



Enantio- and diastereoselective cyclopropanation with *tert*-butyl α -diazopropionate catalyzed by dirhodium(II) tetrakis[*N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate]

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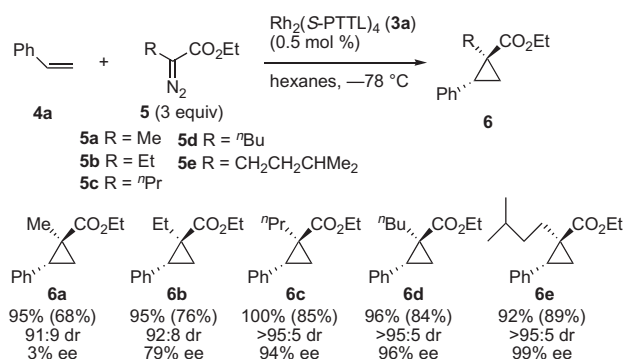
ABSTRACT

The first successful example of a catalytic asymmetric cyclopropanation with α -diazopropionates is described. The cyclopropanation reaction of 1-aryl-substituted and related conjugated alkenes with *tert*-butyl α -diazopropionate has been achieved by catalysis with dirhodium(II) tetrakis[*N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate], $\text{Rh}_2(\text{S-TBPTTL})_4$, providing the corresponding cyclopropane products containing a quaternary stereogenic center in good to high yields and with high diastereo- and enantioselectivities (*trans*:*cis* = 90:10 to >99:1, 81–93% ee).

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Substituted cyclopropanes are commonly encountered structural subunits in a wide variety of biologically important natural products and medicinal agents.¹ Since the pioneering work of Nozaki and Noyori in 1966,² the transition metal-catalyzed asymmetric cyclopropanation of alkenes with diazo compounds has emerged as one of the most direct and efficient routes to optically active cyclopropane building blocks.³ Over the past two decades, a number of powerful catalytic systems based on Cu(I),⁴ Co(II),⁵ Rh(II),⁶ Ru(II),⁷ and Ir(III)⁸ complexes of well-designed chiral ligands have been developed to achieve high enantio- and diastereoselectivity for cyclopropanation reactions with various types of diazo compounds.^{9–20} While the majority of successful asymmetric cyclopropanations reported involved the use of acceptor-substituted diazo compounds,^{4–8,10} most commonly diazoacetates,^{4–8} substantial progress in this field has recently been achieved by expanding the reaction scope to include donor/acceptor-substituted diazo compounds^{11–14} such as vinyl diazoacetates¹¹ and aryl diazoacetates,¹² as well as acceptor/acceptor-substituted carbene precursors^{15–22} such as nitrodiazoacetates,¹⁵ nitrodiazoketones,¹⁶ amidodiazoacetates,¹⁷ cyanodiazoacetamides,¹⁸ diazomalonates^{19,20} and related phenyliodonium ylide variants.²¹ However, asymmetric cyclopropanation with α -alkyl- α -diazooesters^{23–25} has remained elusive due to the propensity to form α,β -unsaturated esters via a 1,2-hydride

shift²⁶ in metal-carbene intermediates until a recent breakthrough by Fox et al.²⁷ Fox et al. developed highly enantio-, diastereo-, and chemoselective cyclopropanations of terminal aromatic alkenes and benzofuran with α -alkyl- α -diazooesters using dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**),²⁸ as a chiral catalyst in hexanes at -78°C . While this work was a notable landmark, the enantioselectivity was highly sensitive to the structure of the diazoester. Exceptionally high levels of enantioselectivity

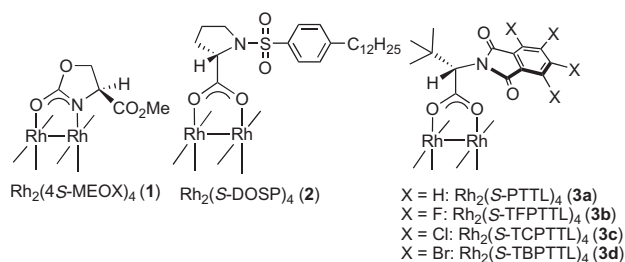


Scheme 1. Catalytic asymmetric cyclopropanation of styrene with α -alkyl- α -diazooesters catalyzed by $\text{Rh}_2(\text{S-PTTL})_4$ reported by Fox.²⁷ The isolated yields in parentheses were obtained when 1.1 equiv of styrene and 1.0 equiv of diazoesters were used.

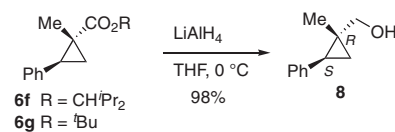
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(up to 99% ee) in cyclopropanations of styrene were achieved with diazoesters bearing larger α -alkyl groups than the α -ethyl substituent as the reaction with ethyl α -diazopropionate (**5a**) and ethyl α -diazobutanoate (**5b**) gave the corresponding cyclopropane products in 3% and 79% ee, respectively (Scheme 1).²⁷ Very recently, we reported the first example of catalytic asymmetric cyclopropanation of 1-alkynes with α -alkyl- α -diazoesters.²⁹ In this process, $\text{Rh}_2(\text{S-TBPTTL})_4$ (**3d**), a brominated analog of $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**), emerged as the catalyst of choice for achieving exceptionally high levels of asymmetric induction (up to 99% ee) as well as good to high selectivities over alkene formation via a 1,2-hydride shift. As part of our interest in further extension of the scope and utility of **3d**, we now address the issue of enantiocontrol in cyclopropanations with α -diazopropionates.²⁵ a virtually unmet challenge in Fox's cyclopropanation methodology.²⁷



