ORGANIC LETTERS

2009
Vol. 11, No. 19
4434−4436

Rhodium-Mediated Enantioselective Cyclopropanation of Allenes

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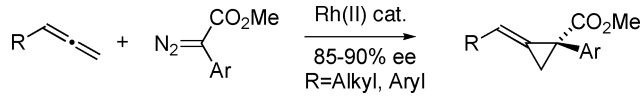
Received August 4, 2009

ABSTRACT



Reaction of monosubstituted allenes with aryldiazoacetate esters under dirhodium tetracarboxylate catalysis led to alkylidene cyclopropane products in 80−90% ee. Monosubstituted alkyl- and arylallene substrates gave 60−75% yield under standard conditions, while yields for 1,1-disubstituted allenes were significantly lower. Cyclopropanation of 1-methyl-1-(trimethylsilyl)allene proceeded in higher yield than other 1,1-disubstituted substrates, suggesting rate enhancement mediated by a significant *β*-silicon effect.

Rhodium-stabilized carbenoid reactions are powerful methods for synthesizing complex organic structures with high levels of chemo-, diastereo-, and enantioselectivity.[1] Cyclopropanation of alkenes with rhodium carbenoids has been examined systematically, indicating the broad scope of suitable alkenes and providing important mechanistic insight into the reaction.[2] Although a number of different allene substrates have been reported in cyclopropanation reactions,[3] there has been no systematic investigation of the scope of allene derivatives that can be used nor have there been any reports on the degree of enantioselectivity that might be feasible given the wide array of available chiral catalysts.

A better understanding of allene cyclopropanation will have an important impact on the chemistry of alkylidene cyclopropanes (ACP).[4] Applications of ACP synthesis include: use as mechanism-based enzyme inhibitors,[5] use as conformationally restricted ligand analogues,[6] potential for extending the serum stability of prodrugs,[7] and applicability toward development of cyclopropane and alkylidene cyclopropane nucleoside analogues as antiviral agents.[8]

To extend our understanding of allene cyclopropanation, we investigated substituent effects and enantioselectivity in cyclopropanation of allenes using rhodium carbenoids derived from aryldiazoacetate esters (eq 1, Scheme 1).

The carbenoid intermediate derived under such conditions is well suited for rapid cyclopropanation of styrene, so it was surprising that reaction of **2** with phenylallene, **1a**, catalyzed by Rh_2(*S*-DOSP)$_4$, **4**, with toluene as solvent, gave

(1) For leading references on cyclopropanation, see: (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1–326. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (c) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538–4583. For C−H activation, see: (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (e) Liu, Y.; Xiao, W.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2007**, *9*, 4107–4110. (f) Doyle, M. P. *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 341−355. For carbene-initiated ylide reactions, see: (g) Padwa, A. *Progress Heterocycl. Chem.* **2009**, *20*, 20–46. (h) DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 1435–1439. For O−H insertion, see: (i) Zhang, W.; Romo, D. *J. Org. Chem.* **2007**, *72*, 8939–8942.

(2) (a) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871–4880. (b) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902–15911. (c) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253–9260. Howell, J. A. S. *Dalton Trans.* **2007**, 3798–3803.

(3) (a) Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020–2024. (b) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183–187. (c) Ma, S.; Lu, L. *J. Org. Chem.* **2005**, *70*, 7629–7633. (d) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835–838. (e) Yao, T.; Hong, A.; Sarpong, R. *Synthesis* **2006**, *2006*, 3605–3610.

(4) ACP references: (a) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526–8535. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–636. (c) Zohar, E.; Stanger, A.; Marek, I. *Synlett* **2005**, *14*, 2239–2241. (d) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521–5524. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(5) (a) Cane, D. E.; Bowser, T. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1127–1132. (b) Zhao, Z.; Chen, H.; Li, K.; Du, W.; He, S.; Liu, H.-w. *Biochemistry* **2003**, *42*, 2089–2103.

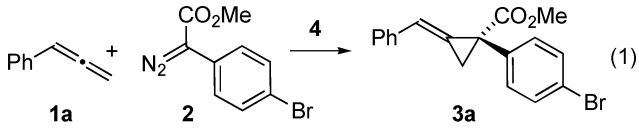
(6) (a) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433–442. (b) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538–4583.

