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In Search of High Stereocontrol for the Construction of *cis*-Disubstituted Cyclopropane Compounds. Total Synthesis of a Cyclopropane-Configured Urea-PETT Analogue That Is a HIV-1 Reverse Transcriptase Inhibitor

Wenhao Hu, Daren J. Timmons, and Michael P. Doyle*

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

mdoyle@u.arizona.edu

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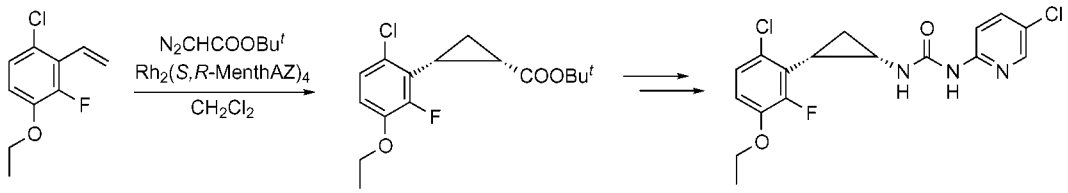
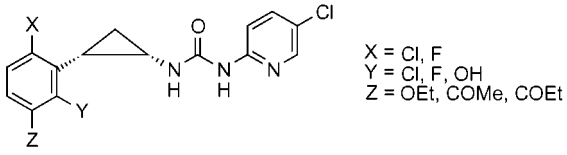
ABSTRACT



A new azetidine-ligated dirhodium(II) catalyst that possesses a *l*-menthyl ester attachment provides significant diastereocontrol and high enantiocontrol for the formation of *cis*-cyclopropane products from reactions of substituted styrenes with diazo esters.

Recently considerable attention has been directed to a new class of potent non-nucleoside HIV-1 reverse transcriptase inhibitors structurally defined as phenylethylthiazolylthiourea (PETT) derivatives.[1−4] Subsequent research revealed that the urea-PETT analogues had toxicological and pharmacokinetic advantages over the thiourea derivatives and that their antiviral activity in cell culture in the presence of human serum was superior to that of the thiourea compounds.[5,6] The most advantageous of the compounds examined were *cis*-cyclopropyl derivatives, designated by **1**, but stereoselective synthesis of the *cis*-disubstituted ring from a multisubstituted styrene was the greatest obstacle.



1

The preparation of *cis*-disubstituted cyclopropane compounds has been particularly challenging, but several catalytic

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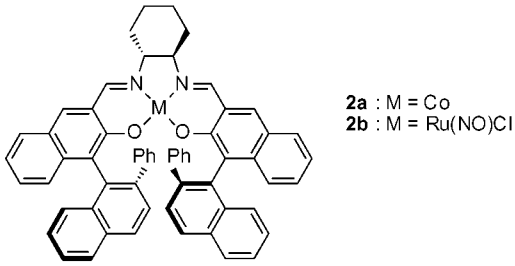
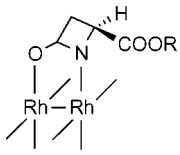
methodologies have been advanced to address this need. Katsuki has reported remarkably high *cis*-selectivity (up to 98:2) and very high enantioselectivity (up to 98% ee) for reactions of styrene with *tert*-butyl diazoacetate.[7,8] Use of the cobalt-salen complex **2a** showed distinct advantages in reactivity and product yield over the ruthenium complex **2b**. Other reports have documented enhanced *cis*-selectivity over



2a : M = Co
2b : M = Ru(NO)Cl

standard copper catalysts, but none with high enantiocontrol.[9−11] We have previously reported that dirhodium(II) tetrakis[alkyl 2-oxaazetidine-4(*S*)-carboxylates] (**3**) offer



