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Catalyst-Controlled Formal [4 + 3] Cycloaddition Applied to the Total Synthesis of (+)-Barekoxide and (−)-Barekol

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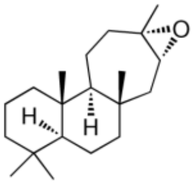
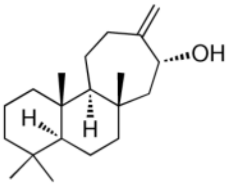
Abstract

The tandem cyclopropanation/Cope rearrangement between bicyclic dienes and siloxyvinyldiazoacetate, catalyzed by the dirhodium catalyst $Rh_2(R\text{-PTAD})_4$ effectively accomplishes enantiodivergent [4 + 3] cycloadditions. The reaction proceeds by a cyclopropanation followed by a Cope rearrangement of the resulting divinylcyclopropane. This methodology was applied to the synthesis (+)-barekoxide (**1**) and (−)-barekol (**2**).

Fused seven-membered carbocycles are present in a wide-variety of terpene natural products.[1] An effective method for the stereoselective synthesis of seven-membered rings is the formal [4 + 3] cycloaddition between vinylcarbenoids and dienes, which gives predictable diastereocontrol, proceeding through a Cope rearrangement of a *cis*-divinylcyclopropane intermediate.[2,3] Furthermore, chiral dirhodium tetracarboxylate catalysts enable high enantioselectivity to be achieved in these transformations.[4] Recently, the Sarpong group applied the formal [4 + 3] cycloaddition in a stereodivergent approach to the core of the cyanthane diterpenes.[5] This paper describes a collaborative study between the Davies and Sarpong groups, resulting in a greatly enhanced level of enantiomeric differentiation for this chemistry and its application to the synthesis of (+)-barekoxide (**1**) and (−)-barekol (**2**).[6]


barekoxide **(1)**


barekol **(2)**

The original studies by Sarpong were conducted on the diene (*S*)-**3** and the unsubstituted vinyldiazoacetate **4a** using the enantiomers of $Rh_2(DOSP)_4$[7] as catalysts (Table 1, entries 1 and 2).[5] Each enantiomer of the catalyst gave moderate control of which diastereomer of the tricyclic products (**5a** or **6a**) was formed. Davies has recently demonstrated that siloxyvinyldiazoacetate **4b** with $Rh_2(PTAD)_4$[8] is a good combination for highly enantioselective [4 + 3] cycloadditions.[3b,c] Therefore, the reactions of (*S*)-**3** were re-examined using siloxyvinyldiazoacetate **4b** as the carbenoid precursor.

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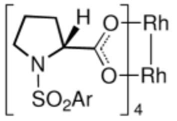
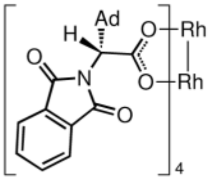
Supporting Information Available. Full experimental data for the compounds described in the paper; X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.



Ar = p-$(C_{12}H_{25})C_6H_4$

Rh_2(*R*-DOSP)$_4$



Ad = adamantyl

Rh_2(*R*-PTAD)$_4$

The reaction of (*S*)-**3** with **4b** catalyzed by Rh_2(*R*-DOSP)$_4$ gave exclusively the tricycle **5b**, whereas the reaction catalyzed by Rh_2(*S*-DOSP)$_4$ still gave a slight preference of **5b** over **6b** (entries 3 and 4). These results indicate that the substrate control in the reaction between (*S*)-**3** and **4b** favors the formation of **5b**, which is enhanced in the matched reaction using Rh_2(*R*-DOSP)$_4$ as catalyst. The mismatched reaction, however, with Rh_2(*S*-DOSP)$_4$ as catalyst gives a mixture of products.

The diastereocontrol of the [4 + 3] cycloaddition is further enhanced when the enantiomers of Rh_2(PTAD)$_4$ are used as catalysts. Once again in the matched reaction with Rh_2(*R*-PTAD)$_4$ as catalyst, **5b** is formed with high diastereoselectivity (entry 5). In this case, however, the mismatched reaction with Rh_2(*S*-PTAD)$_4$ as catalyst is also highly diastereoselective, generating **6b** exclusively (entry 6).

