ORGANIC LETTERS

2007
Vol. 9, No. 24
4971−4974

Balance between Allylic C–H Activation and Cyclopropanation in the Reactions of Donor/Acceptor-Substituted Rhodium Carbenoids with *trans*-Alkenes

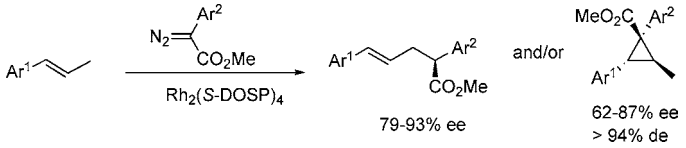
Huw M. L. Davies,* Michael G. Coleman, and Dominic L. Ventura

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

hdavies@acsu.buffalo.edu

Received September 10, 2007

ABSTRACT



Rhodium(II)-catalyzed reactions of aryldiazoacetates with (*E*)-aryl-substituted alkenes generate C–H insertion products and/or cyclopropanes. The product distribution is influenced by the nature of the donor group on the carbenoid, the structure of the (*E*)-aryl-substituted alkenes, and the rhodium catalyst.

Donor/acceptor-substituted rhodium carbenoids are capable of a wide range of highly selective intermolecular reactions.[1] Due to the presence of the donor group, typically aryl or vinyl, these carbenoids are more stabilized than the conventional acceptor- or acceptor/acceptor-substituted carbenoids such as the carbenoid derived from ethyl diazoacetate.[1] When the reactions of the donor/acceptor-substituted carbenoids are catalyzed by the dirhodium tetraprolinate, Rh_2(*S*-DOSP)$_4$, high enantioinduction is possible. The cyclopropanation can be conducted on a wide range of alkenes,[2] dienes,[3] and electron-rich heterocycles[4] and is broadly applicable to carbenoids derived from vinyldiazoacetates and aryldiazoacetates.

A more recent development is intermolecular C−H functionalization by these carbenoids through a C−H insertion process.[1,5] This reaction is especially effective at allylic C−H bonds.[6] Considering that both the intermolecular C−H activation and the cyclopropanation have broad applications, a question arises about which factors control the selectivity

(1) (a) Davies, H. M. L.; Beckwith, E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (c) Davies, H. M. L.; Walji, A. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 301−340.

(2) (a) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243. (b) Davies, H. M. L.; Peng, Z. Q.; Houser, J. H. *Tetrahedron Lett.* **1994**, *35*, 8939. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (d) Corey, E. J.; Grant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (e) Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Commun*. **1998**, 2377. (f) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133. (g) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; Garcia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129. (h) Davies, H. M. L.; Nagashima, T.; Klino, J. L., III. *Org. Lett*. **2000**, *2*, 823.

(3) (a) Davies, H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853. (b) Davies, H. M. L.; Oldeburg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Henretta, J. P.; Romines, K. R. *Tetrahedron Lett.* **1988**, *29*, 975. (c) Davies, H. M. L.; McAfee, M. J.; Oldeburg, C. E. M. *J. Org. Chem*. **1989**, *54*, 930. (d) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299. (e) Davies, H. M. L.; Clark, T. J.; Kimmer, G. F. *J. Org. Chem*. **1991**, *56*, 6440. (f) Davies, H. M. L.; Clark, T. J. *Tetrahedron* **1994**, *50*, 9883. (g) Davies, H. M. L.; Doan, B. D. *J. Org. Chem*. **1998**, *63*, 657. (h) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *64*, 8501. (i) Deng, L.; Giessert, A. J.; Gerlitz, O. O.; Dai, X.; Diver, S. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2005**, *127*, 1342.

(4) (a) Davies, H. M. L.; Clark, D. M.; Smith, T. K. *Tetrahedron Lett.* **1985**, *26*, 559. (b) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265. (c) Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett*. **1989**, *30*, 4653. (d) Davies, H. M. L.; Saikali, E.; Young, W.B. *J. Org. Chem.* **1991**, *56*, 5696. (e) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305. (f) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1747. (g) Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5349. (h) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10321.

(5) Davies, H. M. L.; Loe, O. *Synthesis* **2004**, 2595.

(6) (a) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc*. **2004**, *126*, 10862. (b) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176.

10.1021/ol702218w CCC: $37.00
Published on Web 10/23/2007

between these two transformations, especially in allylic substrates. This paper will help define the boundary between the cyclopropanation and C−H functionalization reactivity and also illustrate the subtle controling influences that are possible with donor/acceptor-substituted carbenoids.

