ORGANIC LETTERS

2004
Vol. 6, No. 23
4347−4350

Rh(II)-Catalyzed Enantioselective Cyclopropanation of Olefins with Dimethyl Malonate via in Situ Generated Phenyliodonium Ylide

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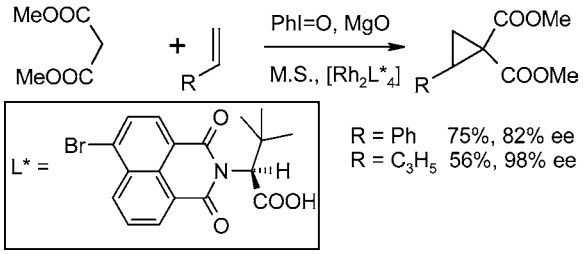
Received September 13, 2004

ABSTRACT



Olefins are cyclopropanated with dimethyl malonate (1a) iodosylbenzene (PhI═O) and a Rh(II) carboxylate catalyst via an in situ generated phenyliodonium ylide (1c). Enantioselectivities of up to 90% for 4-bromostyrene and 98% for pent-1-ene have been observed with (*S*)-*N*-4-bromo-1,8-naphthanoyl-*tert*-leucine (4c) as the chiral ligand. The same catalyst was effective for olefin cyclopropanation with Meldrum's acid, giving cyclopropanes with 96% (with styrene) and 87% ee (with pent-1-ene), respectively.

The transition-metal-catalyzed asymmetric cyclopropanation of olefins with diazomalonate esters is notoriously difficult.[1] Cu catalysts are generally not sufficiently reactive to effect decomposition of the diazo esters under mild conditions and, in addition, produce only modest enantioselectivities.[2] The same applies to the majority of the Rh(II) carboxamidate catalysts, except Doyle's $[Rh_2\{(S)\text{-bnaz}\}_4]$.[1] The Rh(II) carboxylates, in turn, are capable of decomposing diazomalonates but do not lead to satisfactory enantioselectivities in olefin cyclopropanations.[3] Thus, the highest enantioselectivity reported so far for dimethyl diazomalonate (**1b**) is 50% for the cyclopropanation of 4-trifluoromethylstyrene with $[Rh_2\{(S)\text{-bnaz}\}_4]$. The parent styrene, in turn, was cyclopropanated with only 40% ee.[1]

Some years ago, we reported olefin cyclopropanations upon decomposition of the phenyliodonium ylide **1c** derived from dimethyl malonate (**1a**) in the presence of $[Rh_2(OAc)_4]$.[4] Selectivity studies revealed that the main pathway of these reactions involved metallocarbene intermediates, although there was also evidence for competing secondary reactions of unknown nature. Apparently, metallocarbene intermediates are also formed upon decomposition of phenyliodonium ylides with copper catalysts,[5,6]

Phenyliodonium ylides may be generated and decomposed in situ. Thus, Dauban recently described the cyclopropanation of styrene in 55% yield with dimethyl malonate and iodosylbenzene (PhI═O) in the presence of $[Cu(acac)_2]$ via the intermediate ylide **1c**.[7] By analogy, Cu-catalyzed asym-

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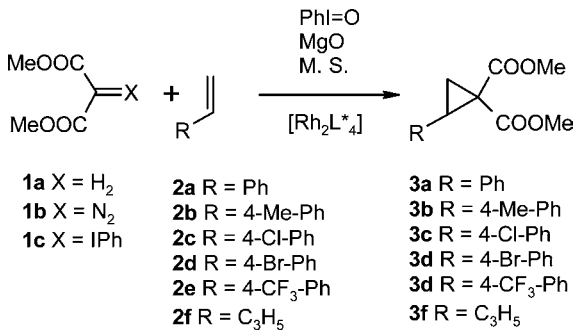
10.1021/ol048159u CCC: $27.50
Published on Web 10/12/2004

Scheme 1. Rh(II)-Catalyzed Cyclopropanation with Diethyl Malonate (**1a**)



1a X = H_2
1b X = N_2
1c X = IPh

2a R = Ph
2b R = 4-Me-Ph
2c R = 4-Cl-Ph
2d R = 4-Br-Ph
2e R = 4-CF_3-Ph
2f R = C_3H_5

