Catalytic Asymmetric Synthesis of Highly Functionalized Cyclopentenes by a [3 + 2] Cycloaddition

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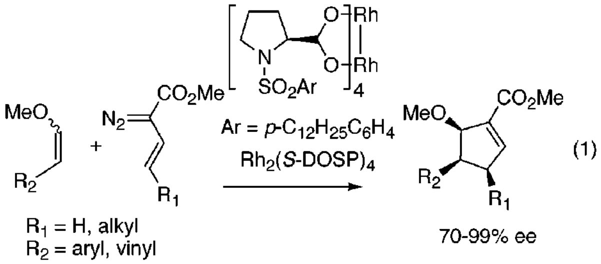
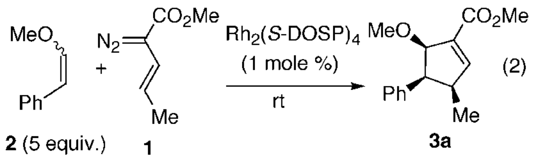
The stereoselective construction of five-membered carbocycles by means of [3 + 2] cycloadditions has been actively studied in recent years.[1] In this paper we describe a novel [3 + 2] cycloaddition protocol involving the metal-catalyzed decomposition of vinyldiazocarbonyl derivatives in the presence of vinyl ethers. The catalyst that is used in these reactions is $Rh_2(S\text{-DOSP})_4$, which has been shown to be exceptionally effective for the asymmetric transformations of vinyldiazocarbonyl derivatives.[2] Cyclopentenecarboxylates are formed in 70−99% ee with full control of relative stereochemistry at up to three contiguous stereogenic centers (eq 1). Furthermore, conjugate addition of nucleophiles to the cyclopentenecarboxylates generates, stereoselectively, cyclopentanes with up to five stereogenic centers.



The reaction of vinyldiazocarbonyl derivatives with vinyl ethers is very sensitive to the structure of both reactants. Cyclopropanation of unsubstituted vinyl ethers with vinyldiazoacetates substituted at the vinyl terminus is well established.[3] In contrast, $Rh_2(S\text{-DOSP})_4$ catalyzed decomposition of the vinyldiazoacetate **1** at room temperature in CH_2Cl_2 in the presence of the vinyl ether **2** (5 equiv) results in a remarkable reaction (eq 2). A single diastereomer of the cyclopentene **3** was formed (79% yield), in which all three substituents were in a cis arrangement. Also, even though the reaction was carried out at room temperature, **3** was formed in 98% ee. A further surprising feature of the reaction is that a highly diastereoselective [3 + 2] cycloaddition is obtained, even when the vinyl ether **2** is a mixture of double bond isomers, because only the cis vinyl ether reacts with the carbenoid.



2, Z/E ratio	solvent	**3a**, yield, %	**3a**, ee, %
19 : 1	CH_2Cl_2	79	98
1 : 1	CH_2Cl_2	65	98
19 : 1	hexane	86	95

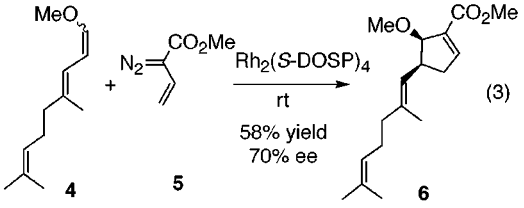
Table 1. [3 + 2] Cycloadditions According to Eq 1

product	R_1	R_2	yield, %	ee, %^{a}
3a	Me	Ph	79^{a,c}	98^f
3b	Me	p-BrPh	71^{b,d}	>99^f
3c	Me	*E*-CH=CHEt	49^{b,e}	99^f
3d	n-Bu	Ph	55^{b,b}	>94^g
3e	H	Ph	61^{a,c}	82^f
3f	H	*E*-CH=CHEt	74^{b,e}	79^f

[a] CH_2Cl_2 as reaction solvent. [b] Hexanes as reaction solvent. [c] *Z/E* ratio of vinyl ether is 19:1. [d] *Z/E* ratio of vinyl ether is >19:1. [e] *Z/E* ratio of vinyl ether is 1:1. [f] ee determined by HPLC using Chiralcel OJ or OD columns, see Supporting Information for details. [g] ee determined by ^1H NMR using a chiral shift reagent.