Both the cyclopropanation and the C−H functionalization proceed through a concerted nonsynchronous manner, and sites that can stabilize buildup of positive charge during the reactions are electronically favored.[1] The donor/acceptor-substituted carbenoids are much more sensitive to steric influences than the conventional acceptor-only carbenoids. With electron-neutral alkenes, cyclopropanation of 1-substituted, 1,1-disubstituted, and cis-1,2-disubstituted alkenes are favorable, while trans-1,2-disubstituted and more highly substituted alkenes are typically unreactive (Figure 1).[2b] In

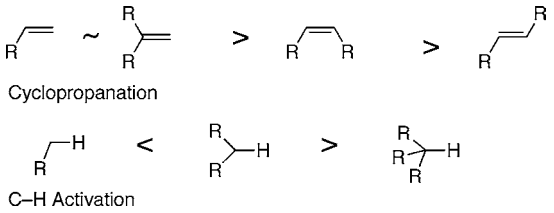
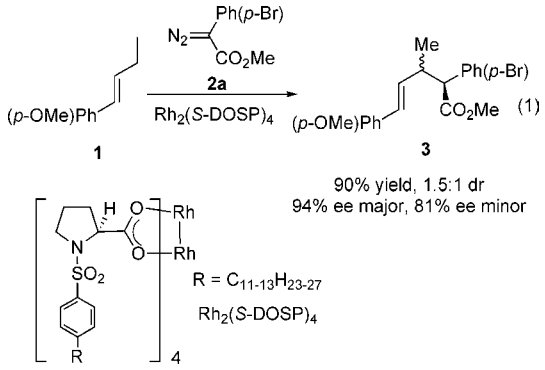


Figure 1. General reactivity trends of donor/acceptor carbenoids.

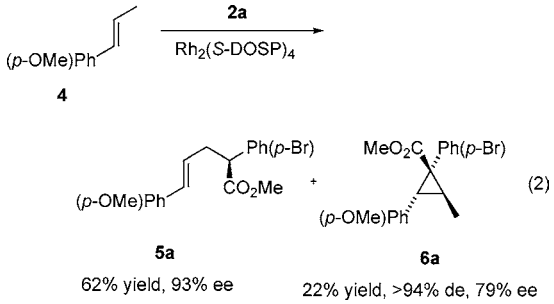
contrast, rhodium-catalyzed cyclopropanation by ethyl diazoacetate is possible even on the tetrasubstituted alkene 2,3-dimethyl-2-butene.[7]

The C−H functionalization chemistry of the donor/acceptor carbenoids is also sensitive to steric effects. In general, insertion into a secondary C−H bond is most favored because a secondary site will best provide positive charge stabilization without being too sterically crowding (Figure 1).[8] A primary C−H bond can still be functionalized when it is electronically activated,[9] while certain accessible tertiary C−H bonds, such as those in adamantane, can also be functionalized.[8a] If a site is too crowded, however, the C−H functionalization can be completely blocked, even though it might be electronically activated.[8c]

With these general trends in mind, we have conducted a study to define what structural features control the selectivity between cyclopropanation and C−H insertion in the reaction of donor/acceptor-substituted carbenoids. Substrate **1** contains a trans double bond in addition to a secondary allylic C−H site. Both of these sites are electronically activated; however, a trans double bond is generally considered to be too sterically crowded for cyclopropanation.[2b] Therefore, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of the *p*-bromophenyldiazoacetate **2a** with **1** would be expected to favor C−H activation, and this is indeed the case (eq 1). The C−H activation product **3** is produced in 90% yield as a 1.5:1 mixture of diastereomers (94% ee for major, 81% ee for minor).[10]



Predicting the reaction outcome of the next substrate, *trans*-anethole (**4**), is less certain. It contains a *trans*-alkene and primary allylic C−H bonds, neither of which would be expected to be especially reactive toward the donor/acceptor carbenoids, but both sites are electronically activated by the *p*-methoxy group. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **4** with **2a** gives a mixture of the C−H activation product **5a** and the cyclopropane **6a** (eq 2). Both are produced with good stereocontrol as is characteristic of the Rh_2(*S*-DOSP)$_4$-catalyzed reactions. Only a single diastereomer of cyclopropane **6a** is formed. Its relative configuration was assigned on the basis of the distinctive lack of shielding of the methyl ester, and the absolute configuration was confirmed by X-ray crystallography.



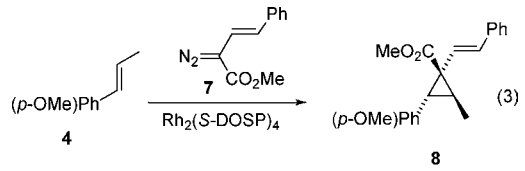
The other major class of donor/acceptor carbenoids are the vinylcarbenoids derived from styryldiazoacetates such as **7**. The reactivity profile of **7** toward **1** and **4** was quite different from the reactions of aryldiazoacetates. The reaction of **7** with **1** gave a complex mixture of uncharacterizable products. In contrast, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **7** with **4** produced only cyclopropane **8** (eq 3). No evidence of any C−H insertion product was observed. Thus, the styryldiazoacetate **7** has a lesser tendency to undergo C−H insertion versus cyclopropanation compared to the aryldiazoacetate **2a**.

