6**. From these results it is clear that the carbene structure is critical for effective C−H insertions with silyl enol ethers, but $Rh_2$(*S*-DOSP)$_4$ also enhances the C−H insertion pathway.

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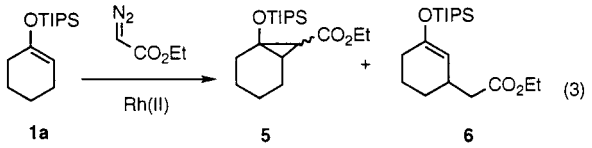
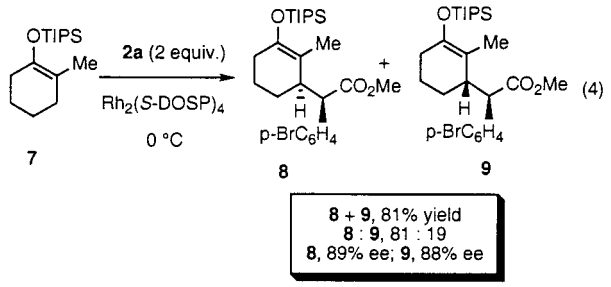
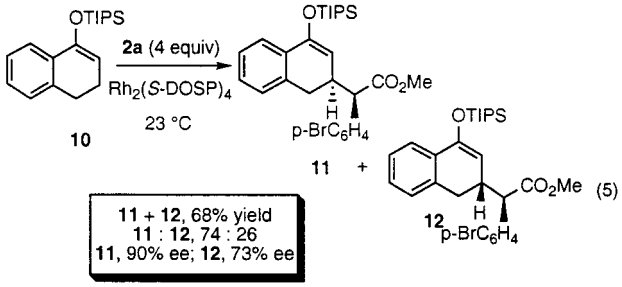



| Rh(II) | yield, **5** + **6**, % | ratio, **5** : **6** |
|---|---|---|
| $Rh_2$(*S*-DOSP)$_4$ | 54 | 76 : 24 |
| $Rh_2$(OOct)$_4$ | 66 | 96 : 4 |

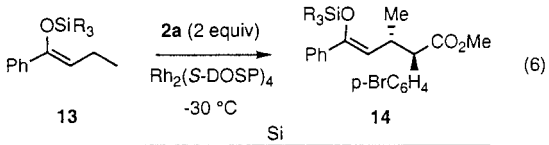
In our previous studies on the C−H activation, we have found that highly diastereoselective reactions are possible at methylene sites as long as the methylene substituents are of different size.[10a,11,12] Consequently, the reaction of the vinyl ether **7** was explored. This resulted in the formation of the diastereomeric C−H insertion products **8** and **9** in an 81% overall yield and an improved ratio of 81:19. A trace (2−3%) of the primary C−H insertion product was also observed. The enantioselectivity for the formation of both **8** and **9** was high (89% ee and 88% ee, respectively). Considering that the vinyl ether **7** has three allylic positions, the selective formation of one diastereomeric pair of the possible C−H insertion products underscores the chemoselectivity that is possible in these C−H insertions.




The C−H insertions can also be carried out with the more elaborate silyl enol ether **10**. The $Rh_2$(*S*-DOSP)$_4$-catalyzed reaction of **2a** with **10** resulted in the formation of the major diastereomer **11** in 90% ee and the minor diastereomer **12** in 73% ee with a combined yield of 68%. This transformation is an excellent example of the potential of this chemistry because the corresponding Michael reaction would not be possible as the required enone would be the keto tautomer of 1-naphthol.



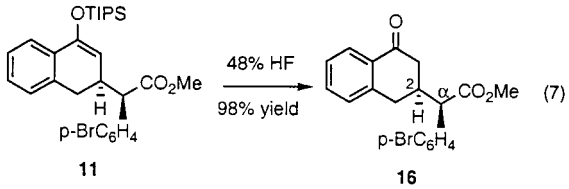

Extension of the chemistry to the acyclic TIPS enol ether **13a** resulted in a major change in the chemistry. With this substrate, the diastereoselectivity of the C−H insertion was very high (>90% de), presumably because the methylene substituents (C=C(OSi$R_3$)Ph and Me) are very different in size. Under the standard conditions, with the silyl enol ether **13a** as the limiting agent at −30 °C, the C−H insertion product **14a** was formed in




| | Si$R_3$ | yield, % | de, % | ee, % |
|---|---|---|---|---|
| **a** | TIPS | 66 | >90 | 71 |
| **b** | TBDPS | 65 | >90 | 84 |

66% isolated yield and 71% ee. Under these conditions, the conversion of **13a** is essentially quantitative but 25−30% of the cyclopropanation product is also formed.[17] This is the first example of an aryldiazoacetate undergoing intermolecular cyclopropanation of a trisubstituted alkene. A similar reaction with the TBDPS enol ether **13b** generated **14b** in 84% ee and >90% de.

Demonstration that the C−H insertion products could be converted to the equivalent products of a Michael addition was readily achieved (eq 7). Desilylation of **11** generated the ketone




**16** in 98% yield, which could be recrystallized to enantiomeric purity (>99% ee). The absolute stereochemistry of **16** was determined by X-ray crystallography to be α*R*,2*S*.[18]

In summary, the efficient C−H insertion of vinyl ethers by aryldiazoacetates demonstrates the broad range of C−H activation chemistry that is possible with this system. The carbenoid structure and catalysts are crucial for the success of this chemistry. The reaction with the acyclic enol silyl ethers **13** is especially promising because excellent diastereocontrol is possible with this system. Studies are underway to determine the full scope of this reaction for the synthesis of compounds that would be typically made by an asymmetric Michael reaction.

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**Supporting Information Available:** Full experimental data for compounds **3a**, **4a**, **3b**, **4b**, **8**, **9**, **11**, **12**, **14**, **15**, and **16**, and X-ray crystallographic data for **16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The cyclopropane product **15** was formed in >90% de and 92% ee. The highly stereoselective cyclopropanation is typical of $Rh_2$(*S*-DOSP)$_4$-catalyzed aryldiazoacetate cyclopropanations (see ref 6).

(18) The absolute stereochemistry for the major diastereomers of the other C−H insertion products is tentatively assigned by assuming a similar mode of asymmetric induction for all the substrates. The stereochemistry of the minor C−H insertion product was determined by epimerization of the major product. Treatment of **3a** (89%ee, α*R*,1*S*) with DBU at 80 °C overnight resulted in equilibration to α*S*,1*S* diastereomer **4a** (85%ee), which, according to the retention time on HPLC, is the enantiomer of the minor diastereomer **4a** from the C−H insertion. Hence, the minor C−H insertion product **4a** is assigned to be the (α*R*,1*R*) configuration.