

Enantioselective Synthesis of  
2-Arylbicyclo[1.1.0]butane Carboxylates

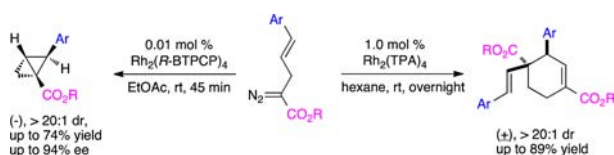
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## ABSTRACT



The rhodium-catalyzed reaction of 2-diazo-5-arylpent-4-enoates can be controlled by the appropriate choice of catalyst and catalyst loading to form either 2-arylbicyclo[1.1.0]butane carboxylates or cyclohexene derivatives. Both products are produced in a highly diastereoselective manner, with 2-arylbicyclo[1.1.0]butane carboxylates preferentially formed under low catalyst loadings. When the reaction is catalyzed by  $\text{Rh}_2(\text{R-BTPCP})_4$ , the 2-arylbicyclo[1.1.0]butane carboxylates are generated with high levels of asymmetric induction (70–94% ee).

The bicyclo[1.1.0]butane ring system has fascinated chemists because it challenges chemical bonding models<sup>1</sup> and

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offers utility in complex molecule synthesis.<sup>2</sup> General synthetic routes to access bicyclo[1.1.0]butanes include Wurtz coupling, reductive dehalogenation of 1,3-dihalocyclobutanes, anionic-type ring closure, and 1,3  $\gamma$ -silyl elimination.<sup>3</sup> The metal-catalyzed synthesis of the bicyclo[1.1.0]butane system is relatively undeveloped. Previous approaches include the cyclopropanation of cyclopropenes<sup>4</sup> and intramolecular cyclopropanation of  $\alpha$ -allyl diazo compounds,<sup>5</sup> neither of which has been conducted in an enantioselective manner. Herein, we report the asymmetric synthesis of bicyclo[1.1.0]butanes rings by the rhodium-catalyzed decomposition of 2-diazo-5-arylpent-4-enoates (eq 1).



Our initial studies began with the rhodium-catalyzed decomposition of  $\alpha$ -cinnamyl diazoacetate **1**. 1,2-Hydride migration could be a competing process in this transformation,<sup>6</sup>

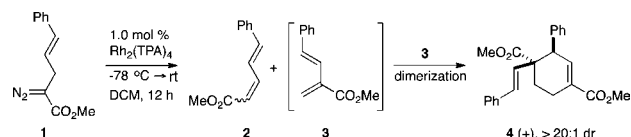
(4) (a) Baird, M. S.; Hussain, H. H. *Tetrahedron* **1987**, *43*, 215. (b) Mahler, W. *J. Am. Chem. Soc.* **1962**, *84*, 4600. (c) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912. (d) Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 735. (e) Small, A. *J. Am. Chem. Soc.* **1964**, *86*, 2091. (f) Jautelat, M.; Schwarz, V. *Tetrahedron Lett.* **1966**, *7*, 5101.

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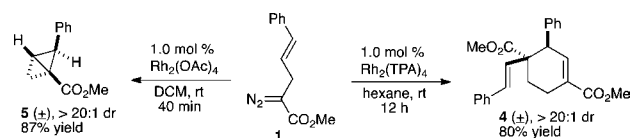
but recent studies by Fox suggested that it would be possible to circumvent this problem with the use of very bulky dirhodium catalysts.<sup>7</sup> Consequently, we began our investigation with  $\text{Rh}_2(\text{TPA})_4$ , an electron-rich and sterically crowded catalyst (Scheme 1). Although  $\text{Rh}_2(\text{TPA})_4$  catalyzed the decomposition of **1**, the catalyst failed to provide the desired bicyclo[1.1.0]butane product. Instead, a mixture of diene **2** and cyclohexene **4**<sup>8</sup> was obtained. Cyclohexene **4**, isolated in 69% yield, was presumably formed by dimerization of the diene **3**, which was produced *in situ*.

**Scheme 1.**  $\text{Rh}_2(\text{TPA})_4$ -Catalyzed Decomposition of **1**



Further exploratory studies revealed that the product outcome was dependent on the reaction solvent, time, and catalyst (Scheme 2). When the reaction with  $\text{Rh}_2(\text{TPA})_4$  was conducted in hexane at room temperature in 12 h, cyclohexene **4** could be isolated in 80% yield; however, when  $\text{Rh}_2(\text{OAc})_4$  was used as catalyst in dichloromethane, the desired 2-phenyl bicyclo[1.1.0]butane carboxylate **5** was obtained in 87% yield.

