Asymmetric Cyclopropanation of Olefins with an in situ Generated Phenyliodonium Ylide

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Abstract: A procedure for the in situ generation of the phenyliodonium ylide (**2**) derived from Meldrum's acid (**1**) and its Rh(II)-catalyzed decomposition to afford an intermediate metallocarbene is described. In the presence of olefins, cyclopropanes are formed with yields and enantioselectivity comparable to that resulting from cyclopropanation with the isolated ylide **2**.

Key words: asymmetric catalysis, alkenes, carbenes, rhodium, ylides

Asymmetric carbene transfer has seen spectacular development during the recent 15 years thanks to the development of highly efficient and selective catalysts.[1] The reaction involves the transition metal-catalyzed decomposition of a diazo precursor[2] to afford a metallocarbene as reactive intermediate, which then transfers the carbene moiety to an appropriate substrate. The enantioselectivity of the reaction may be controlled by chiral ligands surrounding the metal.

The application of asymmetric carbene transfer reactions is limited owing to the toxic, carcinogenic and potentially explosive nature of diazo compounds required for the generation of metallocarbenes.[3] Accordingly, only a few industrial applications of diazo decompositions are known.[4] The development of carbene transfer reactions avoiding diazo precursors is therefore of considerable interest. Over the past years, we have investigated phenyliodonium ylides as potential substitutes for diazo compounds in transition metal-catalyzed transfer of carbenes and nitrenes. We have shown that phenyliodonium ylides derived from 1,3-dicarbonyl compounds react upon decomposition with Rh(II)-or Cu(I)-catalysts via the same reactive intermediate as the corresponding diazo compounds, and exhibit the typical characteristics of carbene transfer reactions.[5] An exception to this general behavior is found in the intramolecular cyclopropanation of phenyliodonium ylides, where a competing unspecific and uncatalyzed secondary pathway may intervene.[6]

Recently, we reported the Rh(II)-catalyzed intermolecular olefin cyclopropanation using the ylide **2**, derived from Meldrum's acid (**1**) (Figure 1).[7] The reaction is stereospecific. Enantioselectivities of up to 63% have been reported with the $[Rh_2\{(S)\text{-nttl}\}_4]$, and no evidence for a secondary reaction was found in the intermolecular cyclopropanation with **2**. Similarily, the Rh(II)-catalyzed olefin aziridination with the iminoiodinane **3** derived from *p*-nitrobenzenesulfonamide, NsN=IPh, is stereospecific,[8] and the intermolecular CH insertion proceeds with retention of configuration.[9] Apparently, there is a mechanistic analogy between the carbon derived phenyliodonium ylides such as **2** and their nitrogen-derived counterparts **3**.

One of the most promising recent developments in catalytic nitrene transfer is the in situ generation and metal-catalyzed decomposition of imino phenyliodinanes to afford aziridines. A system using tosylamide ($TsNH_2$) and iodosylbenzene (PhIO) in conjunction with Cu(I)-catalysts was proposed by Dauban for calaytic and asymmetric olefin aziridination. When $TsNH_2$ was replaced by dimethyl malonate, cyclopropanes were formed.[10] In parallel, and independently, DuBois et al. optimized a system based on $PhI(OAc)_2$ and Rh(II)-catalysts for intramolecular nitrene transfer of carbamates and sulfamates via in situ generated iminophenyliodinanes.[11] This reagent combination has been applied to asymmetric aziridinations.[12] It appeared that all requirements were met for the development of an asymmetric cyclopropanation procedure using in situ generated phenyliodonium ylides.

Accordingly, we have adapted the intermolecular olefin cyclopropanation of the phenyliodonium ylide **2** in such a way that the ylide was generated from Meldrum's acid and $PhI(OAc)_2$ and decomposed in situ by an appropriate Rh(II)-catalyst in the presence of an olefin. The announced report of Charette[13] on carbene transfer with an in situ generated phenyliodonium ylide prompts us to reveal our own findings in this area.