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a : Rh_2(4*S*-IBAZ)$_4$

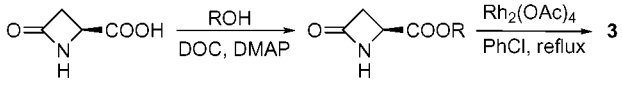
b : (1*R*, 2*S*, 5*R*) Rh_2(4*S*,*S*-MenthAZ)$_4$

c : (1*S*, 2*R*, 5*S*) Rh_2(4*S*,*R*-MenthAZ)$_4$

modest *cis*-selectivity in reactions of diazoacetates with styrene (up to 69:31 with **3a**),[12] but their advantages in ligand simplicity did not outweigh the much lower selectivities that characterized their applications. We now report a new azetidine-ligated dirhodium(II) catalyst that, possessing a chiral ester attachment, offers dynamic match/mismatch for cyclopropanation of substituted styrenes that favors formation of *cis*-cyclopropane isomers with high enantiocontrol. Application to the synthesis of one representative structure for **1** has allowed the resolution of significant reactivity/selectivity problems associated with the cyclopropanation of ortho-substituted styrenes.

Menthyl esters of 2-oxaazetidine-4(*S*)-carboxylate were prepared in good yield and affixed to the dirhodium(II) core by standard methods (Scheme 1). Spectral characterization

Scheme 1



ROH = *d*-menthol (**b**)
or *l*-menthol (**c**)

established them as the (*cis*-2,2)-dirhodium(II) isomers, meaning that each rhodium was linked to two nitrogen and two oxygen atoms and that each set had their atoms *cis* rather than *trans*. The menthyl esters were selected from a series of 2-oxaazetidine-4(*S*)-carboxylates having chiral ester substituents, including those from methyl lactate and methyl mandelate, on the basis of the selectivities that their derivative catalysts exhibited in cyclopropanation reactions, but only those with the menthyl esters, Rh_2(*S*,*S*-MenthAZ)$_4$ and Rh_2-(*S*,*R*-MenthAZ)$_4$, will be reported here.

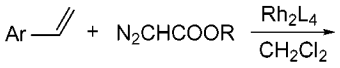
In preliminary determinations with styrene and a series of diazoacetates (Table 1), both diastereoselectivities and

Table 1. Cyclopropanation of Styrene with Various Diazoacetates Catalyzed by Rh_2(*S*,*S*-MenthAZ)$_4$ (**3b**) and Rh_2(*S*,*R*-MenthAZ)$_4$ (**3c**)[a]

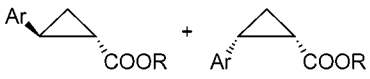
$N_2CHCOOR$, R =	catalyst	product yield, %[b]	***c*-4:*t*-4**[c]	% ee ***c*-4**[c]	% ee ***t*-4**[c]
Et	**3b**	68	63:37	67	23
	3c	67	73:27	83	48
t-Bu	**3b**	53	58:42	77	25
	3c	47	74:26	94	71
d-menthyl	**3b**	85	50:50	83	38
	3c	65	54:46	83	54
l-menthyl	**3b**	78	58:42	83	47
	3c	70	66:34	90	70

[a] Reactions were performed with 1.0 mol % of catalyst in refluxing CH_2Cl_2 with a 1-h addition of the diazo compound to 10 equiv of styrene. [b] Isolated yield of cyclopropane products following column chromatography. [c] Determined by GC.

enantioselectivities were seen to reflect structural match/mismatch with the diastereomeric dirhodium(II) catalysts (eq



a : R = Et
b : R = *t-Bu*
c : R = *d*-menthyl
d : R = *l*-menthyl



***t*-4** ***c*-4** (1)

1). Catalyst **3c** gives higher preference for the *cis*-diastereomer and higher enantiocontrol than does catalyst **3b**. The

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menthyl diazoacetates offered no advantage, especially because diastereoselection was diminished relative to reactions in which smaller diazoacetates were used. Optimal results were obtained with the use of *tert*-butyl diazoacetate and $Rh_2(S,R\text{-MenthAZ})_4$.

The absolute configuration of ***c*-4** was established by comparing the observed optical rotation with that of the known compound previously reported by Katsuki.[8] Its positive rotation corresponded to an absolute configuration for ***c*-4** of (1*S*,2*R*). That for ***t*-4** was not determined but was assumed by analogy to be (1*R*,2*R*).

