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Substituent effects on rates of rhodium-catalyzed allene cyclopropanation

Timothy M. Gregg *, Russell F. Algera, John R. Frost, Furqan Hassan, Robert J. Stewart

Department of Chemistry and Biochemistry, Canisius College, Buffalo, NY 14208, United States

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ABSTRACT

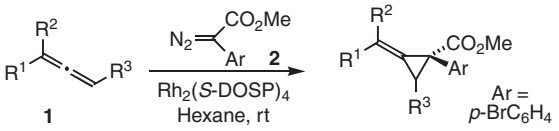
Rates of cyclopropanation for mono- and disubstituted allenes have been measured relative to standard substrates in reaction with aryldiazoacetate esters catalyzed by Rh_2(*S*-DOSP)$_4$. Phenylallene derivatives exhibited a linear correlation of rate with σ^+ coefficients, indicating a resonance-based effect, though the magnitude of the effect for allenes is less than that reported for other cyclopropanations. Relative reaction rates for aliphatic allenes were found to be similar to those for aryl-substituted allenes, but silicon substitution was found to give a 5- to 14-fold rate increase. The rate enhancement effect for 1-silyl allenes can partially make up for loss of rate and regioselectivity, with 1-trimethylsilyl-1,2-butadiene exhibiting high levels of enantioselectivity and diastereoselectivity in reaction with the chiral catalyst.

Intermolecular alkene cyclopropanation has been shown to be an effective enantioselective methodology for the preparation of densely functionalized cyclopropanes in good yields and high enantiomeric excess.[1–5] The reaction of aryl-substituted alkenes is particularly high-yielding and provides very high levels of diastereoselectivity in rhodium(II) mediated reactions with donor-substituted diazoacetates. This efficiency is attributed, in part, to rate enhancement due to conjugation between the reacting alkene and the aromatic ring.[6]

We have recently reported the highly enantioselective cyclopropanation of substituted allenes using aryldiazoacetate-derived rhodium carbenoids, but inconsistent yields were suggestive of significantly reduced cyclopropanation rates, because slower reactions allow competitive dimerization and other side-reactions of the carbenoid species.[7] The rate of allene cyclopropanation may suffer due to the lack of conjugation-derived stabilization in the transition state as well as to the inherent lower reactivity of an sp-hybridized nucleophile proceeding through a three-membered ring transition state.[8]

The literature of allene addition reactions paints a varied picture of factors that affect reactivity of the allene π-bonds. For osmylation[9] and epoxidation,[10] substituents activate the nearer bond for reaction, while with palladium[11–13] and other metal species,[14–16] an alkyl substituent at one end hinders addition, leading to preferential involvement of the less substituted bond. Allene cyclopropanation using malonate- and acetate-derived rhodium carbenoids is also strongly directed by such steric factors, and is well precedented.[17]

In our earlier work with aryldiazoacetate-derived carbenoids, electronic influences also seemed to play a role in substrate reactivity, with an electron-withdrawing substituent causing reduced yield and an electron-donor substituent greatly improving the yield.[7] To get a better understanding of steric and electronic constraints in allene cyclopropanation, we have undertaken the current study, with the aim of rationalizing effects of specific groups and substitution patterns. We compare reaction rates for a variety of allenes (Eq. 1), observing effects that either accelerate or decelerate their reaction with diazoacetate **2** in the presence of a Rh(II) catalyst.



(1)

For arylallenes (**1**, R^1 = Ar, R^2 = R^3 = H), cyclopropanation occurs at the terminal π-bond, which is not conjugated with the aryl ring. Electronic effects are not communicated from the aryl ring to the reactive π-bond via direct resonance. We sought to characterize the kind of effects aryl substituents have on the kinetics of cyclopropanation.

We compared the reaction rate of phenylallene, **3**, with that of *para*-substituted arylallene substrates **4a–d** by direct competition. A 1:1 mixture of two allenes (**3** and one of **4a–d**) with **2** (0.1 equiv relative to allene) in the presence of Rh_2(*S*-DOSP)$_4$ (see Fig. 1) in hexane at rt gave a mixture of cyclopropanation products. The ratio of products in the crude reaction mixture, as observed by ^{1}H NMR, was taken to be the ratio of reaction rates, k_{Ar}/k_{Ph}. The observed rate ratios for substrates **4a–d** relative to **3** are reported in Table 1.

* Corresponding author. Tel.: +1 716 888 2259; fax: +1 716 888 3112.
E-mail address: greggt@canisius.edu (T.M. Gregg).

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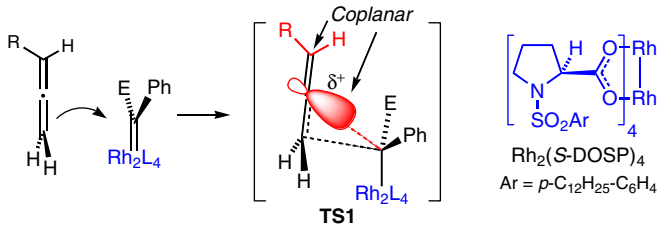
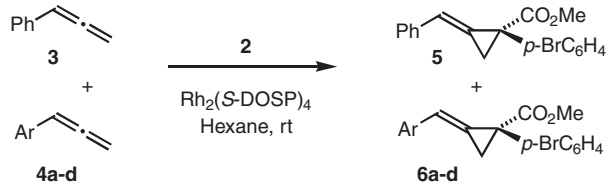


Figure 1. Calculated allene cyclopropanation TS, which suggests bond formation out of conjugation when R is an aromatic ring.