**Scheme 2.** Divergent Synthesis of **4** and **5**



As  $\text{Rh}_2(\text{OAc})_4$  is only partially soluble in dichloromethane, we reasoned that only a trace amount of catalyst may be required to decompose the diazo compound **1** and generate the bicyclobutane **5**, but **5** may be undergoing a slower rhodium-catalyzed rearrangement to **3** and subsequent dimerization into product **4**. On the basis of this hypothesis, we examined a series of catalysts at standard (1.0 mol %) and low catalyst loadings (0.01 mol %) (Table 1). As shown in Table 1, the formation of bicyclo[1.1.0]butane was favored at low catalyst loadings in all cases. Under conditions with 0.01 mol % of  $\text{Rh}_2(\text{OOct})_4$ , **5** was formed in 85% isolated yield.

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(8) The crystal structures of **4** and **7h** have been deposited at the Cambridge Crystallographic Data Centre, and the deposition numbers CCDC 910504 and 910501, were allocated, respectively. For X-ray crystallographic data of **4** and **7h**, see the Supporting Information. The quality of the data for **7h** is not sufficient for an unambiguous assignment of the absolute configuration, but further analysis by determining the Hooft parameter (using Platon software) confirmed the tentative assignment.

**Table 1.** Catalyst Loading Evaluation

entry	catalyst	cat. loading (mol %)	yield ratio (2/4/5) <sup>a</sup>	yield (%) <sup>b</sup>
1	$\text{Rh}_2(\text{OPiv})_4$	1.0	10/10/80	62
2	$\text{Rh}_2(\text{OPiv})_4$	0.01	4/trace/96	80
3	$\text{Rh}_2(\text{OOct})_4$	1.0	16/18/66	60
4	$\text{Rh}_2(\text{OOct})_4$	0.01	2/trace/98	85
5	$\text{Rh}_2(\text{TPA})_4$	1.0	25/64/11	10
6	$\text{Rh}_2(\text{TPA})_4$	0.01	8/33/59	47

<sup>a</sup> Ratio was calculated from the NMR of the reaction mixture prior to chromatographic purification and takes into account that 2.0 equiv of **1** are required for the formation of **4**. <sup>b</sup> Isolated yield of **5** (>20:1 dr).

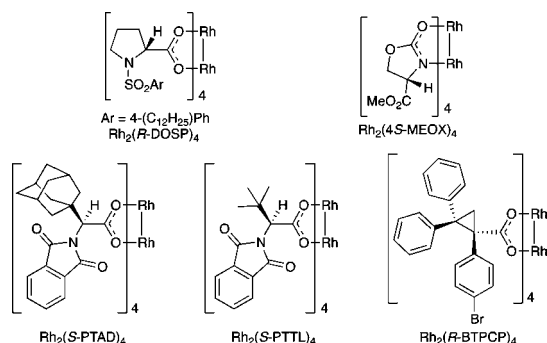
Having developed a practical entry into the bicyclo[1.1.0]butane system, we subsequently focused on achieving an asymmetric version of this process with a chiral dirhodium catalyst (Figure 1) at a very low catalyst loading (0.01 mol %). The standard chiral dirhodium tetracarboxylate catalysts,<sup>9</sup>  $\text{Rh}_2(R\text{-DOSP})_4$ ,  $\text{Rh}_2(S\text{-PTAD})_4$ , and  $\text{Rh}_2(S\text{-PTTL})_4$ , resulted in the effective formation of **5**, but the level of enantioinduction was relatively low in each case (Table 2, entries 1–3). The dirhodium tetracarboxamidate catalyst,  $\text{Rh}_2(4S\text{-MEOX})_4$ ,<sup>10</sup> a less reactive catalyst, also resulted in the formation of **5** with a higher catalyst loading (0.5 mol %), but bicyclo[1.1.0]butane carboxylate **5** was still produced with low levels of enantioselectivity (Table 2, entry 4). The breakthrough catalyst for high asymmetric induction was the triarylcyclopropane carboxylate complex  $\text{Rh}_2(R\text{-BTPCP})_4$ ,<sup>11</sup> which provided **5** in 72% yield and 90% ee in dichloromethane (Table 2, entry 5). Furthermore, when ethyl acetate was used as solvent, the asymmetric induction of this transformation can be improved to 94% ee (Table 2, entry 8).

