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Catalytic Asymmetric Synthesis of *Syn*-Aldol Products from Intermolecular C–H Insertions between Allyl Silyl Ethers and Methyl Aryldiazoacetates

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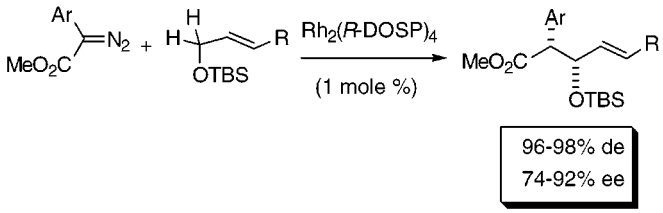
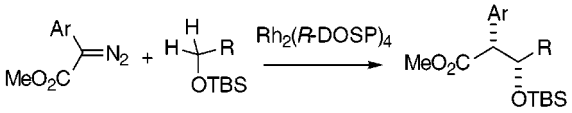
ABSTRACT



Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of methyl aryldiazoacetate in the presence of allyl silyl ethers results in a regioselective C–H insertion. The resulting β-siloxy esters are formed with high enantioselectivity (74–92% ee) and diastereoselectivity (96–98% de) when *trans*-disubstituted allyl silyl ethers are used as substrates.

The aldol reaction is a central transformation in organic synthesis.[1] Not only is the reaction a powerful carbon−carbon bond-forming process, but also the reaction can be made highly diastereoselective by using enolates of defined geometry.[1] Furthermore, high enantioselectivity can be achieved by using chiral auxiliaries[1] or, more recently, by using chiral catalysis.[2] In this paper we describe a novel method for the catalytic asymmetric synthesis of *syn*-aldol products which is based on an intermolecular C−H insertion of rhodium−carbenoid intermediates (Scheme 1).[3] The equivalent aldol reaction would be the reaction between the enolate of arylacetates and aldehydes. Recently, an analogous aldol reaction between the silylketene acetal of phenylacetate and benzyloxyacetaldehyde using a Cu(II) bisoxazoline complex has been shown to give low enantioselectivity (9%) and no diastereoselectivity.[4] However, other silylketene acetals gave high enantioselectivity. Reasonable asymmetric induction has been achieved in such analogous aldol reactions by using chiral enolates,[5] but a process of this type occurring

Scheme 1



(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, CA, 1984; Vol. 3, Chapter 2. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(2) For a comprehensive review of catalytic enantioselective aldol reactions, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

(3) For representative examples of intermolecular C−H insertions, see: (a) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322. (b) Ambramovitch, R. A.; Roy, J. *J. Chem. Soc., Chem. Commun.* **1965**, 542. (c) Adams, J.; Poupart, M.-A.; Greainer, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749. (d) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (e) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc. Chim. Belg.* **1984**, *93*, 945. (f) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Mol. Catal.* **1988**, *49*, L13. (g) Callott, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321. (h) Callott, H. J.; Metz, F. *Nouv. J. Chim.* **1985**, *9*, 167.

(4) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S., Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

(5) Lutzen, A.; Koll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1193.

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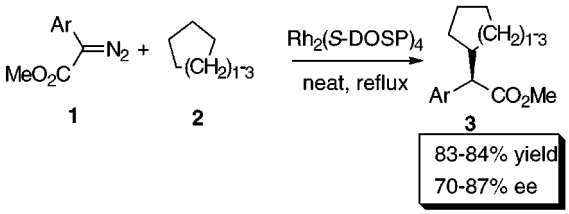
in high yield with good diastereo- and enantiocontrol has not been reported.