[3 + 2] cycloadditions have been observed previously in reactions between vinyldiazoacetates and vinyl ethers[4] but they are likely to involve a different mechanism than the reactions described herein. The previous [3 + 2] cycloadditions occurred when the vinyl terminus of the vinyldiazoacetate was unsubstituted.[4] These previous reactions were also nonstereospecific, enhanced by bulky ester substituents on the vinyldiazoacetate, and totally blocked when nonpolar solvents were used.[4] On the basis of these characteristics the reactions were considered to involve stepwise ionic processes initiated by reaction of the vinyl ether at the vinylogous position of the vinylcarbenoid. Further confirmation that the formation of **3a** occurs by a different mechanism to the previously described [3 + 2] cycloadditions[4] was obtained by repeating the reaction of **1** and **2** in hexane. The solvent change had very little effect on the reaction as **3a** was formed in 86% yield and 95% ee.

Various highly functionalized cyclopentenecarboxylates can be formed in this reaction as shown in Table 1. Very high enantioselectivities (>94% ee) are obtained when the vinyldiazoacetates are substituted with an alkyl substituent at the vinyl terminus position and the vinyl ethers are substituted with either an aryl or a vinyl group. In all cases, the all cis products are exclusively formed. An unsubstituted vinyldiazoacetate results in the formation of the [3 + 2] cycloadduct **3e** with lower enantioselectivity (82% ee). An interesting example is shown in eq 3, where a selective [3 + 2] cycloaddition by **5** occurs on the vinyl ether component of **4** to form the cyclopentene **6** in 58% yield. The absolute configuration of **3b** was determined to be (3*R*,4*S*,5*R*) by X-ray crystallography, while the absolute configuration of the other [3 + 2] cycloadducts is tentatively assigned, assuming a similar mode of asymmetric induction.



An especially attractive feature of this [3 + 2] cycloaddition is that the resulting products are well-functionalized for further

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(1) For recent examples, see: (a) Urabe, H.; Suzuki, K.; Saito, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014. (b) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775. (c) Hoffmann, M.; Buchert, M.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 283. (d) Barluenga, J.; Tomas, M.; Ballesteros, A.; Santamaria, J.; Brillet, C.; Garcia-Granda, S.; Pinera-Nicolas, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516.

(2) (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459. (b) Davies, H. M. L. *Aldrichim. Acta* **1997**, *30*, 105.

(3) (a) Davies, H. M. L.; Kong, N.; Churchill. M. R. *J. Org. Chem.* **1998**, *63*, 6586. (b) Davies, H. M. L.; Hu, B. B. *J. Org. Chem.* **1992**, *57*, 3186.

(4) Davies, H. M. L.; Hu, B. B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535.

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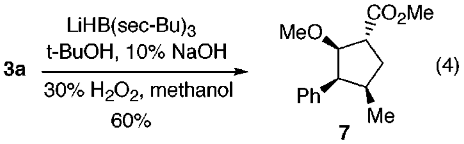
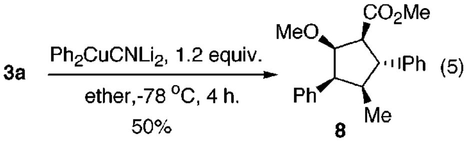
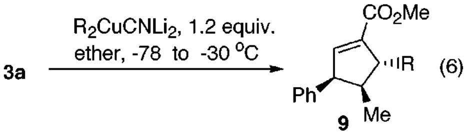
elaboration. For example, reaction of **3a** with L-selectride generated the cyclopentanecarboxylate **7** as a single diastereomer whose configuration was assigned by nOe difference experiments (eq 4). Furthermore, addition of a higher order cuprate at −78 °C to **3a** generates the cyclopentane **8** with full control of stereochemistry at five stereocenters (eq 5).

