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Divergent reactivity of allene-containing α-diazoesters using Cu and Rh catalysis

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ABSTRACT

A versatile intramolecular reaction of allene-containing diazomalonates that exhibits excellent chemoselectivity for either allenic C–H insertion or cyclopropanation is demonstrated. The identity of the product depends on the transition metal catalyst that is employed for the reaction. Rh catalysts promote exclusive C–H insertion with good diastereoselectivity for the *trans* product, while Cu catalysis enables intramolecular cyclopropanation to yield methylenecyclopropanes with moderate to good *E*:*Z* ratios.

1. Introduction

The chemoselective functionalization of alkenes has been extensively studied in the context of nitrene and carbene chemistry.[1] In contrast, the development of catalysts and conditions that permit the controlled introduction of new sp^3 carbon–nitrogen or carbon–carbon bonds into allenes has received much less attention.[2] Previous work in our group has shown that the chemoselective amination of homoallenic carbamates or sulfamates can be facilitated by simple changes in the nitrene precursor or the catalyst to give bicyclic methylene aziridines or allenic amines (Scheme 1, top).[3] Both of these reactive scaffolds proved to be convenient precursors to permit facile access to a diverse array of amine-containing stereotriads, tetrads, and heterocycles.[4,5] We thought that application of the same strategy to chemoselective carbon–carbon bond-forming reactions of allene-containing diazo compounds could provide stereoselective approaches to bicyclic methylenecyclopropanes and functionalized allenes (Scheme 1, bottom). These intermediates could be further transformed into valuable stereodefined motifs for the construction of biologically active molecules. In the case of allene cyclopropanation, transfer of the axial chirality of the substrate to the methylenecyclopropane could produce chiral intermediates poised for further manipulation to enantioenriched stereotriads and tetrads.

In this communication, we describe the identification of catalysts that can be employed to promote divergent reactivity of allenic diazomalonates. Our goal was to permit selective transformation of a single substrate via either intramolecular C-H activation or cyclopropanation.[4,5] The promotion of successful chemoselective C–H activation of allenes to generate new C–C bonds required us to address many of the same issues that faced us in our studies on the amination of allenic C–H bonds, including competing reactions of the π bonds of the allene.[6]

2. Results and discussion

Our first goal was to investigate the surprising neglect of allenes as substrates for C–H activation (Scheme 1, **IIIa**–**IVb**). To our knowledge, there has been only a single reported example of allenic C–H activation, noted as a minor product that was produced during an intermolecular allene cyclopropanation under photocatalytic conditions.[2b] Investigations of common Rh-based catalysts employing **1a** as the allene precursor (Table 1) showed that the bulky $Rh_2(TPA)_4$ catalyst (TPA=triphenylacetate), which gave good results in previous studies on allene amination,[3a] did not perform well in the C–C bond-forming reaction. The addition of molecular sieves to remove any adventitious water did improve the reaction (compare entries 1 and 2), but the yield was still low. A control experiment was carried out to ensure the reaction was not being catalyzed by the molecular sieves. $Rh_2(esp)_2$ resulted in no product formation in the absence of an additive or using $MgSO_4$ (entries 3 and 4), but the inclusion of 4 Å molecular sieves (entry 5) gave the