The background behind this current study was the discovery that the decomposition of aryldiazoacetate by Rh_2-(*S*-DOSP)$_4$[6] in the presence of cycloalkanes resulted in highly enantioselective intermolecular C−H insertions (Scheme 2).[7]

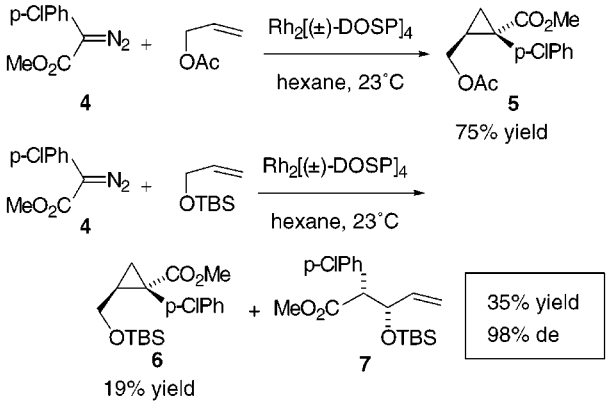
Scheme 2



Furthermore, the reaction with tetrahydrofuran occurred with excellent regiocontrol favoring C−H insertion adjacent to oxygen, although the diastereoselectvity was poor. This paper describes further studies to explore the scope of the asymmetric intermolecular C−H insertion with particular emphasis on the chemoselectivity and diastereoselectivity of the reaction.

Simple allyloxy substrates and Rh_2[(±)-DOSP]$_4$ (1 mol %) as catalyst were initially used to explore the selectivity of the C−H insertions. In the case of the reaction of 4-chlorophenyldiazoacetate **4** and allyl acetate (2 equiv) at room temperature, cyclopropanation was the exclusive reaction and **5** was formed in 75% yield (Scheme 3). In contrast,

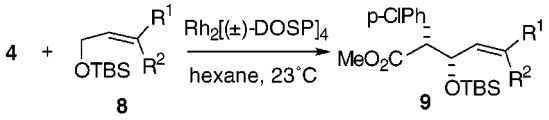
Scheme 3



in the reaction of **4** with allyl silyl ether, the C−H insertion product **7** was the major product (**7**:**6** ratio = 1.9:1), and remarkably, it was formed in >98% de. Interestingly, the Rh_2[(±)-DOSP]$_4$ catalyst has a major influence on the product distribution because in the reaction with Rh_2(OOct)$_4$ as catalyst the ratio of C−H insertion product **7** to cyclopropane **6** was 1:2.5.

The preferential formation of the C−H insertion product **7** is an unprecedented result because monosubstituted alkenes generally undergo cyclopropanation in high yield on reaction with methyl phenyldiazoacetate.[8] On repeating the reaction with more highly substituted allyl ethers **8**, cyclopropanation could be fully eliminated (Scheme 4). However, the diaste-

Scheme 4

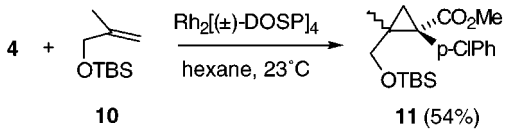


	R^1	R^2	yield, %	de, %
a	H	Et	48	76
b	Me	Me	44	70
c	Me	H	72	96

reoselectivity of the C−H insertion was dependent on the allyl ether substitution pattern. With the *cis*-disubstituted or trisubstituted allyl ethers **8a** and **8b**, the C−H insertion products **9a** and **9b** were formed with a *syn*/*anti* ratio of about 7:1. However, with the *trans*-disubstituted allyl ether **8c**, the C−H insertion product **9c** was formed in 72% yield and >96% de.

The steric influences on the C−H insertion versus cyclopropanation are subtle as can be seen in the reaction with 2-methylpropenyl silyl ether **10** (Scheme 5), which results

Scheme 5



in the formation of the cyclopropane **11** without any evidence for the C−H insertion product. Due to the nonsynchronous nature of aryldiazoacetate cyclopropanation,[6a] the silyl ether **10** has an accessible vinyl terminus for cyclopropanation, while the methyl substituent in **10** is presumably interfering with the C−H insertion.

Having discovered that the *trans*-allyl silyl ether is a promising substrate for diastereoselective C−H insertion, the study was extended to explore the issue of asymmetric induction within this system. Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of **4** in the presence of a series of allyl silyl ethers was examined, and the results are summarized in

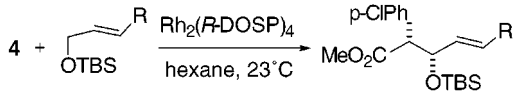
(6) (a) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463. (b) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107.