Having discovered that the siloxyvinyldiazoacetate **4b** gives much better stereodifferentiation than **4a**, the next series of reactions explored whether a resolution would be possible using (±)−**3**. The reaction of **4b** catalyzed by Rh_2(*R*-DOSP)$_4$ was highly diastereoselective, but the major diastereomer **5b** was produced in only 53% ee. In contrast, the reaction catalyzed by Rh_2(*R*-PTAD)$_4$ had excellent reagent control, in which **5b** was produced in 90% ee and the other diastereomer (*ent*-**6b)** was produced in 99% ee.

This transformation can also be effectively extended to a more sterically hindered diene (*S*)-**7,** using TIPS as the protecting group. The Rh_2(*R*-PTAD)$_4$-catalyzed reaction of (*S*)-**7** and the siloxydiazoacetate **4b** generated product **8** as a single diastereomer (entry 1, Table 3), whereas the reaction initiated by Rh_2(*S*-PTAD)$_4$ afforded the other isomer **9** with excellent diastereoselectivity (entry 2, Table 3). Extension of the study from a bicyclo[4.3.0]nonane to a bicyclo[4.4.0]decane system revealed the subtle controlling influences assocciated with this selectivity. The Rh_2(*R*-PTAD)$_4$-catalyzed reaction of diene (*S*)-**10** with siloxydiazoacetate **4b** generated two diastereomers of the formal [4 + 3] cycloadducts, **11** and **12** in a 9:1 ratio (entry 3, Table 2). The same reaction catalyzed by Rh_2(*S*-PTAD)$_4$ switched the diastereoselectvity, favoring **12** with a 4: 1 dr. These results indicate that the chiral catalyst has a conrolling influence on the diastereoselectvity in the bicyclo[4.4.0]decane system but the effect is not as overwhelming as it is in the bicyclo[4.3.0]nonane system.

With access to a range of diasteromeric bicyclo[4.4.0]decane-derived dienes, studies were then conducted to determine if the catalyst control could be extended to generate different pairs of diastereomeric products. Substrate (*S*)-**13** is epimeric to (*S*)-**10** at the siloxy carbon, which is closely positioned next to the diene. However, the catalyst effect is not greatly influenced by this change. The reaction of (*S*)-**13** with the siloxydiazoacetate **4b** catalyzed by Rh_2(*R*-PTAD)$_4$ afforded the formal [4 + 3] cycloadducts, **11** and **12** in a 4:1 dr (entry 5) whereas the Rh_2(*S*-PTAD)$_4$-catalyzed reaction favored **12** by a 7:1 dr (entry 6). The next series of experiments examined the influence of the ring fusion configuration on the selectivity. All the compounds to date have been cis-fused, but diene (*S*)-**16** is trans-fused. The Rh_2(*R*-PTAD)$_4$-catalyzed reaction of (*S*)-**16** with **4b** showed poor diastereoselectvity as the formal cycloadducts **17** and **18** were produced in only a 2: 1 dr (entry 7). However, the Rh_2(*S*-PTAD)$_4$-catalyzed reaction was much more diastereoselective, favoring **18** (16: 1 dr, entry 8). Even though these reactions do not display perfect catalyst control, they are still effective for the diastereoselective synthesis of the tricyclic product because six distinct diastereomers wre generated in isolated yields rnaging from 55–81%.

The stereochemistry of the [4 + 3] cycloaddition is controlled in the initial cyclopropanation. Theoretical calculations have shown that the alkene approaches in essentially an end-on mode,[9] whereas the Cope rearrangement of the divinylcyclopropane proceeds through a boat transition state.[2] Several studies have demonstrated that the same sense of asymmetry is obtained in the reaction catalyzed by either Rh_2(*R*-DOSP)$_4$ or Rh_2(*R*-PTAD)$_4$.[3b,c] These catalysts will cause the diene to approach from the front face as illustrated in Figure 1.[3b,c] This results in a matched double stereoselection because the siloxy group of the diene (*S*)-**3** is pointing away from the carbenoid during the cyclopropanation. The Cope rearrangement of the divinylcyclopropane would generate **5b**. The reaction of (*S*)-**3** catalyzed by Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$ are mismatched reactions, but the stereodirecting influence of Rh_2(*S*-PTAD)$_4$ is sufficiently strong to overwhelm the inherent stereodirecting influence of (*S*)-**3**, leading to the clean formation of **6b**.

