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Catalytic Asymmetric Allylic C–H Activation as a Surrogate of the Asymmetric Claisen Rearrangement

Huw M. L. Davies,* Pingda Ren, and Qihui Jin

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

hdavies@acsu.buffalo.edu

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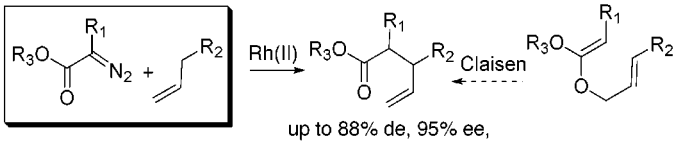
ABSTRACT



Tetrakis[*N*-[4-dodecylphenyl)sulfonyl]-(*S*)-prolinato]-dirhodium [Rh_2(*S*-DOSP)$_4$] catalyzed decomposition of methyl aryldiazoacetates in the presence of alkenes results in allylic C–H activation by means of a rhodium-carbene induced C–H insertion. The resulting γ,δ-unsaturated esters are equivalent to products that would be traditionally obtained from an asymmetric Claisen rearrangement. Highly regio- and enantioselective C–H insertions can be achieved, and in certain cases, good diastereocontrol is also possible.

C−H activation is conceptually a very attractive strategy for the functionalization of simple alkanes[1] and for the synthesis of complex structures.[2] The development of practical methods for C−C bond formation by means of a catalytic asymmetric C−H activation has long been considered to be a major challenge.[1] A major breakthrough toward this goal has been made with the discovery of the asymmetric intramolecular C−H insertion of metal-carbenoid intermediates.[3] Traditional metal carbenoids containing one or two electron-withdrawing groups are effective in these intramolecular C−H insertions but are not especially useful in asymmetric *intermolecular* C−H insertions.[4] We have recently reported that such C−H insertions can be obtained if rhodium-carbenoids functionalized with both an electron-withdrawing and an electron-donating group are used.[5] These carbenoids are much more chemoselective than the traditional carbenoids and are far less prone to side reactions such as carbene dimer formation. The wide variety of asymmetric C−H activations that have been reported using this chemistry has led us to the realization that the C−H activation process could have general applicability to the synthetic design of complex molecules. We have previously reported that the C−H activation α to an *O*-silyl group is equivalent to an aldol reaction,[6] while C−H activation α to a *N*-Boc group is equivalent to a Mannich reaction.[7] Also, the allylic C−H

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(4) 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. Chimie* **1985**, *9*, 167.

(5) Aryldiazoacetates and vinyldiazoacetates have been used as carbenoid precursors in asymmetric intermolecular C−H insertions. Other diazo compounds that generate chemoselective donor/acceptor substituted carbenoids are alkynyldiazoacetates and heteroaryldiazoacetates. For a general review, see: Davies, H. M. L.: Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617−618*, 47

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(7) (a) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc*. **1999**, *121*, 6509. (b) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773.

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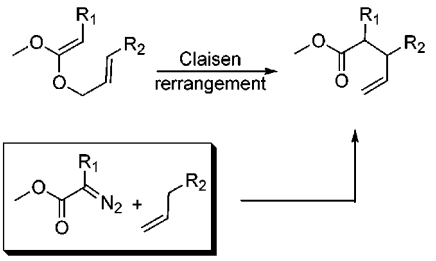
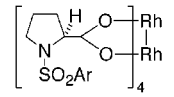
activation of silyl enol ethers can be considered as a surrogate of a Michael reaction.[8] In this paper we describe our preliminary studies on allylic C−H activation of alkenes. As illustrated in Scheme 1, the successful implementation

Scheme 1



of this process would lead to γ,δ-unsaturated esters containing two stereocenters. The standard synthetic strategy to prepare such compounds would be by the Claisen rearrangement.[9]