Based on our previous work,²⁹ we initially explored the cyclopropanation of styrene (**4a**) (4 equiv) with 2,4-dimethyl-3-pentyl α -diazopropionate (**5f**) using 1 mol % of $\text{Rh}_2(\text{S-TBPTTL})_4$ (**3d**) in dichloromethane at -60°C . The reaction proceeded to completion within 7 h, giving the *trans*-cyclopropane product **6f** in 92% yield and 97:3 dr with no signs of the formation of alkene **7f** (Table 1, entry 1). As with the $\text{Rh}_2(\text{S-TBPTTL})_4$ -catalyzed cyclopropanation system,²⁹ no slow addition of **5f** was required. The *trans*-stereochemistry of **6f** was established by ^1H NOE between the C1 methyl group and *ortho* protons on the benzene ring. The enantioselectivity of this reaction was determined to be 84% ee by HPLC using a



Scheme 2. Determination of the absolute stereochemistry of **6f** and **6g**.

Daicel Chiralpak IC column. The preferred absolute stereochemistry of **6f** [$[\alpha]_D^{21} -104.2$ (c 1.01, CHCl_3) for 84% ee] was established as 1*R*,2*S* by its transformation [LiAlH_4 , THF, 0°C , 3 h] to the known *trans*-1-phenyl-2-methylcyclopropane-1-methanol [$[\alpha]_D^{22} -15.4$ (c 0.64, CHCl_3); lit.,²⁹ $[\alpha]_D^{21} -17.2$ (c 0.17, CHCl_3) for 95% ee of (1*R*,2*S*)-enantiomer] (Scheme 2). We next evaluated the performance of other dirhodium(II) carboxylates, $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**),²⁸ $\text{Rh}_2(\text{S-TFPTTL})_4$ (**3b**)³⁰ and $\text{Rh}_2(\text{S-TCPTTL})_4$ (**3c**).^{31,32} While all of these catalysts provided the *trans*-cyclopropane **6f** in high yields and with the same sense of asymmetric induction and similar high diastereoselectivity as those observed with $\text{Rh}_2(\text{S-TBPTTL})_4$ (**3d**), the highest level of enantioselectivity was only 69% ee, which was obtained using $\text{Rh}_2(\text{S-TCPTTL})_4$ (**3c**) (entries 1 vs 2–4). Clearly, **3d** proved to be by far the best choice for this transformation as well as for the asymmetric cyclopropanation reaction. An examination of the temperature profile demonstrated that lowering the reaction temperature from -60 to -78°C resulted in perfect *trans*-diastereoselectivity, though catalysis at -78°C required a significantly longer reaction time to reach completion and resulted in 86% ee (entry 5). Not unexpectedly, increasing the reaction temperature to -40 or -20°C was accompanied by a significant decrease in enantioselectivity while maintaining high diastereoselectivity (75% and 66% ee, entries 6 and 7). Using $\text{Rh}_2(\text{S-TBPTTL})_4$ as a catalyst, the effect of the ester moiety was also evaluated at -60°C . While the use of ethyl ester **5a** resulted in lower enantioselectivity (35% ee, entry 8), the reaction with *tert*-butyl ester **5g** afforded the *trans*-cyclopropane product **6g** as a single diastereomer in high yield and with somewhat higher enantioselectivity

Table 1
Enantio- and diastereoselective cyclopropanation of styrene with α -diazopropionates catalyzed by dirhodium(II) carboxylates^a

Reaction scheme showing the cyclopropanation of **4a** (4 equiv) with **5** (diazoester) in the presence of a Rh(II) complex (1 mol %) in CH_2Cl_2 to form cyclopropane **6**. A side reaction shows the formation of **6f** from **5** and a diazoester with $\text{R} = \text{CH}^i\text{Pr}_2$, with a 2.5% NOE indicated. A box lists: **7f** $\text{R} = \text{CH}^i\text{Pr}_2$, **7g** $\text{R} = ^i\text{Bu}$, **7a** $\text{R} = \text{Et}$, and "not detected".

Entry	α -Diazoesters		Rh(II) catalyst	Temp ($^{\circ}\text{C}$)	Time (h)	Cyclopropanes			
		R				Yield ^b (%)	<i>trans</i> : <i>cis</i> ^c	Ee ^d (%)	
1	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-60	7	6f	92	97:3	84
2	5f	CH^iPr_2	$\text{Rh}_2(\text{S-PTTL})_4$ (3a)	-60	4	6f	89	94:6	47
3	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TFPTTL})_4$ (3b)	-60	3	6f	86	92:8	33
4	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TCPTTL})_4$ (3c)	-60	3	6f	89	95:5	69
5	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-78	48	6f	86	>99:1	86
6	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-40	2	6f	92	96:4	75
7	5f	CH^iPr_2	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-20	0.5	6f	90	94:6	66
8	5a	Et	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-60	2	6a	80	91:9	35
9	5g	^iBu	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-60	2	6g	94	>99:1	88
10	5g	^iBu	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-78	6	6g	92	>99:1	90
11 ^e	5g	^iBu	$\text{Rh}_2(\text{S-TBPTTL})_4$ (3d)	-78	8	6g	87	>99:1	92

^a All reactions were carried out as follows: Rh(II) catalyst (1 mol %) was added to a solution of **4a** (0.8 mmol, 4 equiv) and **5** (0.2 mmol) in CH_2Cl_2 (0.1 M).

^b Isolated yield.

^c Determined by ^1H NMR spectroscopy of the crude reaction mixture.

^d Determined by HPLC analysis. See Supplementary data for details.

^e 2 equiv of **4a** was used.

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