With an understanding of the factors influencing optimal stereocontrol in hand, we then applied it to the synthesis of (+)-barekoxide and (−)-barekol. The requisite diene was prepared in three steps from commercially available scalerolide (see the Supporting Information for details). Due to the more sterically crowded nature of the double bond in the diene **19**, a higher temperature (70 °C) and 3–5 equivalents of **4b** were required for an efficient reaction. The Rh_2(*R*-PTAD)$_4$ catalyzed reaction gave a 6: 1 mixture of diastereomers favoring **20**, whereas the Rh_2(*S*-PTAD)$_4$ catalyzed reaction gave a 9: 1 mixture of diastereomers favoring **21**. The mixture of **20** and **21** was only slightly separable by chromatography on silica gel impregnated with 5% $AgNO_3$, but fortunately **20** could be selectively crystallized. In the Rh_2(*R*-PTAD)$_4$ catalyzed reaction, the pure desired diastereomer **20** was isolated in 47% yield after recrystallization. In this way, the configuration of a demanding quaternary stereocenter at the B–C ring fusion was effectively controlled.

The synthesis of (+)-barekoxide (**1**) and (−)-barekol (**2**) from the tricycle **20** was readily achieved as illustrated in Scheme 1. Palladium catalyzed hydrogenation of **20** generated **22** in essentially quantitative yield. Reduction of the ester in **22** followed by acidic hydrolysis of the silyl enol ether generated the enone **23** in 64% overall yield for the two steps. DIBAL-H reduction of the enone **23** generated the allylic alcohol **24**, an epimer of (−)-barekol (**2**), in 95% yield. Deoxygenation of **24** with double bond isomerization using the Gevorgyan procedure[10] followed by epoxidation with *m*-CPBA generated (+)-barekoxide (**1**) in 58% yield over two steps. Acid-catalyzed isomerization of (+)-barekoxide (**1**) to (−)-barekol (**2**)[11] was achieved in 73% yield using the reported literature procedure.[6a]

In summary, these studies demonstrate that the combination of the siloxyvinyldiazoacetate and Rh_2(*R*-PTAD)$_4$ is very effective in enantiodivergent [4 + 3] cycloadditions. The chiral catalyst controls the diastereoselectivity of the [4 + 3] cycloaddition and can overwhelm the inherent selectivity of the chiral substrate. Even in the system used for the synthesis of (+)-barekoxide (**1**) and (−)-barekol (**2**), which required elevated temperatures for an effective reaction, good levels of diastereocontrol was possible, enabling the stereoselective synthesis of an all-carbon quaternary center.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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2. For reviews, see: (a) Davies HML, Denton JR. Chem Soc Rev. 2009; 38:3061. [PubMed: 19847341] (b) Davies, HML. Advances in Cycloadditions. Harmata, M., editor. Vol. 5. JAI Press; Greenwich, CT: 1998. p. 119-164.
3. For recent examples, see: (a) Olson JP, Davies HML. Org Lett. 2008; 10:573. [PubMed: 18215048] (b) Reddy RP, Davies HML. J Am Chem Soc. 2007; 129:10312. [PubMed: 17685525] (c) Schwartz BD, Denton JR, Lian Y, Davies HML, Williams CM. J Am Chem Soc. 2009; 131:8329. [PubMed: 19445507]
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7. $Rh_2(S\text{-DOSP})_4$: Tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]-dirhodium (Cas 179162-34-6).
8. $Rh_2(S\text{-PTAD})_4$: Tetrakis[(*S*)-(+)-(1-adamantyl)-(*N*-phthalimido)acetato]-dirhodium(II) (Cas 909393-65-3).
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10. Gevorgyan V, Rubin M, Benson S, Liu J, Yamamoto Y. J Org Chem. 2000; 65:6179. [PubMed: 10987957]
11. The crystal structure of (−)-barekol (2) has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC-776944 has been allocated. It adopts two conformations in the crystal, which supports the structure analysis by Kashman.[6b]