(7) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.

(8) (a) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437. (b) Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. H. *J. Org. Chem.* **2003**, *68*, 6126. (c) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462.

(9) (a) Davies, H. M. L.; Jin, Q. H.; Ren, P. D.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165. (b) Davies, H. M. L.; Jin, Q. H. *Tetrahedron Asymmetry* **2003**, *14*, 941. (c) Davies, H. M. L.; Jin, Q. H. *Org. Lett.* **2004**, *6*, 1769.

(10) Davies, H. M. L.; Ren, P. D. *J. Am. Chem. Soc.* **2001**, *123*, 2070.



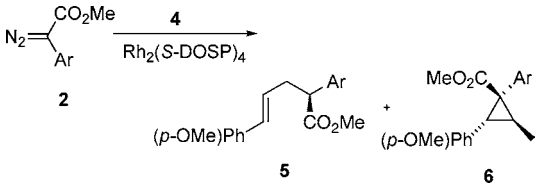
61% yield, >94% de, 74% ee

As the product distribution in the reaction between *trans*-anethole (**4**) and the aryldiazoacetate **2a** produced a mixture of C−H insertion and cyclopropanation products, a systematic study was conducted to determine what factors would govern the product ratio. The influence of the carbenoid donor group on the product distribution is summarized in Table 1. In all instances, a mixture of products was formed, but more electron-rich aryldiazoacetates favor C−H insertion over cyclopropanation to a greater extent than electron deficient aryldiazoacetates. The methoxyphenyl derivative **2b** gave an 8:1 ratio favoring C−H insertion while the electron deficient trifluorophenyl derivative **2f** gave only a 2:1 ratio.

Since *p*-methoxyphenyl derivatives are expected to electronically activate both C−H insertion and cyclopropanation, alterations to the substituents on the substrate dramatically influence the product ratios (Table 2). Substrates lacking a donating group such as **9a** and **9b** lead to the exclusive formation of the C−H insertion products **10a** and **10b**. The 3,4,5-trimethoxy derivative **9c** gave a ratio of products similar to that of the *trans*-anethole (**4**). In contrast, the 2,4,6-trimethoxy derivative **9d** resulted in formation of only the cyclopropane **11d**. These results indicate that donor groups on the substrate drive the reaction toward cyclopropanation over C−H insertion.

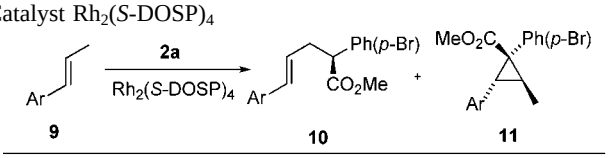
Another controlling element in these reactions is the dirhodium catalyst. Even though some of the standard catalysts such as $Rh_2(OAc)_4$ and $Rh_2(TFA)_4$ give nearly a 1:1 mixture of products, two other catalysts display very impressive levels of regiocontrol on this chemistry (Table 3). The sterically crowded catalyst, $Rh_2(OCCPh_3)_4$,[11] strongly favors

Table 1. Reactions of Aryldiazoacetates **2** with *trans*-Anethole (**4**)



	Ar	(**5**:**6**)	**5** yield (%)	**5** ee (%)	**6** yield (%)	**6** ee (%)
b	4-OMeC$_6$H$_4$	8:1	67	79	5	82
c	C$_6$H$_5$	6:1	53	91	8	80
d	4-MeC$_6$H$_4$	3:1	58	92	19	62
e	4-ClC$_6$H$_4$	3:1	46	92	18	85
f	4-CF$_3$C$_6$H$_4$	2:1	37	80	11	72

Table 2. Reactivity of *trans*-Aryl Alkenes with Diazo **2a** and Catalyst $Rh_2(S\text{-DOSP})_4$



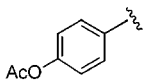
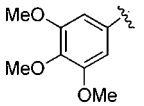
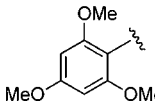
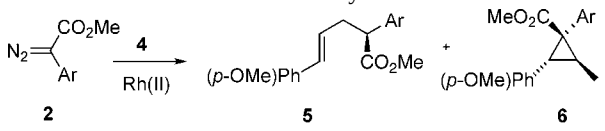
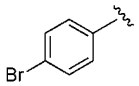
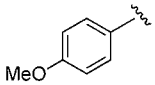
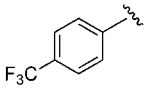
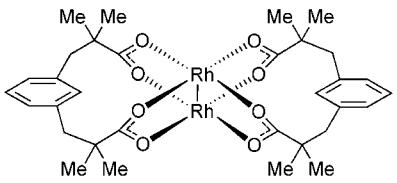
	Ar	(**10**:**11**)	**10** yield (%)	**10** ee (%)	**11** yield (%)	**11** ee (%)
a		>15:1	51	84	0	–
b		>15:1	72	86	0	–
c		3:1	64	88	20	87
d		<1:15	0	–	74	87