3a R = Ph
3b R = 4-Me-Ph
3c R = 4-Cl-Ph
3d R = 4-Br-Ph
3d R = 4-CF_3-Ph
3f R = C_3H_5

metric nitrene transfer to olefins occurred upon treatment of sulfonamides with PhI═O in the presence of Cu catalysts via intermediate iminoiodinanes.[7,8]

In parallel, Du Bois developed a system capable of nitrene transfer from sulfonamidates and carbamates via in situ generated phenyliodinanes by means of iodobenzene diacetate ($PhI(OAc)_2$) in the presence of Rh(II) carboxylate catalysts.[9] This suggested the possibility of Rh(II)-catalyzed carbene transfer using CH acidic compounds and $PhI(OAc)_2$ as precursors for phenyliodonium ylides. Charette reported the first Rh(II)-catalyzed enantioselective carbene transfer starting from α-nitro esters or ketones and $PhI(OAc)_2$.[10] An analogous system, using Meldrum's acid as ylide precursor, was independently developed by ourselves.[11] We have now optimized Rh(II)-catalyzed cyclopropanations of terminal olefins with dimethyl malonate (**1a**) via the intermediate phenyliodonium ylide **1c** (Scheme 1).

The reaction conditions were optimized with $[Rh_2(OAc)_4]$ as catalyst. Initially, reactions were carried out with $PhI(OAc)_2$ as oxidant for the generation of the ylide, as previously reported for Meldrum's acid;[11] however, more satisfactory results were obtained with iodosylbenzene (PhI═O)[7] in the presence of MgO and molecular sieves (Table 1).

The asymmetric cyclopropanation of styrene was examined with a series of Rh(II) catalysts with 1,8-naphthoyl-protected *tert*-leucine as the ligand (Table 2). The ee of the product was determined by capillary GC[12,13] and the absolute configuration from the optical rotation.[14] The parent $[Rh_2\{(S)\text{-nttl}\}_4]$ catalyst,[15] which had been particularly suitable for cyclopropanations with (silanyloxyvinyl)diazoacetate,[16] was only moderately successful and afforded the cyclopropane **3a** with 37% ee. However, to our surprise the situation improved markedly when substituents were introduced into the 4-position of the naphthalene ring of the chiral ligand and the enantioselectivities reached 82% with the 4-bromo derivative,[17] $[Rh_2\{(S)\text{-4-Br-nttl}\}_4]$ (**4c**) at room temperature, while $[Rh_2\{(S)\text{-4-Cl-nttl}\}_4]$ (**4b**) and $[Rh_2\{(S)\text{-4-NO}_2\text{-nttl}\}_4]$ (**4d**) were somewhat less efficient, although still superior to the parent **4a** (Figure 1). When the temperature was lowered, yield and ee decreased significantly. This unexpected trend may be due to solubility problems.

Table 1. Optimization of Reaction Conditions for Cyclopropanation of Styrene (**2a**) with $[Rh_2OAc)_4]$[a]

entry	oxidant	additive[b]	MS[c]	yield of **3a** (%)
1	$PhI(OAc)_2$	MgO	+	9
2	$PhI(OAc)_2$	Al_2O_3	+	6
3	PhI═O	none	−	20
4	PhI═O	MgO	−	67
5	PhI═O	Al_2O_3	−	25
6	PhI═O	none	+	33
7	PhI═O	MgO	+	80
8	PhI═O	Al_2O_3	+	45

[a] In CH_2Cl_2 (10 mL) at 10 °C for 10 min and then stirring at rt for 4 h, 1.4 equiv of oxidant, 5 mol % of $[Rh_2(OAc)_4]$, 10 equiv of styrene (**2a**), 1.5 mmol of **1a** (added last). [b] 2.3 equiv of additive. [c] MS: molecular sieves 4 Å, 250 mg.

