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# Asymmetric Catalysis of the [5 + 2] Cycloaddition Reaction of Vinylcyclopropanes and $\pi$-Systems

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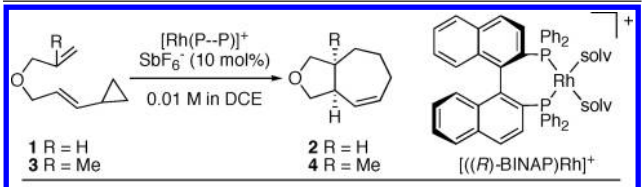
As part of our studies on the design and development of new metal-catalyzed reactions, we previously reported the first examples of metal-catalyzed [5 + 2] cycloadditions of vinylcyclopropanes (VCPs) and $\pi$-systems.[1] Rh(I) catalysts have proven to be the most general for this process,[2] working for both inter-[3] and intramolecular cycloadditions, the latter with alkynes, alkenes, or allenes as the 2-$\pi$ component. In addition to commercial Rh(I) sources, we have reported arene−Rh(I) complexes that catalyze these reactions in minutes at room temperature[4] and a water-soluble Rh(I) complex that effects the reaction in water without organic solvents.[5] The application of this new reaction class to many targets of biomedicinal importance[6,7] requires a solution to the problem of controlling absolute stereochemistry.[8] Toward this end, we describe a comparative evaluation of several chiral catalysts found to effect this process, evaluation of a preferred catalyst with substrates differing in substitution and tether types—producing enantiomeric excesses ≥95% for several systems—and a predictive model for the selectivity.

In a preliminary study of catalysts,[1g] we previously observed that the use of $[Rh(C_2H_4)_2Cl]_2$ modified with silver triflate and (*S*,*S*)-bis(diphenylphosphino)butane resulted in moderate enantioselectivity (up to 63% ee) in a single substrate studied. Subsequent investigations (unpublished) with other substrates and this catalyst system produced similar results often with poor conversions. To address these selectivity and efficiency problems, we have more recently conducted a screen of catalyst systems using the readily available VCP **1** as a test substrate (Table 1). The modest selectivity observed for this tethered ene-VCP contrasts the high enantioselectivity observed with some chiral catalysts in rhodium-catalyzed [4 + 2] cycloadditions of ether tethered ene-dienes.[9] Nevertheless, while the selectivity with substrate **1** and its methallyl analogue (**3**) were modest, the conversion (>99%) and yield (96%) for the formation of **2**[10] with $[((R)\text{-BINAP})Rh]^+$ $SbF_6^-$[11] observed in this screen were sufficiently encouraging to warrant further investigation of this catalyst system.

Structure−selectivity studies for a range of substrate variations with the BINAP catalyst are summarized in Table 2. Significantly, high yields and excellent enantioselectivities are obtained in several cases, most including synthetically versatile sulfonamide and malonodiester groups. For example, reaction of VCP **7** bearing a methyl group at the internal carbon of the alkene (entry 1) proceeds with high selectivity (>95%). The benzyloxymethyl-substituted alkene **9** reacts with similarly high selectivity (>99%). In contrast and providing information on the stereochemistry-determining step of this process, VCP **11**, which possesses a hydrogen on the internal alkene carbon, provides cycloadduct **12** in only modest selectivity, similar to that found for the analogously substituted system **1**. In addition to substitution effects, the substrate tether is also found to influence the selectivity. For example, in contrast to VCP **11**, VCP **13** affords a cycloadduct in high yield and enantiomeric excess.

***Table 1.*** Screening of Ligands[d]




| entry | substrate, ligand (P—P) | temperature | conversion | ee |
|---|---|---|---|---|
| 1 | **1**, (*S*,*S*)-DIOP | rt | 80% | 28% |
| 2 | **1**, (*R*,*R*)-CARBOPHOS | 70 °C | >99% | -51%[a] |
| 3 | **1**, (*R*,*R*)–Et,Et-DUPHOS | 70 °C | >99% | -23%[a] |
| 4 | **1**, (*S*,*S*)-BDPP | 70 °C | >99% | -44%[a] |
| 5 | **1**, (*R*)-BINAP[b] | rt | 5% | 69% |
| 6 | **1**, (*R*)-BINAP | 50 °C | >99% (96%)[c] | 60% |
| 7 | **1**, (*R*)-*tol*-BINAP[b] | rt | 15% | 66% |

[a] Opposite sense of induction. [b] 10 mol % excess ligand was used. [c] Parenthetical value is GC yield. [d] DCE = 1,2-dichloroethane. Conversion and ee were measured by GC.

***Table 2.*** Asymmetric [5 + 2] Cycloaddition Reactions[e]

| entry | substrate | cycloadduct | conditions | yield, ee |
|---|---|---|---|---|
| 1 | **7** R = Me | **8** R = Me | 70 °C, 2 d, 0.05 M | 72%, >95%[a] |
| 2 | **9** R = $CH_2OBn$ | **10** R = $CH_2OBn$ | 70 °C, 2 d, 0.01 M | 80%, >99%[b] |
| 3 | **11** R = H | **12** R = H | 50 °C, 1.5 d, 0.03 M | 73%, 52%[c] |
| 4 | **13** | **14** | 40-60 °C, 8 d, 0.01 M | 90%, 96%[c] |
| 5 | **15** | **16** | 70 °C, 6 d, 0.01 M | 92%, 95%[c] |
| 6 | **17** | **18** X = TsN | rt, 2 d, 0.01 M | 87%, 56%[b] |
| 7 | **19** | **20** X = O | 70 °C, 2 d, 0.01 M | 95%,[d] 22%[a] |

[a] Determined by GC. [b] Determined by HPLC, i-PrOH/hexane eluent, CHIRALPAK AD column. [c] Determined by GC following treatment with *m*-CPBA. [d] Conversion determined by GC; 10 mol % excess BINAP was used. [e] Conditions: 10 mol % $[Rh((R)\text{-BINAP})]^+$ $SbF_6^-$. E = $CO_2Me$.