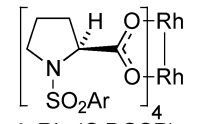
(7) Bender, D. M.; Peterson, J. A.; McCarthy, J. R.; Gunaydin, H.; Takano, Y.; Houk, K. N. *Org. Lett.* **2008**, *10*, 509–511.

(8) Zhou, S.; Zemlicka, J.; Kern, E. R.; Drach, J. C. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 231–43.

10.1021/ol9017968 CCC: $40.75
Published on Web 08/27/2009

Scheme 1





4: Rh_2(*S*-DOSP)$_4$
Ar = *p*-$C_{12}H_{25}$-C_6H_4

solvent	temp (°C)	% yield
toluene	0	< 1
toluene	23	< 1
hexane	23	76

only a trace of allene cyclopropanation and at least three different products from reaction of the carbenoid with the solvent.[9] However, use of hexane as solvent gave a good yield of benzylidene cyclopropane **3a**. Though toluene is a useful solvent for alkene cyclopropanation, the ability of toluene to compete for the carbenoid when an allene is the substrate, presumably via aromatic ring cyclopropanation and/or α-methyl C−H bond insertion, suggests that reaction of the allene is significantly slower than what is typically seen for cyclopropanation of monosubstituted alkenes.[2b,10]

Under standard conditions, good yields of **3a** were reproducible, giving material of 90% ee. Compound **3a** could be recrystallized to greater than 99% ee.[11] The *E*-alkene geometry and the (*R*)-absolute configuration of **3a** were confirmed by single-crystal X-ray analysis (Figure 1). The

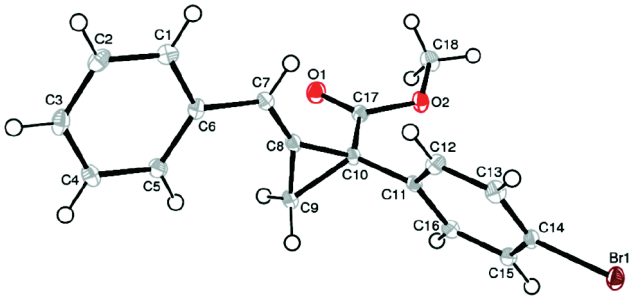


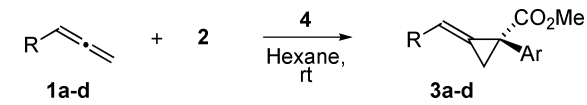
Figure 1. ORTEP drawing of (*R*)-**3a**.

(*R*)-stereocenter of **3a** is consistent with the expected approach of the substrate to the *re* face of the carbenoid formed by the reaction of **2** and **4**.[2b]

As seen in Table 1, other monosubstituted allenes gave similar yields and enantioselectivities. Chlorophenyl allene **1b** gave 61% yield and 84% ee. Alkyl-substituted allenes were satisfactory substrates for cyclopropanation, giving **3c** and **3d** in 60% yield and 88% ee and 54% yield and >80% ee, respectively. In all of these reactions, NMR analysis revealed a single alkene geometry, and **3b**−**d** are all assigned *E*-alkene configuration by analogy to that seen for compound **3a**.

Although the nature of the substituent on allenes **1a**−**d** had minimal effect on the cyclopropanation reaction, addition

Table 1. Cyclopropanation of Monosubstituted Allenes



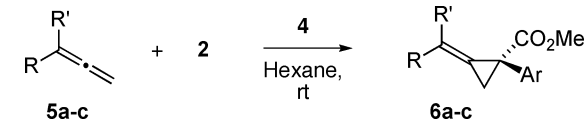
1a-d 3a-d

allene	R	product	% yield	% ee
1a	Ph	**3a**	76	90
1b	*p*-ClC_6H_4	**3b**	61	84
1c	C_5H_{11}	**3c**	60	88
1d	CH_2Ph	**3d**	54	>80[a]

[a] Estimated by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$.