Table 1
Arylallene cyclopropanation rate relative to phenylallene, **3**



Allene	Ar	Product ratio (**6**:**5**)	k_{Ar}/k_{Ph}
4a	*p*-*i*PrOC$_6$H$_4$	1.5:1	1.5
4b	*p*-*i*PrC$_6$H$_4$	1:1	1.0
4c	*p*-ClC$_6$H$_4$	1:1.2	0.83
4d	*p*-CF$_3$C$_6$H$_4$	1:1.5	0.67

Substrate **4a** is activated by the electron-releasing alkoxy group, while **4c** and **4d** are deactivated by electron-withdrawing groups,[18] consistent with a species reacting with an electron-deficient carbenoid.[19] A linear correlation of log (k_{Ar}/k_{Ph}) with Hammett σ^+ coefficients[20] indicates that substituents exhibit a resonance effect on the aromatic ring. The observed ρ value of −0.25, however, suggests that the ring's effect, in turn, on the allene reaction is greatly attenuated compared to that observed for rhodium carbenoid cyclopropanation of styrenes and cyclopropenation of aryl alkynes.[21] Results in the literature support ρ values of around −0.9 for similar reactions of substituted styrenes[22] and arylacetylenes.[23]

While a resonance-like electronic effect gives a small increase in reactivity to donor-substituted arylallenes, nonetheless, they are not conjugated, and we expected arylallene reactivity to be greatly diminished relative to that of styrenes. This has been discussed in light of our TS model for allene cyclopropanation, **TS1** (see Fig. 1).[7] **TS1** depicts developing δ^+ associated with an electron-deficient orbital *in the plane* of the styryl π-bond (R = Ar). As such, developing charge is not stabilized by conjugation with the aryl group.[24]

Support for this came from an experiment wherein styrene and **3** reacted in direct competition under standard cyclopropanation conditions (Table 2, entry 1). Products derived from both substrates were observed by ^{1}H NMR. However, the very small proportion of product formed from **3** allowed only a rough estimate of the reaction rate ratio, which we put as between 20 and 40 to 1 (see Supplementary data). This rate enhancement of styrene over **3** is roughly the same as that reported for styrene over other nonconjugated alkenes. Davies reported a 50 to 1 ratio for styrene versus 1-hexene.[6]

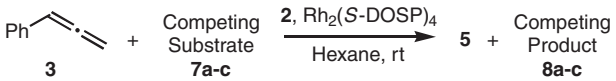
Because allenes gain no reactivity increase when substituted with a phenyl ring, rates of cyclopropanation of aryl allenes and alkyl allenes should be similar. Competition between **3** and 1,2-nonadiene gave products in a 1 to 2 ratio (Table 2, entry 2), confirming the lack of rate enhancement with aromatic substituents. Moving to a consideration of steric effects, for cyclopropanation of monosubstituted allenes, **TS1** suggests that a single R group, whether alkyl or aryl, would not appear to offer hindrance to substrate–carbenoid interaction. For 1,1-disubstituted allenes, however, one group would be oriented away, and the second group (the smaller of the two if they are not identical) would be projecting toward the carbenoid, potentially raising the TS energy and slowing the reaction rate. We first addressed the question of what might be the magnitude of this geminal substitution effect.

Cyclopropanation of **3** in competition with 3-phenyl-1,2-butadiene, **7c**, gave a mixture of products (Table 2, entry 3). The more-substituted allene, **7c**, reacted 8 times slower than **3**. The 8-fold rate reduction may be rationalized as a result of steric crowding of the allene approach trajectory. It should be noted that this by no means rules out an electronic rate effect due to the methyl group that may be partially offsetting the steric effect.

For 1,1-disubstituted allenes, we again compared aryl and alkyl substituents (Table 3, entry 1), with the aryl substrate, **7c**, reacting 3 times slower than the alkyl, **9**. The general observation of reduced rate for aryl substrates compared to alkyl may be steric or electronic in origin, and examination of rate effects for a wider array of substrates may shed light on such effects in the future. The value of such studies, though, may be limited because most of the 1,1-disubstituted allenes we have investigated suffer from low yields in these cyclopropanation reactions.