Application to a series of substituted styrenes and *tert*-butyl diazoacetate provided the results that are reported in Table 2. Here comparison is made to the diastereoselectivities

Table 2. Cyclopropanation of Substituted Styrenes with *tert*-Butyl Diazoacetate Catalyzed by $Rh_2(S,R\text{-MenthAZ})_4$ (**3c**)[a]

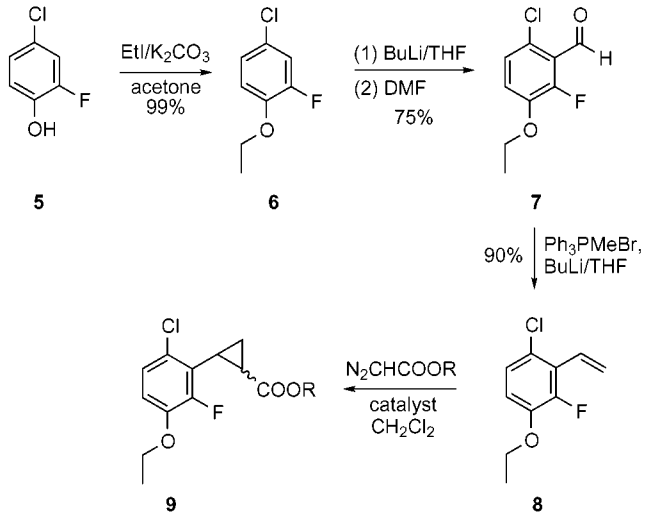
Z-styrene, Z =	catalyst	product yield, %[b]	***c*-4**:***t*-4**[c]	% ee ***c*-4**[d]	% ee ***t*-4**[d]
a: *p*-methyl	$Rh_2(OAc)_4$	68	35:65		
	3c	54	72:28	93	nd
b: *p*-trifluoromethyl	$Rh_2(OAc)_4$	64	34:66		
	3c	25	72:28	81	81
c: *o*-chloro	$Rh_2(OAc)_4$	63	34:66		
	3c	47	71:29	95	nd
d: 2,6-dichloro	$Rh_2(OAc)_4$	60	45:55		
	3c	39	86:14	97	nd
e: 2,4,6-trimethyl	$Rh_2(OAc)_4$	69	42:58		
	3c	44	92:8	97	76

[a] Reactions were performed with 1.0 mol % of catalyst in refluxing CH_2Cl_2 with a 5-h addition of *tert*-butyl diazoacetate to 10 equiv of the substituted styrene. [b] Isolated yield of cyclopropane products following column chromatography. [c] Determined by GC using a SPB-5 column. [d] Determined by GC on Chiraldex columns. nd = not determined.

obtained from $Rh_2(OAc)_4$. Enantioselectivities from the use of $Rh_2(S,R\text{-MenthAZ})_4$ are remarkably similar, except for cyclopropanation of the styrene having the electron-withdrawing *p*-trifluoromethyl substituent. When both ortho positions of styrene are substituted, diastereoselectivity favoring the *cis*-cyclopropane isomer increases without diminishing enantioselectivity (with **3c**). With 2,4,6-trimethylstyrene, for example, the *cis*:*trans* product ratio reached 92:8 with $Rh_2(S,R\text{-MenthAZ})_4$, and enantioselectivity for the dominant isomer was 97% ee. However, the reactivities of the ortho-disubstituted styrenes were slower than that for styrene, presumably because of the inability of the alkene to achieve orbital alignment with the benzene ring. In a competing experiment in which 10 equiv each of styrenes and 2,4,6-trimethylstyrene were used, the cyclopropane products, each set exhibiting the same selectivities as are reported in Table 2, showed a relative reactivity of styrene to 2,4,6-trimethylstyrene of 1.6:1. This structural congestion is the probable cause for the significantly enhanced diastereoselectivity achieved in these cyclopropanation reactions. The absolute configurations of these products were assumed to be the same as those formed by cyclopropanation of styrene.