of a second substituent to the allene had a profound effect on reactivity. The reaction of 1-methyl-1-phenylallene, **5a**, under our conditions for cyclopropanation (Table 2) gave

Table 2. Cyclopropanation of 1,1-Disubstituted Allenes



5a-c 6a-c

allene	R	R′	product	% yield	% ee
5a	Ph	CH_3	**6a**	33	86
5b	CH_3	CH_3	**6b**	30	90
5c	$(CH_3)_3Si$	CH_3	**6c**	79	85

the expected cyclopropane product, **6a**, in 33% yield, the other observed products being alkene and azine byproducts derived from the diazoacetate starting material. Only a single alkene geometry was observed in the crude reaction mixture, and this was assigned the *E* configuration by analogy to **3a**.

The reduced yield of **6a** may be attributed to a decrease in cyclopropanation rate due to the added methyl group. Whereas a simple alkene can approach the carbenoid face-on in a concerted transition state and project substituents away from the reactive center, the 1,1-disubstituted allene would project one of its groups away from, and one toward,

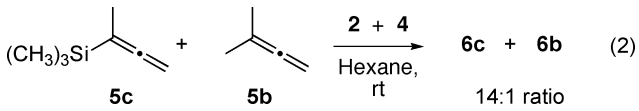
(9) Inseparable byproducts were tentatively identified by ^{1}H NMR and GCMS.

(10) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165–4169.

(11) A solution of **4** (0.01 mmol) and **1a** (1.75 mmol) in hexane (2 mL) was stirred at rt while a solution of **2** (1.15 mmol) in hexane (4 mL) was added dropwise over 1 h. After stirring at rt overnight, the reaction was concentrated at reduced pressure and chromatographed in 10% Et_2O/ pet. ether to give 0.87 mmol (76% yield) of **3a** in 91% ee as a white solid: R_f 0.26 (10% Et_2O/hexane); HPLC (RR-Whelk, 5% isopropanol/hexane), t_R (major) 12.5 min, t_R (minor) 18.2 min. ^{1}H NMR (250 MHz) δ 7.50−7.57 (2H, m), 7.44 (2H, d, J = 8.5 Hz), 7.22−7.40 (5H, m), 7.07 (1H, t, J = 2.6 Hz), 3.67 (3H, s), 2.76 (1H, dd, J = 9.4, 2.6 Hz), 1.99 (1H, dd, J = 9.4, 2.6 Hz); 13C NMR (63 MHz). δ: 171.9 (C), 137.0 (C), 136.2 (C), 131.3 (CH), 130.8 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 126.7 (C), 121.4 (C), 120.1 (CH), 52.6 (CH_3), 29.5 (C), 21.5 (CH_2). IR (neat) cm^{-1}: 3027, 2950, 1727, 1242. EIMS (70 eV) *m*/*z*: 342, 327, 205 (100). Anal. calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.41. Found: C, 63.01; H, 4.32. Recrystallization from warm hexane gave colorless needles: mp 119−122 °C; 99.6% ee; $[\alpha]_D^{25}$ +67.4 (*c* 1.0, $CHCl_3$).

the approaching carbenoid. In this hypothesis, a second group on the allene, even a methyl group, slows cyclopropanation to the point that the diazoacetate competes more successfully for the carbenoid, resulting in decreased yield and increased byproduct. A similar decreased yield was observed for the reaction of 1,1-dimethylallene, **5b**, supporting the idea that a methyl group represents sufficient steric bulk to interfere with approach of the carbenoid.

In contrast to the reduced yields for **5a** and **5b**, 1-methyl-1-(trimethylsilyl)allene, **5c**, reacted cleanly under standard conditions giving **6c** in 79% yield and 85% ee. The silyl allene substrate appears to be subject to significant rate enhancement despite the steric hindrance caused by the methyl substituent. This idea is supported by results of a competition reaction between allenes **5c** and **5b** (eq 2). An equimolar mixture of these substrates was allowed to react with 0.1 equiv of diazoacetate **2** in the presence of catalyst **4**. The crude reaction mixture was analyzed by NMR and found to contain a 14:1 mixture of ACP products **6c** and **6b**. The silyl substituent is thus responsible for a more than 10-fold increase in cyclopropanation rate compared to the methyl substituent.