(7) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.

(8) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133.

Scheme 6.[9] In all instances the diastereocontrol was between 96 and 98% de favoring the *syn* (vide infra) isomer and the enantioselectivity ranged from 74 to 90% ee.

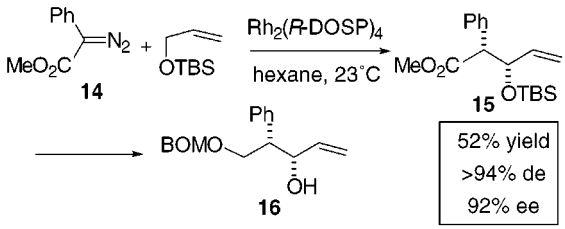
Scheme 6



product	R	yield, %	de, %	ee,%
9c	Me	72	96	80
12	Ph	70	97	85
13	$CH{=}CH_2$	71	98	74
7	H	35	98	90

To determine the absolute stereochemistry of the C−H insertion products, the Rh_2(*R*-DOSP)$_4$-catalyzed reaction of methyl phenyldiazoacetate (**14**) with allyl silyl ether was examined (Scheme 7). This reaction formed *syn* isomer **15** (2*R*,3*S*)[10] as the major product in 52% isolated yield and 92% ee (19% isolated yield of cyclopropane product). Lithium aluminum hydride reduction and subsequent silyl deprotection of **15** followed by conversion of the primary alcohol to its BOM derivative gave **16** whose optical rotation was compared with the literature value.[11] The absolute stereochemistry of the other C−H insertion products is tentatively assigned by assuming a similar mode of asymmetric induction for all the substrates.

Scheme 7



In summary, these studies demonstrate that the intermolecular C−H insertions of carbenoids derived from aryldiazoacetates is a practical method for the asymmetric synthesis of products that are typically derived from an aldol reaction. The reaction proceeds with good chemo- and diastereoselectivity, and by using Rh_2(*R*-DOSP)$_4$ as catalyst, reasonably high levels of asymmetric induction can be obtained. A particularly attractive feature of this chemistry is the low molar equivalent of catalyst that is required. Studies are currently underway to determine the full scope of this reaction.

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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 silyl ether (1.5 mmol), Rh_2(*R*−DOSP)$_4$ (14 mg, 7.5×10^{-3} mmol), and dry hexane (0.5 mL) and stirred under argon at room temperature to give a green solution. A 10 mL gastight syringe was charged with methyl *p*-chlorophenyldiazoacetate (0.75 mmol) in dry hexane (7.5 mL) to give a 0.10 M diazo solution. Addition via syringe pump was initiated at a rate of 7.5 mL/h (1 h addition time), and the green color of the reaction mixture was maintained during the entire addition. 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, 96:4) gave the product as a clear oil. Diastereomeric ratios were determined by GC−MS and/or 500 MHz ^{1}H NMR. Enantiomeric excesses were determined by HPLC using a Chiralcel OD column and 2-propanol in hexane as the eluent.

(10) *Syn* stereochemistry was unambiguously assigned by $LiAlH_4$ reduction and subsequent silyl deprotection of **15** followed by conversion of the resulting diol to the acetonide and comparison of *J* values for H_α and H_β (J = 3.4 Hz) to the literature value (J = 3.7 Hz) (Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343.). *Syn* stereochemistry was assigned to the other C−H insertion products, assuming a similar mode of C−H insertion for all the substrates.

(11) Absolute stereochemistry was determined by comparing the sign of optical rotation of **16** ($[\alpha]^{24.5}_D$ −4.4°, c = 1.00, $CHCl_3$) to the literature value ($[\alpha]^{23}_D$ −7.4°, $c \cong 1$, $CHCl_3$ (Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343)), which assigns the absolute stereochemistry of **15** as (2*R*,3*S*) using Rh_2(*R*-DOSP)$_4$.