Application now to a representative cyclopropane compound from which **1** could be constructed, we targeted **9**, which was prepared by the sequence of steps that is outlined in Scheme 2. Previously the racemic ***cis*-9** was produced in

Scheme 2



only 20% yield with a CuI/$Pd(OAc)_2$ catalyst,[5] but Aggarwal prepared directly the corresponding racemic cyclopropylamine from *N*-vinyl phthalimide and a phenyldiazomethane precursor in 76% yield (*cis*:*trans* = 85:15).[13] Our efforts to prepare **9c** are revealed in the data of Table 3. Note that the

Table 3. Cyclopropanation of Styrene **8**; Catalyst and Diazo Compound Influence on Stereoselectivity[a]

catalyst	$N_2CHCOOR$, R =	yield **9c**, %[b]	**9c**:**9t**[c]	% ee **9c**[d]
$Rh_2(OAc)_4$	Et	30	42:58	
3a	Et	32	75:25	80
	d-menthyl	0		
Cu(box)OTf[e]	Et	29	51:49	89
3c	Et	42	72:28	86
	Et	52[f]	79:21	86
	t-Bu	21[f]	82:18	97

[a] Unless specified otherwise, reactions were performed with 1.0 mol % of catalyst in refluxing CH_2Cl_2 with a 5-h addition of diazoacetate to 10 equiv of **8** with initial [**8**] = 0.2 M. [b] Isolated yield of **9c** only. [c] Determined by GC on a SPB-5 column. [d] Determined by GC on a Chiraldex B-DM column. [e] 5 mol % of catalyst was used. [f] [**8**] = 1.8 M.

yields given for **9c** are those for the pure *cis*-isomer following chromatography.

Diastereoselectivity for cyclopropanation of **8** was predictable from results obtained for 2,6-dichlorostyrene, but as can be seen from results in Table 3 the use of $Rh_2(4S\text{-IBAZ})_4$ (**3a**) afforded modestly higher preference for the *cis*-

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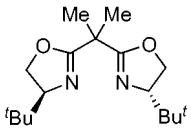
cyclopropane isomer than did Rh_2(*S*,*R*-MenthAZ)$_4$ (**3c**). However, enantioselectivity with Rh_2(*S*,*R*-MenthAZ)$_4$ was greater than with Rh_2(4*S*-IBAZ)$_4$. Modest improvement in diastereoselectivity and in product yield was achieved with highly concentrated **8**, and we attribute this to a solvent effect; enantioselectivity was unaffected by the increase in concentration for **8**. Use of Cu(box)OTf (box = **10**)[14] gave a reasonable level of enantioselectivity for the *cis*-isomer **9c**, but diastereoselectivity was low.



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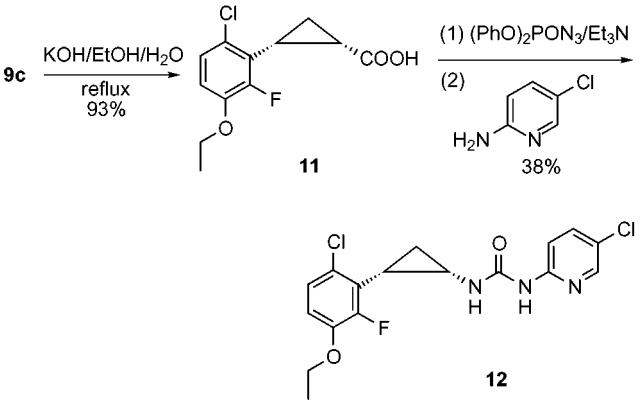
The *cis*-cyclopropane isomer from reaction with ethyl diazoacetate was converted to the urea-PETT derivative **12** by the sequence of steps outlined in Scheme 3. The overall process from styrene **8** could be accomplished in four steps in modest yield but high selectivity. Efforts are underway to improve the overall conversion and to develop the generality of this *cis*-selective cyclopropanation process. The simplicity of the ligands and the tolerance of dirhodium(II) catalysts for multisubstituted styrenes makes this methodology especially attractive.[15]

Scheme 3



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Supporting Information Available: Experimental and spectral data that include the synthesis and characterization of catalysts **3b** and **3c** and relevant information for compounds **4**−**9** and **11**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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