The successful development of the intermolecular C−H activation of rhodium carbenoids requires the availability of appropriate chiral catalysts. A number of chiral catalysts have now been examined,[10] but still the most broadly applicable catalyst is tetrakis[*N*-[4-dodecylphenyl)sulfonyl]-(*S*)-prolinato]-dirhodium [Rh_2(*S*-DOSP)$_4$],[11] the original catalyst that was used in the first effective rhodium carbenoid induced asymmetric intermolecular C−H activation.[12]



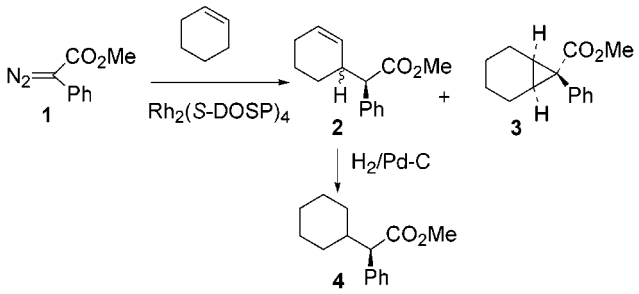
Ar = *p*-($C_{12}H_{25}$)C_6H_4

Rh_2(*S*-DOSP)$_4$

We have previously described that the allylic C−H activation of cyclohexadienes and cycloheptatriene by methyl phenyldiazoacetate occurs in >90% ee.[13] Muller[10a] has reported the only example of asymmetric allylic C−H activation of a simple alkene (Scheme 2). The reaction of methyl phenyldiazoacetate (**1**) with cyclohexene using CH_2Cl_2 as solvent resulted in a 52:48 diastereomeric mixture of the C−H insertion products **2** as well as the cyclopropane **3**. Hydrogenation of the mixture **2** resulted in the formation of the cyclohexyl derivative **4** in 75% ee.

On the basis of our considerable experience with Rh_2(*S*-DOSP)$_4$ catalysis, we realized that the reaction conditions

Scheme 2



Solvent, temp	yield, **2+3**, %	ratio, **2**:**3**	ee, **4**, %
CH_2Cl_2, rt	33[a]	20:80[a]	75[a]
2,2-diMebutane, rt	73[b]	21:79[b]	93[b]

a: Ref 10a
b: current work

used by Muller for the allylic C−H activation of cyclohexene were not optimum. Rh_2(*S*-DOSP)$_4$ results in much higher enantioselectivity when hydrocarbon solvents are used.[14] Thus, by running the reaction using 2,2-dimethylbutane as solvent, the enantioselectivity in the formation of **4** was improved to 93% ee.[15] The diastereoselectivity, however, remained poor, and cyclopropanation was still a competing reaction. In order for this reaction to be realistically described as a surrogate for the Claisen rearrangement, the cyclopropanation side reaction needs to be eliminated and the diastereoselectivity needs to be improved.

One of the intriguing features of cyclopropanations with aryldiazoacetates is that cyclopropanation rarely occurs with trans disubstituted or more highly substituted alkenes.[12] We have also found that in order to control the diastereoselectivity of C−H insertions at methylene positions, considerable size differentiation between the two methylene substituents is required.[5] On the basis of these observations, the silyl derivatives **6** were considered to be attractive substrates for C−H activation. Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of **5** in the presence of the TMS derivative **6a** in 2,2-dimethylbutane resulted in C−H insertion to form **7a** without any cyclopropanation. Furthermore, the diastereoselectivity for **6a** had improved to 70:30.[16] An even greater improvement was obtained with the *tert*-butyldiphenylsilyl derivative **6b**, as the diastereomer ratio of **7b** was 94:6 and the major diastereomer was obtained in 95% ee.