$\text{Rh}_2(R\text{-BTPCP})_4$  proved to be an effective catalyst for the asymmetric synthesis of a range of 2-arylbicyclo[1.1.0]butane carboxylates as summarized in Scheme 3. Generally, 2-arylbicyclo[1.1.0]butane carboxylates were

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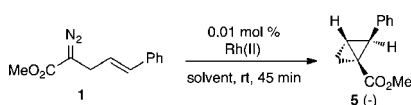


**Figure 1.** Chiral dirhodium catalysts.

**Table 2.** Chiral Catalyst Evaluation

entry	catalyst	solvent	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	Rh <sub>2</sub> ( <i>R</i> -DOSP) <sub>4</sub>	DCM	65	<5
2	Rh <sub>2</sub> ( <i>S</i> -PTAD) <sub>4</sub>	DCM	64	47
3	Rh <sub>2</sub> ( <i>S</i> -PTTL) <sub>4</sub>	DCM	69	52
4 <sup>c</sup>	Rh <sub>2</sub> (4 <i>S</i> -MEOX) <sub>4</sub>	DCM	42	–23
5	Rh <sub>2</sub> ( <i>R</i> -BTPCP) <sub>4</sub>	DCM	72	90
6	Rh <sub>2</sub> ( <i>R</i> -BTPCP) <sub>4</sub>	hexane	64	88
7	Rh <sub>2</sub> ( <i>R</i> -BTPCP) <sub>4</sub>	acetone	60	94
8	Rh <sub>2</sub> ( <i>R</i> -BTPCP) <sub>4</sub>	EtOAc	70	94

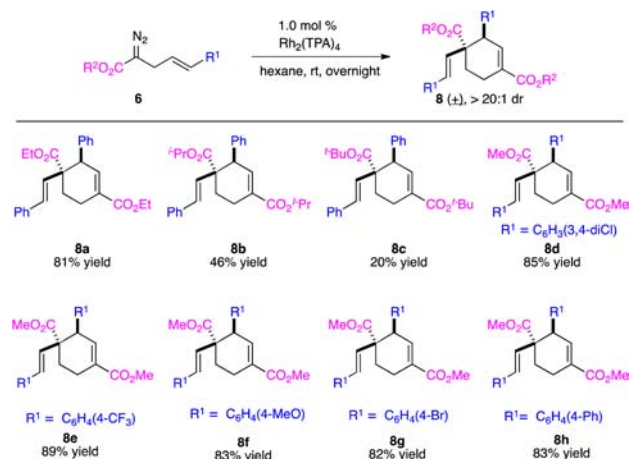
<sup>a</sup> Isolated yield. <sup>b</sup> Analysis by chiral HPLC column, > 20:1 dr. <sup>c</sup> 0.5 mol % catalyst loading.



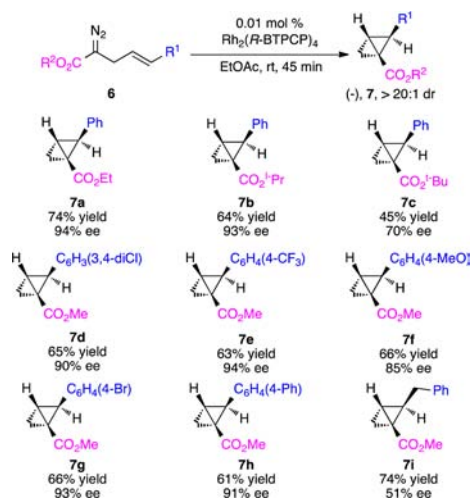
formed in good yield (61%–74%) with high levels of enantioinduction (> 90% ee). However, lower enantioselectivity was observed when the ester group was *tert*-butyl (70% ee) or when the aryl ring was electron rich such as *p*-methoxyphenyl (85% ee) or was changed to a benzyl substituent (51% ee). The absolute configuration of 2-aryl bicyclo[1.1.0]butane carboxylate **7h** was assigned with a relatively high level of confidence by X-ray crystallography (see Supporting Information).<sup>8</sup> The configuration of the other bicyclo[1.1.0]butane products are tentatively assigned by analogy.

Even though bicyclobutanes could be isolated in high yield, these products could be totally eliminated when 1.0 mol % of Rh<sub>2</sub>(TPA)<sub>4</sub> and extended reaction times were used. Under these conditions, cyclohexenes **8** were obtained in good yields (81–89%) for a variety of methyl cinnamyl diazoacetate **6** (Scheme 4). Increasing the size of the ester from methyl, *iso*-propyl to *tert*-butyl caused a steady drop in the isolated yield of **8** (Scheme 4, **8a**: 80%, **8b**: 46%, **8c**: 20%).