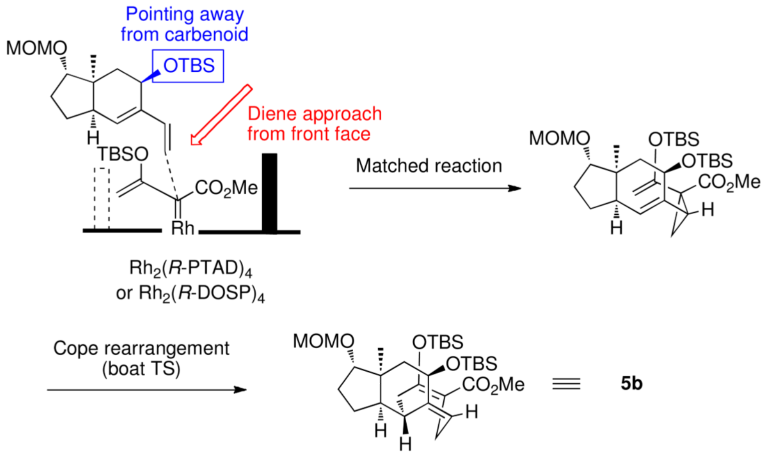
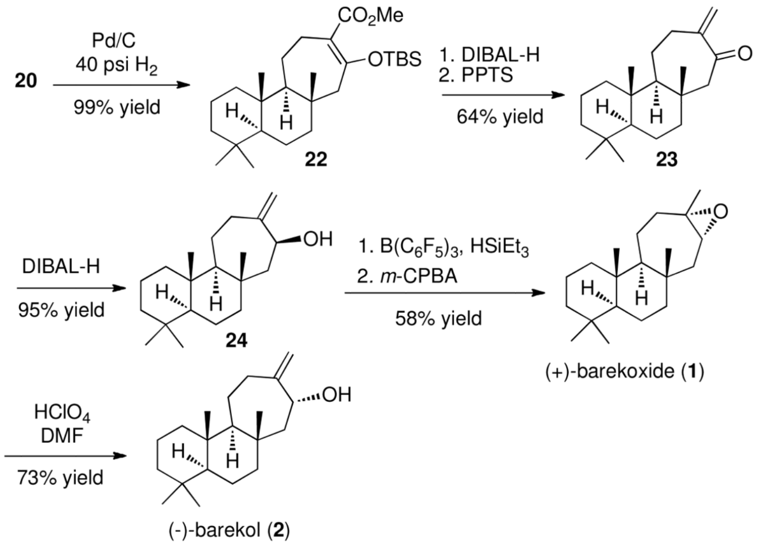


Figure 1.

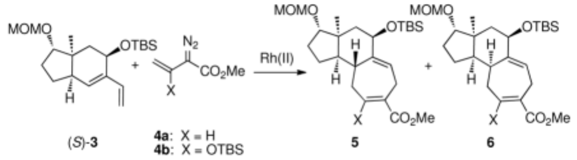
Stereochemical analysis of the matched reactions of (*S*)-**3**


20
Pd/C
40 psi H_2
99% yield
CO_2Me
OTBS
22
1. DIBAL-H
2. PPTS
64% yield
O
23
DIBAL-H
95% yield
OH
24
1. $B(C_6F_5)_3$, $HSiEt_3$
2. m-CPBA
58% yield
O
(+)-barekoxide (1)
$HClO_4$
DMF
73% yield
OH
(-)-barekol (2)
H
H

Scheme 1.

Table 1

Reaction between enantio-pure diene and diazoacetates



entry	substrate	catalyst	diazo	ratio (5/6)	yield (5+6, %)
1[a]	(*R*)-**3**	$Rh_2(R\text{-DOSP})_4$	**4a**	5:1[b]	39[c]
2[a]	(*R*)-**3**	$Rh_2(S\text{-DOSP})_4$	**4a**	1:5[b]	50[c]
3[d]	(*S*)-**3**	$Rh_2(R\text{-DOSP})_4$	**4b**	>19:1	76
4[d]	(*S*)-**3**	$Rh_2(S\text{-DOSP})_4$	**4b**	2:1	63
5[d]	(*S*)-**3**	$Rh_2(R\text{-PTAD})_4$	**4b**	>19:1	81
6[d]	(*S*)-**3**	$Rh_2(S\text{-PTAD})_4$	**4b**	<1:19	80

[a] Reactions were conducted at 8 °C in pentane with 3.0 equivalents of **4a** and 1 mol% catalyst;

[b] Determined by ^1H NMR;

[c] Isolated yields of the reduced ester protected as a *p*-nitrobenzoate;

[d] Reactions were conducted at 0 °C in PhMe with 3.0 equivalents of **4b** and 2 mol% catalyst.