One of the most unexpected aspects of the C−H insertions of aryldiazoacetates is the remarkable level of chemoselectivity that is observed.[5] To determine if similar chemoselectivity is possible for the allylic C−H insertions, the reaction of 1-alkylcyclohexenes and other funtionalized

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(9) For a review, see: (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 827−874.
(10) (a) Muller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725. (b) Axten, J. M.; Ivy, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6511.
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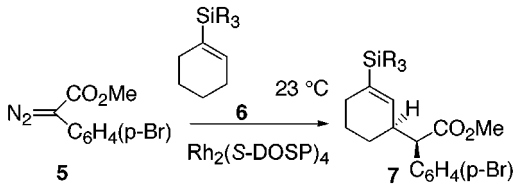
(12) (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.
(13) (a) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T.; Churchill, M. R.; Keil, K. M. *Tetrahedron Lett.* **2000**, *41*, 2035.
(14) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
(15) The absolute configuration of **4** was determined to be (*R*) by comparison to a known sample (see ref 12b). The absolute configuration of the other C−H insertion products is assigned by analogy.
(16) Relative stereochemistry is readily achived on the basis of distinctive chemical shifts in the proton NMR. For details, see: Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.

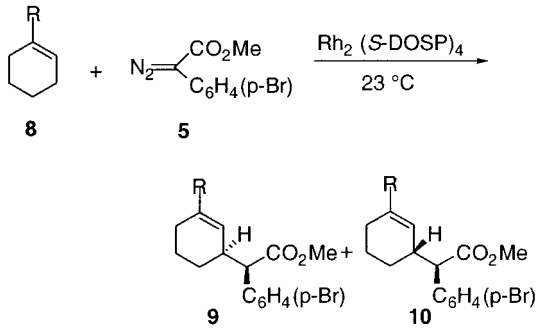
Scheme 3



	SiR_3	yield, %	de, %	ee, %
a	TMS	48	40	88
b	TBDPS	64	88	95

cyclohexenes (**8**) were examined (Table 1). Even though two or three allylic sites are present in each substrate **8**, only a single C−H insertion regioisomer (**9** + **10**) is produced in virtually every case. The only exception is the reaction with

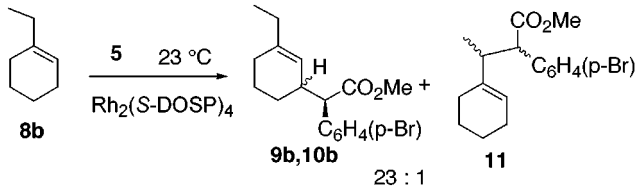
Table 1. C-H Insertion of Substituted Cyclohexenes



Cmpd.	R	Yld,% **9+10**	Ratio, **9 : 10**	ee of **9**, %	ee of **10**, %
a	Me	53	17 : 83	94	98
b	Et	46	25 : 75	90	94
c	^{i}Pr	65	36 : 64	90	93
d	^{t}Bu	46	62 : 38	91	81
e	Ph	65	23 : 77	90	95
f	Cl	58	65 : 35	96	91

ethylcyclohexene **8b**, where a 23:1 mixture of regioisomeric C−H insertion products, **9b**, **10b**, and **11**, is formed (Scheme 4). The reactions with the 1-alkylcyclohexenes **8a**−**d** dem-

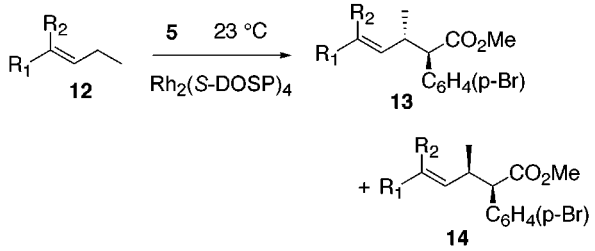
Scheme 4



onstrate the subtle balance of factors that influence the C−H insertion. Reaction at a methyl position is not favored, presumably because the methyl C−H bonds are simply stronger than methylene or methine C−H bonds. The methine C−H bond is expected to be the weakest bond, but tertiary sites are not very accessible for the bulky rhodium carbenoid complex.[5] Even though all of the substrates have at least two allylic methylene groups, the neighboring alkyl substituent sterically hinders attack to the nearest methylene center, leading to the formation of a diasteromeric mixture of a single regioisomer (**9** + **10**). In each case, excellent enantioselectivity is obtained but the diastereoselectivity is moderate.