Table 2. Enantioselective Cyclopropanation of Styrene (**2a**) with Substituted $[Rh_2\{(S)\text{-nttl}\}_4]$ Catalysts[a]

catalyst	no.	*T* (°C)	yield (%)	ee (%)	config (**3a**)
$[Rh_2\{(S)\text{-nttl}\}_4]$	**4a**	rt	72	37	*R*
$[Rh_2\{(S)\text{-4-Cl-nttl}\}_4]$	**4b**	rt	77	66	*R*
$[Rh_2\{(S)\text{-4-Br-nttl}\}_4]$	**4c**	rt	75	82	*R*
$[Rh_2\{(S)\text{-4-Br-nttl}\}_4]$	**4c**	0	56	66	*R*
$[Rh_2\{(S)\text{-4-Br-nttl}\}_4]$	**4c**	−70	40	44	*R*
$[Rh_2\{(S)\text{-4-NO}_2\text{-nttl}\}_4]$	**4d**	rt	60	66	*R*

[a] Conditions: in CH_2Cl_2 (5.0 mL), 10 mmol of **1a** (1.14 mL), 1.4 equiv of PhI═O, 2.3 equiv of MgO, 250 mg of molecular sieves 4 Å, 10 equiv of styrene (**2a**), 5 mol % catalyst. [b] Determined from optical rotation and GC retention time.

Unsatisfactory results were obtained when *tert*-leucine was replaced by phenylalanine as ligand for the Rh(II) catalysts.[18] In addition, use of Mosher's acid as ligand[19] provided the cyclopropane **3a** in 33% yield and with 22% ee.

The electronic substituent effect of the styrene was investigated with $[Rh_2\{(S)\text{-4-Br-nttl}\}_4]$ (**4c**) as catalyst, and

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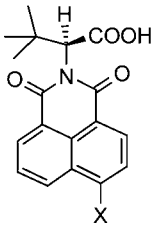

4a X = H [Rh_2{(*S*)-nttl}$_4$]
4b X = 4-Cl [Rh_2{(*S*)-4-Cl-nttl}$_4$]
4c X = 4-Br [Rh_2{(*S*)-4-Br-nttl}$_4$]
4d X = 4-NO_2 [Rh_2{(*S*)-4-NO_2-nttl}$_4$]

Figure 1. Ligands L*H and abbreviations for [Rh_2{(*S*)-nttl}$_4$] catalysts.

the results are summarized in Table 3. Note that in comparison to previous results reported in the literature for

Table 3. Asymmetric Cyclopropanation of Olefins with Dimethyl Malonate (**1a**) in the Presence of [Rh_2{(*S*)-4-Br-ntt}$_4$] (**4c**)[a]

olefin	R	yield (%)	ee (%)	config[b]
2a	Ph	75	82	*R*
2b	4-Cl-Ph	71	65	*R*
2c	4-MePh	62	87	*R*
2d	4-Br-Ph	65	90	*R*
2e	4-CF_3-Ph	63	87	*R*
2f	C_3H_5	56	98	*S*

[a] Conditions: in CH_2Cl_2 (5.0 mL), 10 mmol of **1a** (1.14 mL), 1.4 equiv of PhI=O, 2.3 equiv of MgO, 250 mg of molecular sieves 4 Å, 10 equiv of olefin (**2a**−**f**), 5 mol % of **4c**. [b] Determined from optical rotation and GC retention time for **2a**, **2b**, and **2f**; other assignments by analogy.

cyclopropanation with diazomalonate ester, the ee increased from 40 to 84% for the parent styrene (**2a**) and from 50 to 87% for the 4-trifluoromethyl derivative **2e**,[1] but the best result (90% ee) was obtained with 4-bromostyrene (**2d**). Pent-1-ene (**2f**) reacted in somewhat lower yield but with exceptional enantioselectivity of 98%. The absolute configuration of (*R*)-**3a** follows from its optical rotation: For (*R*)-**3a**, $[\alpha]^{24}_D = +57$ (*c* 0.3, PhH for 82% ee) (lit.[14] $[\alpha]^{23}_D = -124$ (*c* = 2.23, PhH for (*S*)-**3a**)). For (*R*)-**3b**, $[\alpha]^{24}_D = +46.1$ (*c* 0.7, PhH for 65% ee) (lit.[20] $[\alpha]_D = +117$ for (*R*)-**3b**). The (*R*)-configuration of the other cylcopropanes derived from styrenes (**3c**−**e**) was assigned by analogy and on the grounds of their positive optical rotation, which is consistent with that of **3a** and **3b**. Compound **3f** in turn had (*S*)-configuration ($[\alpha]^{24}_D = +82.5$ (*c* 0.4, PhH for 98% ee) (lit.[15] $[\alpha]^{24}_D = +27.4$ (*c* 1.10, $CHCl_3$ for 58% ee)) for (*S*)-**3f**. Thus, the cyclopropanes **3** are homochiral with respect to those obtained upon olefin cyclopropanation with Meldrum's acid in the presence of [Rh_2{(*S*)-nttl}$_4$] as catalyst.[12] Note that the configurational change in going to the (*R*)-phenyl-substituted cyclopropanes **3a**−**e** to the propyl-substituted **3f** is simply a consquence of the CIP priority rules.