Table 3. Effect of Dirhodium Catalyst



	Ar	Rh(II)	(**5**:**6**)	**5** yield (%)	**6** yield (%)
a		$Rh_2(S\text{-DOSP})_4$	3:1	62	22
		$Rh_2(O_2CCH_3)_4$	1:1	19	16
		$Rh_2(O_2CCF_3)_4$	1:1	18	12
		$Rh_2(O_2CCMe_3)_4$	1:4	10	48
		$Rh_2(O_2CCPh_3)_4$	>15:1	74	0
		$Rh_2(esp)_2$	1:>15	0	74
b		$Rh_2(S\text{-DOSP})_4$	8:1	67	5
		$Rh_2(O_2CCPh_3)_4$	>15:1	74	0
		$Rh_2(esp)_2$	1:1	27	30
c		$Rh_2(S\text{-DOSP})_4$	6:1	53	8
		$Rh_2(O_2CCPh_3)_4$	>15:1	88	0
		$Rh_2(esp)_2$	1:3	22	66
f		$Rh_2(S\text{-DOSP})_4$	2:1	37	11
		$Rh_2(O_2CCPh_3)_4$	>15:1	74	0
		$Rh_2(esp)_2$	1:>15	0	75

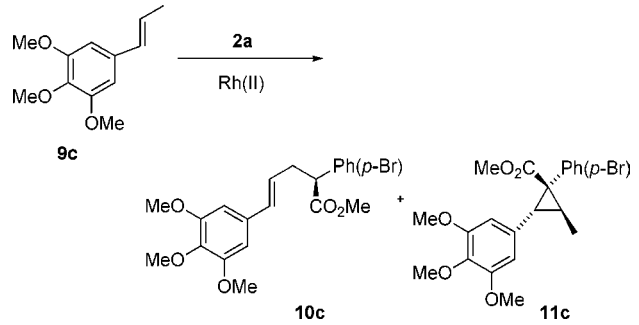


$Rh_2(esp)_2$

C−H functionalization, while Du Bois' bridged catalyst, $Rh_2(esp)_2$,[12] favors cyclopropanation. In the case of the more electron-deficient aryldiazoacetates **2a** and **2f**, the catalyst gives full control over which product is formed.

$Rh_2(OCCPh_3)_4$ and $Rh_2(esp)_2$ can also be used to control the regioselectivity of the chemistry in challenging styrenes (Table 4). Even though a mixture of products is obtained in the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of **2a** with (*E*)-1,2,3-trimethoxy-5-(prop-1-enyl)benzene (**9c**), $Rh_2(OCCPh_3)_4$ produced exclusively the C−H functionalization product **10c**, while $Rh_2(esp)_2$ produced predominantly the cyclopropane **11c**.

Table 4. Effect of Dirhodium Catalyst in Reaction of Diazo **2a** with (*E*)-1,2,3-Trimethoxy-5-(prop-1-enyl)benzene



Rh(II)	(**10c**:**11c**)	**10c** yield (%)	**11c** yield (%)
$Rh_2(S\text{−DOSP})_4$	3:1	64	20
$Rh_2(O_2CCPh_3)_4$	>15:1	87	0
$Rh_2(esp)_2$	1:4	12	49

In conclusion, these studies demonstrate that trans-substituted alkenes are capable of intermolecular C−H insertions as well as highly diastereoselective cyclopropanations. The product distribution in these reactions depends not only on the steric and electronic nature of the alkene, but also on the electronics of the donor/acceptor carbenoid as well as the catalyst structure. This study gives greater insight into the subtle interplay of the controlling influences behind the reactivity of donor/acceptor-substituted carbenoids. These selectivity results will be useful in the implementation of the C−H functionalization to the synthesis of elaborate targets.

Acknowledgment. Financial support of this work by the National Science Foundation (CHE-0350536) is gratefully acknowledged. We thank Dr. Justin Du Bois, Stanford University, for a generous sample of $Rh_2(esp)_2$ and Dr. Marc Messerschmidt, University at Buffalo, for the X-ray crystallographic data.

Supporting Information Available: Experimental data for the reported reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702218W

(11) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.
(12) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.