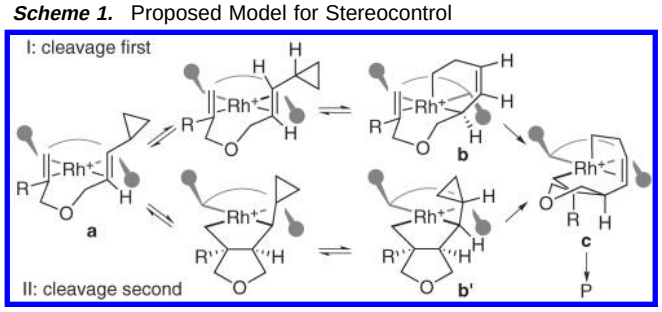
Substitution on the cyclopropane also favors a highly selective process. Reactions of tethered alkyne−VCPs were less selective than alkenes with this catalyst (entries 6 and 7).

Preliminary mechanistic studies revealed that the enantiomeric excess of the product (**8**) is constant over the course of the reaction. Furthermore, the product enantiomeric excess is proportional to that of the catalyst. These observations are consistent with a mechanism that involves a single catalytic species bearing 1 equiv of BINAP

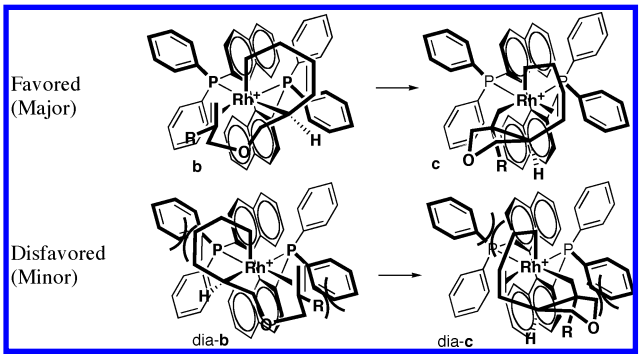


10.1021/ja058590u CCC: $33.50 

***Scheme 1.*** Proposed Model for Stereocontrol




***Scheme 2.*** Stereochemistry-Determining Steps




throughout the reaction. The absolute sense of induction was established by an independent eight-step synthesis of cycloadduct (+)-**2** from ethyl-(*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-(*E*)-2-propenoate (see Supporting Information).

A mechanistic model for the observed sense of induction is outlined in Schemes 1 and 2. The reaction begins with coordination of the VCP to the [((*R*)-BINAP)Rh]$^+$ cation. The proposed structure of this intermediate is based on X-ray data for [((*R*)-BINAP)Rh-(nbd)]$^+$ (nbd = norborna-2,5-diene)[9c] from which the nbd ligand has been removed and replaced with **1** (Scheme 1, **a**). The alkene−VCP fragment aligns itself so that the bulky cyclopropyl and alkenyl R groups are pointed away from the forward-leaning phenyl groups of the BINAP ligand (indicated by bold icons in **a**). Two pathways lead from **a**, differing in the sequence of cyclopropane cleavage and oxidative coupling. DFT studies of an ethyne/VCP [5 + 2] reaction[12] suggest that the step following VCP coordination is cyclopropane opening to give **b** (sequence I, also illustrated in Scheme 2). C−C bond formation follows to give **c**, from which the cycloadduct is formed by reductive elimination. A complementary argument can be made for pathway II proceeding through **b′** (see Supporting Information).

Scheme 2 illustrates the favored and disfavored stereochemistry-determining steps for sequence I, the DFT-preferred path. Stereochemistry would be set irreversibly in the conversion of **b** to **c**, so the relative energies for the transformations of **b** to **c** and dia-**b** to dia-**c** would dictate the sense and degree of enantioselectivity. Examination of models of intermediates **b** and **c** in the favored pathway indicates little destabilizing interaction between the substrate and ligand. In contrast, in the disfavored pathway, destabilizing interactions occur in dia-**b** and persist in the product dia-**c**. One of these interactions is between alkene substituent (R) and a phenyl group of the BINAP ligand. This is consistent with the observation that increased steric bulk at this position gives higher enantiomeric excesses. This model is also consistent with the high selectivity observed for methyl-substituted VCP **15** in which a methyl group would be placed in a space unencumbered by the ligand in the favored starting complex (and transition structure) but would be placed in a sterically occupied space in the disfavored path.

In summary, the first catalyst system for effecting asymmetric [5 + 2] cycloadditions of alkenes and VCPs is described. High yields and high enantioselectivities are obtained with several substrates differing in substitution of the reactive functionality and in the tether. The best results are attained with tethered alkenes as the 2-$\pi$ component. Further studies involving the selectivity of the [5 + 2] reaction are ongoing in our laboratories.

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**Supporting Information Available:** Full synthetic procedures and data (including CIF for adduct **S7**) for all new compounds are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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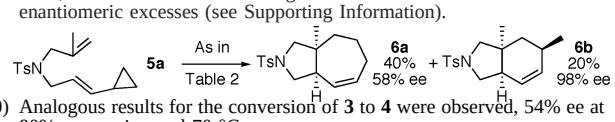


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