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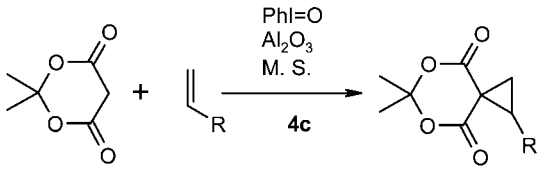
Scheme 2. Rh(II)-Catalyzed Cyclopropanation with Meldrum's Acid (**5**)



5

6a R = Ph 76%, 92% ee
6b R = C_3H_7 65%, 87% ee

The substituent effect observed in this series of catalysts is surprising, and we are unable to propose a satisfactory rationalization. A polar effect of the substituents on the active site of the catalyst seems unlikely owing to the large distance between the Rh atoms and the substituents in the complex. Although Hashimoto has indeed reported significant changes in enantioselectivities in Rh(II)-catalyzed nitrene-transfer reactions upon introduction of halogen substituents into the pttl ligand, the systems are not directly comparable. The enantioselectivity for nitrene insertion of indan increased from 27% with [Rh_2{(*S*)-pttl}$_4$] (*N*-phthaloyl-*tert*-leucine as ligand) to 70% with the tetrachloro derivative [Rh_2{(*S*)-tcpttl}$_4$] at −23 °C.[21] In the case of [Rh_2{(*S*)-tcpttl}$_4$], the effect is due to the presence of four halogen substituents, but only one substituent is present in the [Rh_2{(*S*)-nttl}$_4$]. Modeling studies reveal that the nttl ligands are conformationally mobile owing to rotation around the C−N bonds. Conceivably, dipolar interactions of the substituents might lead to changes in the orientation of the aromatic moieties of the ligands and thereby change the chiral environment of the coordinated carbene. Unfortunately, it was so impossible to obtain crystal structures of any of these catalysts to verify this hypothesis.

In view of these positive results, the previously reported Rh(II)-catalyzed olefin cyclopropanation with Meldrum's acid (**5**) was reinvestigated with catalyst **4c** and styrene (**2a**) and pent-1-ene (**2f**) as substrates using the in situ procedure (Scheme 2). The cyclopropanes **6a** and **6b** were isolated with 92 and 87% ee, respectively. In comparison, the enantioselectivity for cyclopropanation of these olefins with [Rh_2{(*S*)-nttl}$_4$] (**4a**) was 43 and 59%, respectively.[15]

Enantiopure cyclopropane-1,1-dicarboxylates are of synthetic interest. Thus, **3a** has been used as an intermediate in the enantioselective synthesis of sertraline.[14b] In addition, the selective hydrolysis of the *trans*-ester function[22] opens access to a variety of 1,1-difunctionalized cyclopropanes, such 1-aminocyclopropane carboxylic acids.[23] The present procedure is complementary to the enantioselective cyclopropanation with silanyloxyvinyl diacoacetates, which allows

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for diastereo- and enantioselective introduction of two different carbonyl functions.[13]

Acknowledgment. This work was supported by the Swiss National Science Foundation (Project Nos. 20-52581.97 and 2027-048156). The support and sponsorship concerted by COST Action D24 "Sustainable Chemical Processes: Stereoselective Transition Metal-Catalyzed Reactions" are kindly acknowledged. We are indebted to J.-P. Saulnier and A. Pinto for the NMR spectra and to Mr. G. Nicholson (University of Tübingen, Germany) for the mass spectra of the rhodium catalysts.

Supporting Information Available: Experimental procedure, product characterization, and synthesis of rhodium complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048159U