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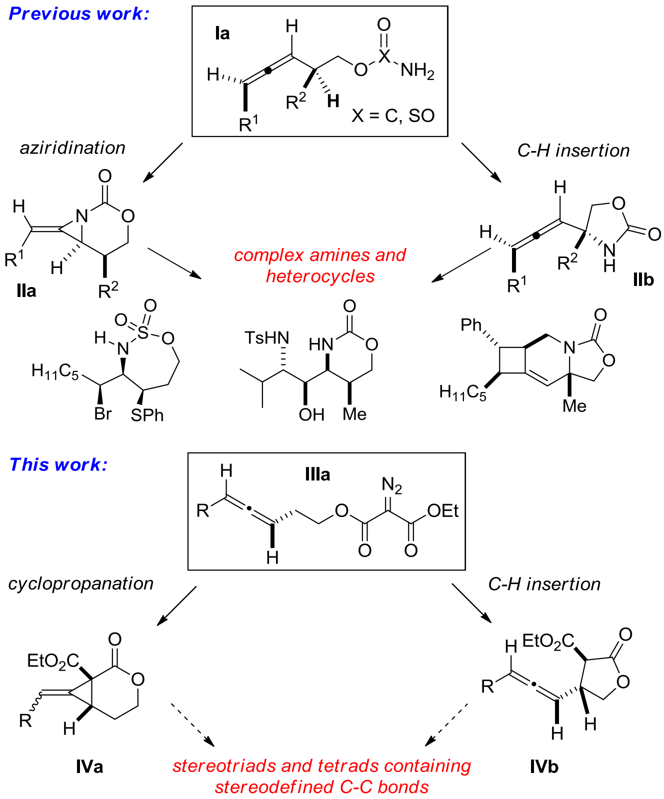
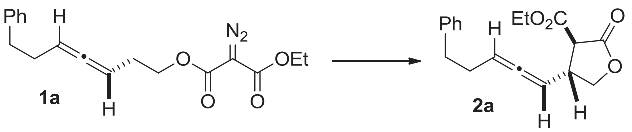


Scheme 1. Chemoselective C–N and C–C bond-forming reactions of allenes.

Table 1

Rh-catalyzed optimization of C–H insertion



Entry	Catalyst	Solvent (M)	Additive[a]	Addn time	Yield
1	Rh$_2$(TPA)$_4$	CH$_2$Cl$_2$ (0.01)	None	6 h	0%
2	Rh$_2$(TPA)$_4$	CH$_2$Cl$_2$ (0.01)	4 Å MS	6 h	43%
3	Rh$_2$(esp)$_2$	CH$_2$Cl$_2$ (0.01)	None	6 h	0%
4	Rh$_2$(esp)$_2$	CH$_2$Cl$_2$ (0.01)	MgSO$_4$	6 h	0%
5	Rh$_2$(esp)$_2$	CH$_2$Cl$_2$ (0.01)	4 Å MS	6 h	57%
6	Rh$_2$(esp)$_2$	C$_6$H$_6$ (0.1)	4 Å MS	3 h	58%
7	Rh$_2$(esp)$_2$	(CH$_2$)$_2$Cl$_2$ (0.1)	4 Å MS	3 h	79%
8	Rh$_2$(esp)$_2$	CH$_2$Cl$_2$ (0.1)	4 Å MS	3 h	80%
9	Rh$_2$(OAc)$_4$	CH$_2$Cl$_2$ (0.1)	4 Å MS	3 h	70%
10	Rh$_2$(esp)$_2$	CH$_2$Cl$_2$ (0.1)	4 Å MS[b]	3 h	60%

[a] Compound **3a** (100 mg/0.1 mmol).

[b] Compound **3a** (200 mg/0.1 mmol).

desired product **2a** in moderate yield. Benzene and dichloroethane were also suitable solvents (entries 6 and 7), but gave no advantage over CH$_2$Cl$_2$ when the final molarity of **1a** was increased from 0.01 M to 0.1 M (entry 8). Additional molecular sieves (entry 10) decreased the yield of **2a** and Rh$_2$(OAc)$_4$ also gave inferior results (entry 9) as compared to Rh$_2$(esp)$_2$; thus, the conditions utilized in entry 8 were adopted as the standard conditions for future studies.

The scope of the reaction was explored (Table 2) using acceptor–acceptor carbenoid precursors, as donor–acceptor carbenoids led to competing side reactions. In the case of 1,3-disubstituted allenes (entries 1–3), good yields and dr of the products were obtained with both Rh$_2$(OAc)$_4$ and Rh$_2$(esp)$_2$. The reported dr refers to the stereochemical relationship between the protons labeled *a* and *b* in the lactone rings of **2a**–**f** and **2h**–**i** (Table 2). The dr between these newly formed stereocenters and the axial chirality of the allene was essentially 1:1. To further ensure that this was the case, hydrogenation of the allene functionality of **2a** gave **2aa** as a single diastereomer. The coupling constant between H$_a$ and H$_b$ in **2aa** was 9.1 Hz, further supporting the assignment of a trans relationship between these two newly formed stereocenters (Scheme 2).