An important rate effect that could make substituted allenes more attractive in carbenoid reactions is the rate acceleration due to silicon substitution.[25] 3-(Trimethylsilyl)-1,2-butadiene (**11**) was found to react 14 times faster than **9** (Table 3, entry 2). In this case, a strong electronic effect is likely at work.[7] Again referring to **TS1**, where R = TMS, the C–Si bond would be coplanar with

Table 2
Rate comparison for other substrates relative to phenylallene, **3**



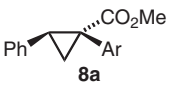
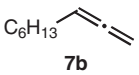
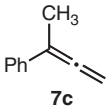
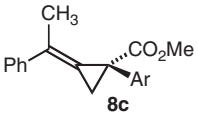
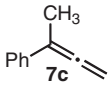
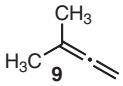
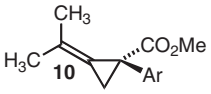
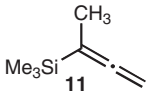
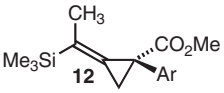
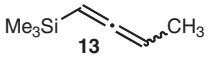
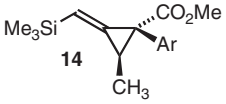
Entry	Competing substrate	Product (**8** Ar = *p*-BrC$_6$H$_4$)	Product ratio (**5**:**8**)
1	 **7a**	 **8a**	1:>20
2	 **7b**	 **8b**	1:2
3	 **7c**	 **8c**	8:1

Table 3
Silylallene rate comparison

Entry	Competing substrates		Cyclopropanation products (Ar = *p*-BrC_6H_4)	Product ratio
1	 **7c**	 **9**	**8c**  **10**	1:3
2	 **11**	**9**	 **12**	**10**	14:1[a]
3	**11**	**3**	**12**	 **5**	5:1
4	**11**	 **13**	**12**	 **14**	1.5:1

[a] See Ref. 7.

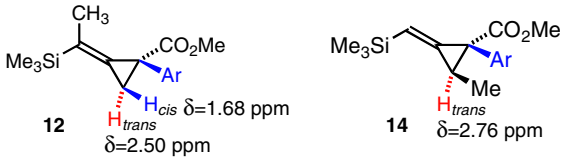
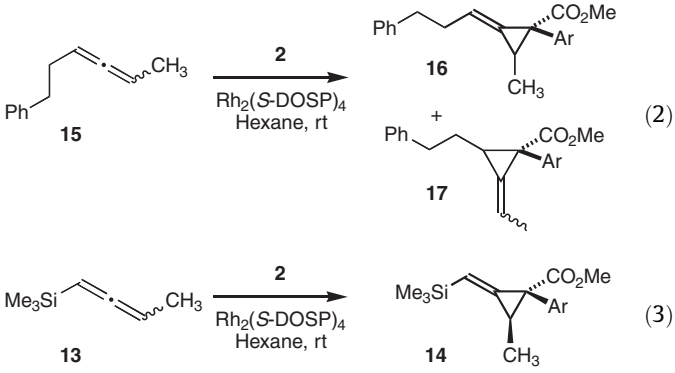


Figure 2. NMR shift correlation puts the methine H of **14** *trans* to Ar.

the evolving cyclopropane bond, ideally oriented to stabilize positive charge developing at the β-position through hyper-conjugation. In direct competition, compound **11** reacted 5 times faster than **3** (Table 3, entry 3). The rate acceleration attributed to the silyl group in compound **11** was more than sufficient to make up for the added steric hindrance attributed to the methyl group.

Considering the rate acceleration provided by a silyl group, we investigated the possibility of performing enantioselective cyclopropanation on 1,3-disubstituted allenes. Such reactions would give alkylidenecyclopropane products with an additional chiral center. Without a silyl substituent, however, rate and regioselectivity for such allenes appear to be compromised. Indeed, we found that 6-phenyl-2,3-hexadiene gave an inseparable mixture of cyclopropanation products, **16** and **17**, indicating limited differentiation of the two ends of the allene in the reaction TS (Eq. 2).

With an eye to boosting the steric and electronic differentiation at work in a 1,3-disubstituted allene, we next investigated 1-(trimethylsilyl)-1,2-butadiene, **13**. A 2-fold excess of racemic **13** reacted with **2**, in the presence of Rh_2(*S*-DOSP)$_4$, and provided a single cyclopropanation product, **14**, with no regio- or diastereoisomeric cyclopropane products discernable by NMR. The product exhibited 91% ee, consistent with the enantioselectivity typically achieved using Rh_2(*S*-DOSP)$_4$.[7]



The relative stereochemistry of **14** was assigned based on the downfield chemical shift of the cyclopropane methine proton *trans* to Ar (see Fig. 2). A shift about 1 ppm further upfield would be expected[26] for the proton *cis* to Ar, as has been seen consistently for products such as **12**.

In conclusion, we have demonstrated that electronic effects can influence reactivity of an allene toward electrophilic rhodium carbenoids, though only a small effect can be attributed to resonance, owing to the cumulene structure of the allene. Silyl groups attached to the non-reacting π-bond, on the other hand have a strong β-silicon effect, accelerating reaction at the other π-bond. Of prime importance for the use of allenes in alkylidenecyclopropane methodology will be overcoming steric encumbrance in the substrate caused by substituents, which can lead to reduced yields.

The feasibility of kinetic resolution of chiral allenes such as **13** and their use in practical methodology for enantioselective construction of densely functionalized alkylidenecyclopropanes are continuing and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated (compound and competition reaction characterization) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.143.

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