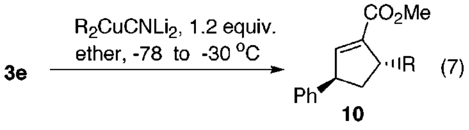




By using slightly more vigorous conditions to carry out the cuprate additions, a conjugate addition followed by elimination of methoxide occurs to form new unsaturated carboxylates **9** and **10**. This is seen in the reaction of either **3a** or **3e** with either butyl or phenyl higher order cuprates (eqs 6 and 7). In all cases, the cuprate approaches from the opposite side to the all cis substituents leading to single diastereomers of the products.

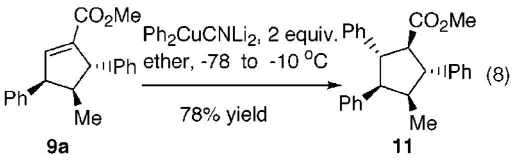


(a) R =Ph, 63%; (b) R = n-Bu, 67%



(a) R =Ph, 46%; (b) R = n-Bu, 55%

Finally, as the addition/elimination sequence generates a new unsaturated carboxylate, a second cuprate addition can be carried out. This is illustrated in the reaction of **9a** with 2 equiv of the higher order cuprate that leads to the stereoselective formation of the pentasubstituted cyclopentane **11** (eq 8), again with full control of relative stereochemistry.



One of the most remarkable features of the [3 + 2] cycloaddition is that the all cis products are formed in each case. Although the mechanistic details of this reaction are not well understood, a plausible explanation for the relative stereochemistry of this reaction is shown in Figure 1. The observed absolute stereochemistry would require attack from the front face of the carbenoid. The reaction may be considered a concerted process in which the vinylcarbenoid substituent and the vinyl ether functionality must point away from the catalyst "wall". This would explain why trans vinyl ethers are incapable of undergoing the [3 + 2] cycloaddition. An alternative mechanism, whereby the rhodium carbenoid undergoes a [4 + 2] cycloaddition to form a metalacyclohexene followed by a reductive elimination, is also a possibility.

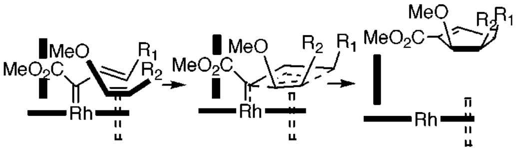


Figure 1. Model for the [3 + 2] cycloaddition.

The high asymmetric induction generated by the Rh_2(*S*-DOSP)$_4$ catalyst has been rationalized by assuming that the catalyst adopts a D_2-symmetric conformation and the arylsulfonyl groups act as blocking groups. In this model, there is a blocking group behind the carbenoid ester and in front of the carbenoid vinyl group, as represented by the thickened and dotted vertical lines, respectively. This model needs to be modified to rationalize the absolute stereochemistry observed here because the blocking group in front of the carbenoid vinyl group would preclude an effective approach for a concerted reaction between the vinyl ether and the vinylcarbenoid. For this model to remain viable for this chemistry, it would be necessary for the blocking group in front of the carbenoid vinyl group to be flexible and move away as the reaction occurs. Some evidence to support this concept was seen in carrying out the reaction of **1** with **2** using the bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$,[5] which has a rigid structure. With this catalyst only a trace of the [3 + 2] cycloaddition product **3a** was obtained in low ee (38%).

The highly stereoselective [3 + 2] cycloaddition reported herein further demonstrates the breadth of diverse reactivity of carbenoids derived from vinyldiazoacetates. Not only does the vinyl group stabilize the carbenoid, leading to highly chemoselective reactions, but it can also enter into new unprecedented carbenoid transformations. By combining the asymmetric [3 + 2] cycloadditions with cuprate conjugate additions, a very general method for the synthesis of cyclopetanecarboxylates with up to five stereogenic centers can be readily achieved.

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Supporting Information Available: Complete experimental data for the [3 + 2] cycloadditions and X-ray crystallographic data for the carboxylic acid derivative of **3b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[5] Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287.