ORGANIC LETTERS

2013
Vol. 15, No. 2
310–313

Enantioselective Synthesis of 2-Arylbicyclo[1.1.0]butane Carboxylates

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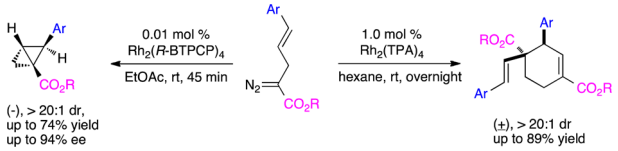
Received November 21, 2012

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 Rh_2(*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[1] and offers utility in complex molecule synthesis.[2] 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 γ-silyl elimination.[3] The metal-catalyzed synthesis of the bicyclo[1.1.0]butane system is relatively undeveloped. Previous approaches include the cyclopropanation of cyclopropenes[4] and intramolecular cyclopropanation of α-allyl diazo compounds,[5] 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 α-cinnamyldiazoacetate **1**. 1,2-Hydride migration could be a competing process in this transformation,[6]

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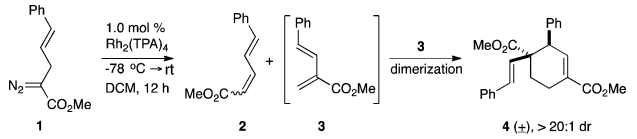
10.1021/ol303217s
Published on Web 01/03/2013

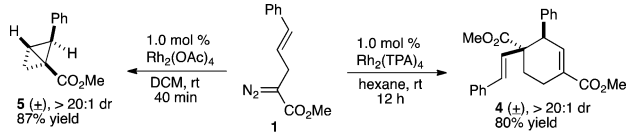
but recent studies by Fox suggested that it would be possible to circumvent this problem with the use of very bulky dirhodium catalysts.[7] Consequently, we began our inveti-gation with $Rh_2(TPA)_4$, an electron-rich and sterically crowded catalyst (Scheme 1). Although $Rh_2(TPA)_4$ catalyzed the decomposition of **1**, the catalyst failed to provide the desired bicyclo[1.1.0]butane product. Instead, a mixture of diene **2** and cyclohexene **4**[8] was obtained. Cyclohexene **4**, isolated in 69% yield, was presumably formed by dimerization of the diene **3**, which was produced *in situ*.

Scheme 1. $Rh_2(TPA)_4$-Catalyzed Decomposition of **1**



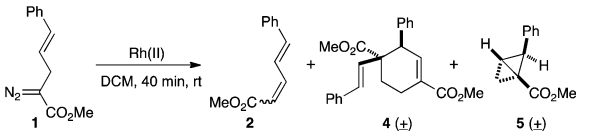
Further exploratory studies revealed that the product outcome was dependent on the reaction solvent, time, and catalyst (Scheme 2). When the reaction with $Rh_2(TPA)_4$ was conducted in hexane at room temperature in 12 h, cyclohexene **4** could be isolated in 80% yield; however, when $Rh_2(OAc)_4$ was 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 $Rh_2(OAc)_4$ 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 $Rh_2(OOct)_4$, **5** was formed in 85% isolated yield.

Table 1. Catalyst Loading Evaluation



entry	catalyst	cat. loading (mol %)	yield ratio (**2**/**4**/**5**)[a]	yield (%)[b]
1	$Rh_2(OPiv)_4$	1.0	10/10/80	62
2	$Rh_2(OPiv)_4$	0.01	4/trace/96	80
3	$Rh_2(OOct)_4$	1.0	16/18/66	60
4	$Rh_2(OOct)_4$	0.01	2/trace/98	85
5	$Rh_2(TPA)_4$	1.0	25/64/11	10
6	$Rh_2(TPA)_4$	0.01	8/33/59	47

[a] 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**. [b] 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,[9] $Rh_2(R\text{-DOSP})_4$, $Rh_2(S\text{-PTAD})_4$, and $Rh_2(S\text{-PTTL})_4$, 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, $Rh_2(4S\text{-MEOX})_4$,[10] a less reactive catalyt, 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 breakthough catalyst for high asymmetric induction was the triarylcyclopropane carboxylate complex $Rh_2(R\text{-BTPCP})_4$,[11] 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).

$Rh_2(R\text{-BTPCP})_4$ 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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(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 unabiguous assigment of the absolute configuration, but further analysis by determining the Hooft parameter (using Platon software) confirmed the tentative assignment.

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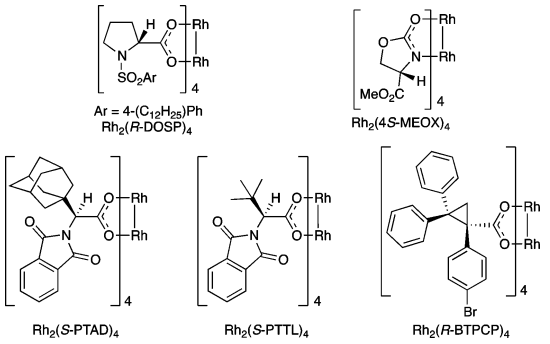
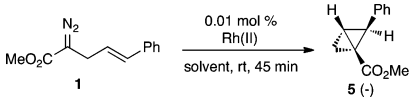


Figure 1. Chiral dirhodium catalysts.