Davies reported electronic effects of *para*-substituents on cyclopropanation of styrene derivatives, finding a good correlation with σ^+ Hammett substituent constants.[8] This direct resonance effect, interpreted as acting on partial positive charge buildup at the benzylic position in the styrene transition state, is not expected to apply in aryl allene cyclopropanation due to the intervening orthogonal π-bond separating the ring from the reacting π-bond. In the case of substrate **5c**, however, silicon hyperconjugation could be providing analogous stabilization of positive charge and thus the observed cyclopropanation rate increase.

To clarify the potential of steric and electronic effects to influence the rate and diastereoselectivity of cyclopropanation, we used DFT methods to investigate the transition state for allene cyclopropanation. As a simplified model system, we considered the reaction of 1,2-butadiene with methyl 2-diazo-3-butenoate. Transition state optimization using Gaussian03[12] gave structure **TS1**, illustrated in Figure 2, wherein both cyclopropane bonds are forming simultaneously, though bonding at the allene terminal carbon is significantly more advanced (C−C bond distance: 2.3 Å) than that at the adjacent carbon (C−C bond distance: 2.8 Å). Bond lengths in this model are consistent with a model for styrene cyclopropanation that correlated well with observed kinetic isotope effects (C−C bond distances were 2.4 and 2.9 Å).[2b]

(12) Frisch, M. J. *Gaussian 03*, revision B.05. The full citation, coordinates, and computational details are found in the Supporting Information.

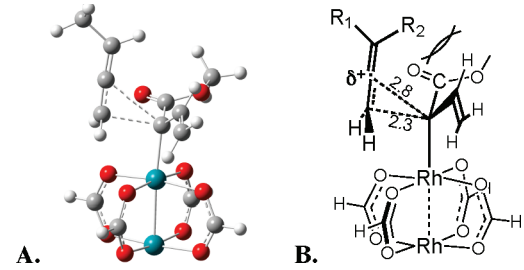


Figure 2. Transition state model **TS1**. Allene Cyclopropanation Model: **A.** DFT transition state model (B3LYP/LANL2DZ) of 1,2-butadiene reacting with the carbenoid derived from methyl 2-diazo-3-butenoate. **B.** Generalized TS model indicating buildup of positive charge on the central carbon of the allene. Calculated bond lengths (Å) and potential steric interactions with an allene substituent when $R_2 \neq H$ are indicated.

The asynchronicity in **TS1** would place partial positive charge at the central carbon of the allene during the reaction. In the case of allene **5c**, the model has the Si−C bond at the R_1 position antiperiplanar to the forming cyclopropane C−C bond, which would be well placed to provide stabilization of this electron-deficient orbital through hyperconjugation. Such an effect would rationalize the large rate enhancement observed in the silyl allene cyclopropanation data.

The mechanistic model approximated by **TS1** justifies the high diastereoselectivity seen for monosubstituted allenes, wherein a group, R_1, projects away from the reaction center, while a hydrogen ($R_2 = H$) projects directly toward it. For 1,1-disubstituted allenes where R_1 is larger than R_2, high diastereoselectivity is still achieved, but the yields suffer due to rate retardation and competition for the carbenoid.

In summary, we have reported the enantioselective cyclopropanation of monosubstituted allenes using methyl aryldiazoacetates mediated by the rhodium tetraprolinate catalyst, $Rh_2(S\text{-DOSP})_4$. Substitution with silicon on the allene substrate has a strong accelerating effect on the reaction. Steric, inductive, and hyperconjugative effects of allene substituents in cyclopropanation are currently under investigation, and these and their correlation with a refined computational model will be reported at a later time.

Acknowledgment. We thank Huw Davies of Emory University for a generous gift of $Rh_2(S\text{-DOSP})_4$ catalyst and Mateusz Pitak of the University at Buffalo for X-ray crystallographic analysis. This work was supported by Canisius College and a Howard Hughes Interdisciplinary Research Fellowship to MKF.

Supporting Information Available: Experimental procedures, full characterization data for new compounds, and atomic coordinates for **TS1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9017968