The study was further extended to acyclic alkenes as summarized in Scheme 5. Rh_2(*S*-DOSP)$_4$ catalyzed decom-

Scheme 5



	R_1	R_2	yield, % **13 + 14**	dr **13 : 14**	ee, % **13**	ee, % **14**
a	Me	Me	67	75 : 25	86	66
b	Et	H	56	56 : 44	92	80
c	Ph	Ph	33	85 : 15	96	30

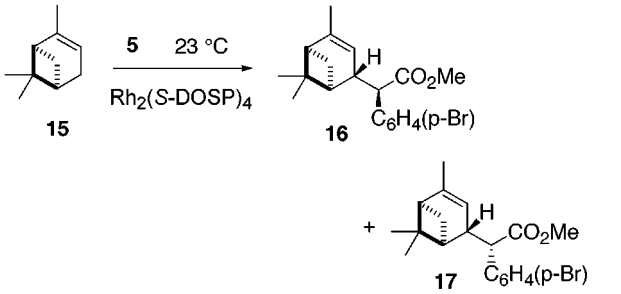
position of **5** in the presence of 2-methyl-2-pentene (**12a**) resulted in the formation of diastereomeric C−H insertion products, **13a** and **14a** in a ratio of 75:25. A trace (4%) of the primary allylic C−H insertion product was also observed. Similar reactivity was seen when *trans*-3-hexene and 1,1-diphenyl-1-butene were used as substrates. In all instances, the major diastereomer **13** was formed with high asymmetric induction, ranging from 86% to 96% ee.

The next substrate that was studied was α-pinene (**15**), which would probe whether kinetic resolution and double stereodifferentiation would be important factors in this chemistry. Very impressive levels of kinetic resolution had been previously observed in C−H insertions on substituted pyrrolidines.[7b] The reaction of (+)-**15** with Rh_2(*S*-DOSP)$_4$ at 23 °C resulted in the highly efficient formation of the C−H insertion products **16** and **17** in 93% combined yield and a diastereomer ratio of 98:2.[17] In contrast, the reaction of (+)-**15** with Rh_2(*R*-DOSP)$_4$ appears to be a miss-matched reaction; only a 62% yield of C−H insertion products **16** and **17** was obtained, and the diastereomer ratio was reversed to 24:76. Repeating the Rh_2(*S*-DOSP)$_4$ catalyzed reaction of **5** at 0 °C but using (±)-**15** as substrate resulted in the

(17) The determination of the relative and absolute stereochemistry for **16** and **17** is described in detail in Supporting Information.

formation of **16** and **ent-17** in a 88:12 ratio. The major diastereomer **16** was produced in 99% ee. On the basis of these results, one can conclude that the kinetic selectivity factor is around six while the high enantioselectivity for the formation of **16** is due to a combination of the kinetic resolution and the chiral differentiation of the catalyst.

Scheme 6



Substrate	Catalyst	yield, %	ratio, **16** : **17**	ee, **16**, %
(+) (0.5 equiv)[a]	Rh_2(*S*-DOSP)$_4$	93	98 : 2	–
(+) (0.5 equiv)[a]	Rh_2(*R*-DOSP)$_4$	62	24 : 76	–
(±) (10 equiv)[b]	Rh_2(*S*-DOSP)$_4$	52	88 : 12	99

a: reaction temperature, 23 °C
b: reaction temperature, 0 °C

In the Rh_2(*S*-DOSP)$_4$ catalyzed reaction with (±)-**15**, reaction of **5** with (+)-**15** preferentially produces the syn product **16**, while the reaction of **5** with (−)-**15**, produces **ent-16a** as the minor product.

The preliminary studies described herein demonstrate that the intermolecular C−H activation by rhodium-carbenoid induced C−H insertion is a promising new method for the stereoselective construction of γ,δ-unsaturated esters, products that would be typically prepared by a Claisen rearrangement. In addition to the excellent regiocontrol that is possible with this chemistry, the reaction can be extended to systems that allow double stereodifferentiation and kinetic resolution to occur. Future studies will be directed toward determination of the full synthetic potential of this novel transformation.

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Supporting Information Available: Full experimental data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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