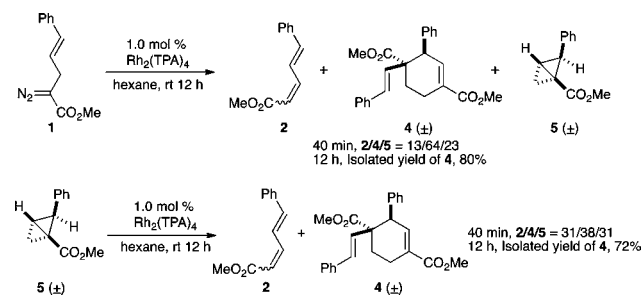
**Scheme 4.** Cyclohexene Formation



**Scheme 3.** Bicyclo[1.1.0]butane Carboxylate Formation

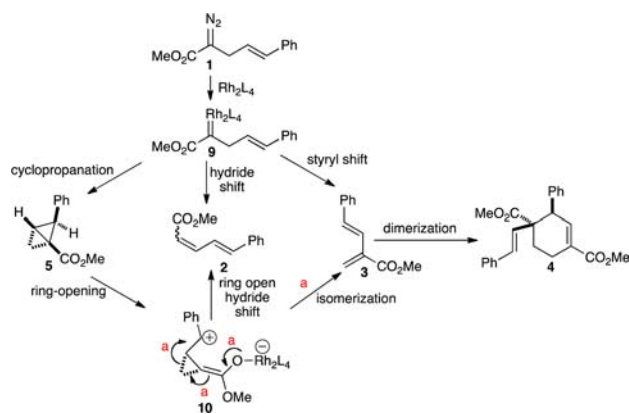


In order to probe the cause in the change in product distribution, further control experiments were conducted as illustrated in Scheme 5. The Rh<sub>2</sub>(TPA)<sub>4</sub>-catalyzed reaction of **1** was re-examined under short (40 min) and long (12 h) reaction times. After 40 min a mixture of the three products (**2**, **4**, **5**) is present, but no 2-phenyl bicyclo[1.1.0]butane carboxylate **5** is present in the reaction mixture after 12 h. Under these conditions, cyclohexene **4** is isolated in 80% yield. Product **5** is stable in solution in the absence of catalyst for several days. However, when exposed to Rh<sub>2</sub>(TPA)<sub>4</sub>, within 40 min, over half of the material rearranges to diene **2** and the cycloadduct **4**. After 12 h, none of **5** remains and **4** is isolated in 72% yield. These experiments show that Rh<sub>2</sub>(TPA)<sub>4</sub> catalyzes the ring opening of **5**. However, as the ratio of **4** formed after 40 min is higher when starting from the diazo compound **1** than when starting from **5**, it appears that at least some of the product **4** is formed directly from the carbenoid derived from **1**.

**Scheme 5.** Control Experiments for Mechanistic Study

A reasonable series of mechanisms for these transformations is shown in Scheme 6. Dienes **2** and **3** can be generated directly from the allyl carbenoid **9** via a 1,2-shift of either a hydride or a styryl group. Direct cyclopropanation of **9** would generate the bicyclo[1.1.0]butane **5**. The bicyclo[1.1.0]butane carboxylate is also unstable in the presence of the dirhodium catalysts, undergoing ring opening to intermediate **10** and then bond breaking to form either **2** by a ring opening–hydride shift mechanism or **3** (electron movement “a”). The rhodium catalyzed ring opening of **5** is slower than the rhodium-catalyzed nitrogen extrusion to form the carbenoid intermediates. Therefore, when a very low catalyst loading and relatively short reaction times are used, the bicyclo[1.1.0]butane **5** can be selectively isolated.

In summary, we have developed a divergent and highly diastereoselective synthesis of 2-arylbicyclo[1.1.0]butane carboxylate and cyclohexene derivatives *via* a dirhodium-catalyzed

**Scheme 6.** Proposed Mechanism for the Reactions of **1**

decomposition of  $\alpha$ -allyldiazoesters. Furthermore, an enantioselective synthesis of 2-arylbicyclo[1.1.0]butane carboxylates was achieved by the use of  $\text{Rh}_2(R\text{-BTCP})_4$  as a catalyst under low catalyst loadings.

**Acknowledgment.** This work was supported by the National Science Foundation (CHE 1213246). We thank Dr. John Bacsá, Emory University, for the X-ray crystallographic analysis.

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

The authors declare no competing financial interest.