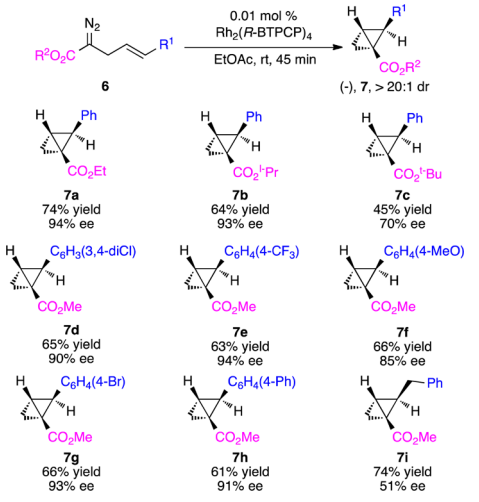
Table 2. Chiral Catalyst Evaluation



entry	catalyst	solvent	yield (%)[a]	ee (%)[b]
1	Rh_2(*R*-DOSP)$_4$	DCM	65	<5
2	Rh_2(*S*-PTAD)$_4$	DCM	64	47
3	Rh_2(*S*-PTTL)$_4$	DCM	69	52
4[c]	Rh_2(4*S*-MEOX)$_4$	DCM	42	−23
5	Rh_2(*R*-BTPCP)$_4$	DCM	72	90
6	Rh_2(*R*-BTPCP)$_4$	hexane	64	88
7	Rh_2(*R*-BTPCP)$_4$	acetone	60	94
8	Rh_2(*R*-BTPCP)$_4$	EtOAc	70	94

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

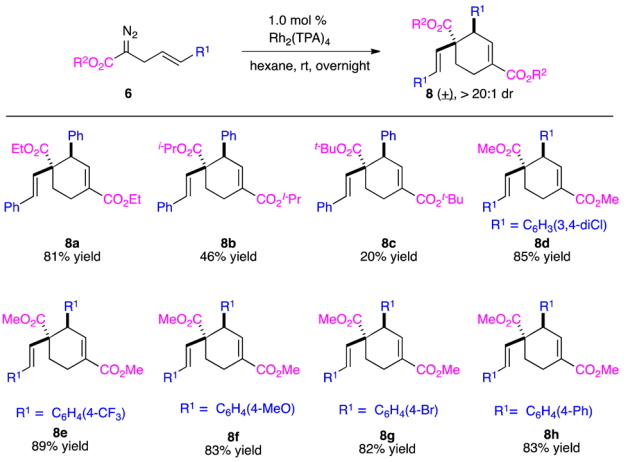
Scheme 3. Bicyclo[1.1.0]butane Carboxylate Formation



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).[8] The configuration of the other bicylco[1.1.0]butane products are tentatively assigned by analogy.

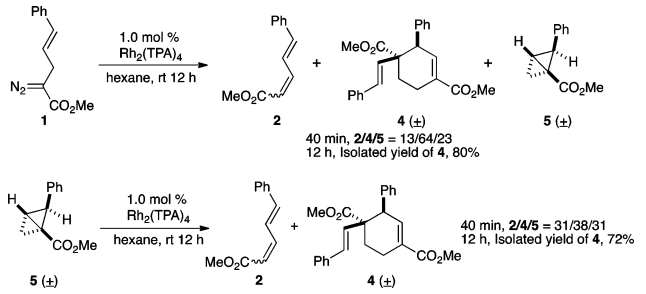
Even though bicyclobutanes could be isolated in high yield, these products could be totally eliminated when 1.0 mol % of Rh_2(TPA)$_4$ and extended reaction times were used. Under these conditions, cyclohexenes **8** were obtained in good yields (81−89%) for a variety of methyl cinnamyldiazoacetate **6** (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

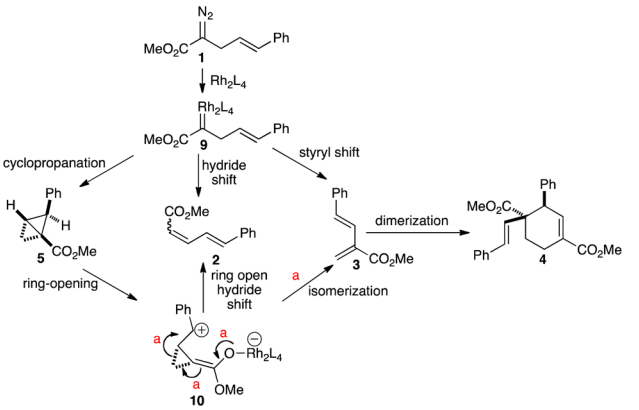


In order to probe the cause in the change in product distribution, further control experiments were conducted as illustrated in Scheme 5. The Rh_2(TPA)$_4$-catalyzed reaction of **1** was re-examined under short (40 min) and long (12 h) reaction times. After 40 min a mixture of the three products (**2**, **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_2(TPA)$_4$, 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_2(TPA)$_4$ 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



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



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 diasteroselective synthesis of 2-arylbicyclo[1.1.0]butane carboxylate and cyclohexene derivatives *via* a dirhodium-catalyzed decomposition of α-allyldiazoesters. Furthermore, an enantioselective synthesis of 2-arylbicyclo[1.1.0]butane carboxylates was achieved by the use of Rh_2(*R*-BTPCP)$_4$ as a catalyst under low catalyst loadings.

Acknowledgment. This work was supported by the National Science Foundation (CHE 1213246). We thank Dr. John Bacsa, 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.