When the allene precursor was the 1,3,3-trisubstituted **1d** (entry 4) or 1,1,3-trisubstituted **1e** (entry 5), the less sterically demanding Rh$_2$(OAc)$_4$ gave improved yields over the bulky Rh$_2$(esp)$_2$. However, this appeared to extend only to alkyl-substituted substrates, as the substitution of a Ph group for an alkyl group resulted in greatly decreased yields of **2f**, even when Rh$_2$(OAc)$_4$ was employed (entry 6). The stereoselectivity of the C–H insertion was explored by employing a diastereoenriched diazo-allene **1g** (dr=86:14). The product **2g** was obtained in with dr of 4.7:2.7:1.5:1 (entry 7). Reduction of the allene functionality of **2g** yielded the lactone **2ga** with a dr of 1.5:1.

The β,β-dimethyl substituted allene **1h** (entry 8) gave good to excellent yields of **2h**, with Rh$_2$(esp)$_2$ superior to Rh$_2$(OAc)$_4$ in this case. The malonate-type diazo precursor could be replaced by the β-ketoester precursor **1i** to give the cyclopentanone **2i** in excellent yield and dr.

We then turned our attention to the chemoselective conversion of allenes to methylenecyclopropanes, which has been previously studied using both Rh- and Cu-based catalysts.[7] However, these substrates were either minimally substituted or did not contain axial chirality. The Rh-catalyzed asymmetric cyclopropanation of achiral allenes containing donor–acceptor carbene precursors has been reported,[8] but in our hands, the use of chiral allenes under these conditions resulted in mixtures of products.[9] Thus, Cu-based catalysts in combination with acceptor–acceptor carbenoid precursors were explored to cleanly access the desired methylenecyclopropanes (Table 3).[5] Initial promising results employed a salen ligand for a Cu(II) catalyst, although slow addition of **1b** to a solution of the catalyst was necessary to minimize dimerization of the substrate, and reflux temperatures were required for complete conversion. Both Cu(salen)[10] and Cu(TBS)$_2$[10] catalysts performed moderately well in the reaction (entries 1–3), although the identity of the ligand did not influence the *E*:*Z* ratio of the methylenecyclopropane to any great extent. Commercially available Cu(I) and Cu(II) salts gave varying yields of the desired **3b**, with triflate counter ions giving poor results (entries 4 and 5), possibly due to generation of small amounts of TfOH during the course of the reaction. Cu(OAc)$_2$ performed better, but still gave only moderate yields of **3b** (entries 6, 7). While longer addition times moderately improved the yield (entry 6 versus 7), increasing the catalyst loading led to increased carbene dimerization and a correspondingly lower yield of the desired product (entry 8). Finally, the simple and commercially available copper(I) iodide salt gave the best combination of yield and *E*:*Z* selectivity (entry 9).

A 10 mol % loading of CuI was utilized in the exploration of the substrate scope of the reaction (Table 4). In all cases, only one diastereomer was observed by ^{1}H NMR and was postulated to be the cis diastereomer resulting from *syn* addition of the metal carbenoid species to the allene.[1a] The success of the cyclopropanation was quite sensitive to the steric environment of the allene. Yields were moderate for the 1,3-substituted substrates **1a** and **1b** (entries 1 and 2), while the 1,3,3-trisubstituted allene **1d** gave a poor yield of **3d** (entry 3). The *E*:*Z* ratios were on the order of 7–8:1. Interestingly, additional substitution in the tether between the allene and the diazo group greatly increased the *E*:*Z* ratios (entries 4–6), although too much steric congestion was detrimental to the