Table 2

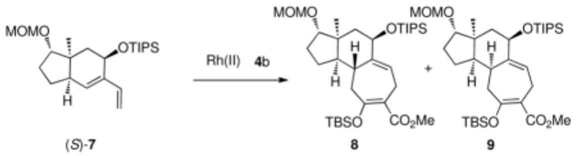
Reaction between racemic **3** and diazoacetate **4b**

catalyst	ratio (5 b/*ent*-6b)	yield (5b, %)	yield (*ent*-6b, %)	ee (5b, %)	ee (*ent*-6b, %)
$Rh_2(R\text{-DOSP})_4$	10:1	48	ND[a]	53	ND[a]
$Rh_2(R\text{-PTAD})_4$	1.7:1	39	25	90	99

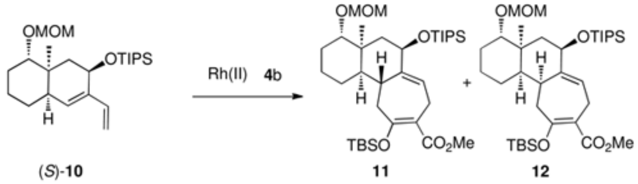
[a] Not determined.

Table 3

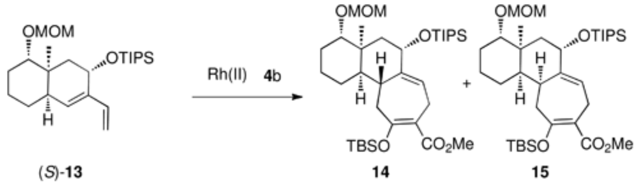
Reaction scope between enantio-pure diene and diazoacetate **4b**



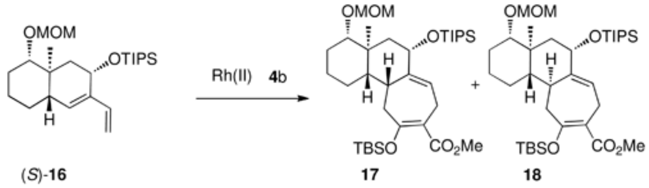
entry	catalyst	ratio (8/9)	yield (major isomer only, %)
1	Rh_2(*R*-PTAD)$_4$	>19:1	82
2	Rh_2(*S*-PTAD)$_4$	<1:19	76



entry	catalyst	ratio (**11**/**12**)	yield (major isomer only, %)
3	Rh_2(*R*-PTAD)$_4$	9:1	77
4	Rh_2(*S*-PTAD)$_4$	1:5	66



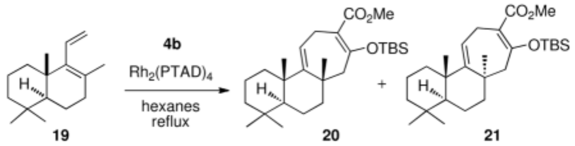
entry	catalyst	ratio (**14**/**15**)	yield (major isomer only, %)
5	Rh_2(*R*-PTAD)$_4$	4:1	63
6	Rh_2(*S*-PTAD)$_4$	1:7	69



entry	catalyst	ratio (**17**/**18**)	yield (major isomer only, %)
7	Rh_2(*R*-PTAD)$_4$	2:1	55
8	Rh_2(*S*-PTAD)$_4$	1:16	81

Table 4

Stereodivergent [4 + 3] cycloaddition



catalyst	ratio (4b/19)	dr (20/21)	yield (20 + 21, %)
Rh_2(*R*-PTAD)$_4$	5:1	6:1	65 (47[a])
Rh_2(*S*-PTAD)$_4$	3:1	1:9	63

[a] Isolated yield of pure **20**.