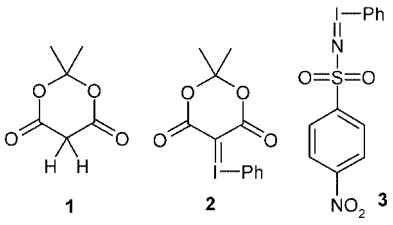

Figure 1

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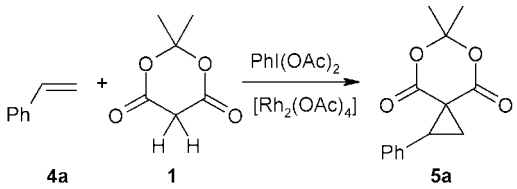
The reaction conditions were optimized with styrene (**4a**) as substrate and with $[Rh_2(OAc)_4]$ in CH_2Cl_2 (Scheme 1). The amount of catalyst was maintained constant at 5 mol%. The effect of olefin concentration and different additives on the yield of cyclopropane **5a** is summarized in Table 1. As the Table reveals, a basic additive is required for neutralization of the AcOH, liberated from $PhI(OAc)_2$ during the reaction. While addition of molecular sieves alone had only a minor effect on the yield of **5a**, the combination of molecular sieves with a basic additive led to the highest yield of cyclopropane (**5a**). In addition, a significant excess of olefin (5–10-fold) is necessary, since otherwise the intermediate metallocarbene decomposes. This has already been noted for Rh(II)-catalyzed olefin cyclopropanations with the isolated phenyliodoniun ylide **2**.[7] No satisfactory yields could be obtained, however, when the reaction was carried out with Meldrum's acid in excess.



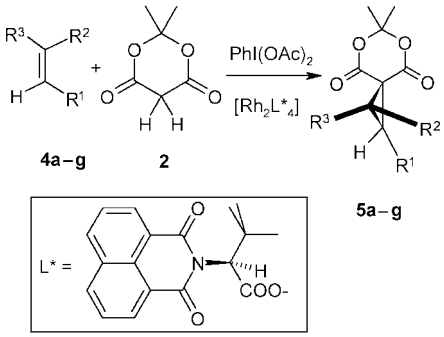
Scheme 1

Table 1 Optimization of Reaction Conditions with Styrene (**4a**)[a]

Entry	Excess **4a**	Additive[b]	Yield of **5a** (%)
1	10	None	23
2	10	MgO	67
3	10	K_2CO_3	69
4	10	Al_2O_3	51
5	10	MS	33
6	10	MgO + MS	80
7	10	K_2CO_3+MS	73
8	10	Al_2O_3 + MS	85
9	8	Al_2O_3 + MS	73
10	6	Al_2O_3 + MS	58
11	4	Al_2O_3 + MS	49
12	2	Al_2O_3 + MS	24
13	0.5	Al_2O_3 + MS	10

[a] Conditions: In CH_2Cl_2 (10 mL), at 30 °C, 10 mmol of **1**, 1.4 equivalents of $PhI(OAc)_2$, 5 mol% of $[Rh_2(OAc)_4]$.
[b] 2.3 Equivalents of additive; MS = molecular sieves 4 Å, 250 mg.

Table 2 shows a comparison of the in situ procedure (Method A) with the results previously reported for cyclopropanation of olefins **4** with isolated ylide **2** under catalysis with $[Rh_2(OAc)_4]$ (Method B).[7,14] In general, the yields of cyclopropanes under otherwise comparable conditions tend to be somewhat lower with the in situ procedure. The cyclopropanation of pent-2-enes **4e**,**f** was found to be stereospecific with both procedures (Scheme 2).



Scheme 2

Table 2 Comparison of in situ Procedure (Method A)[a] with Reaction of Isolated Ylide **2** (Method B)[b] with $[Rh_2(OAc)_4]$

Compound	R^1	R^2	R^3	Method	Yield (%)
4a	Ph	H	H	A	85
4a	Ph	H	H	B	81
4b	*n*-Pr	H	H	A	75
4b	*n*-Pr	H	H	B	87
4c	*t*-Bu	H	H	A	35
4c	*t*-Bu	H	H	B	42
4d	*c*-CH=CHCH$_3$	H	H	A	30
4d	*c*-CH=CHCH$_3$	H	H	B	45
4e	Me	Et	H	A	60
4e	Me	Et	H	B	75
4f	Me	H	Et	A	56
4f	Me	H	Et	B	69
4g	COOEt	H	H	A	0

[a] 10-Fold excess of olefin, 5 mol% of catalyst, 30 °C.
[b] Refs.[7] 5 mol% of catalyst.

No cyclopropane was isolated with ethyl acrylate (**4g**), however.

A third set of experiments was carried out in order to optimize conditions for asymmetric cyclopropanation of styrene (Table 3) with $[Rh_2\{(S)\text{-nttl}\}_4]$ as catalyst. CH_2Cl_2 was found to be the most convenient solvent. The yields

of cyclopropane **5a** depended significantly on the catalyst concentration, which was routinely fixed to 5 mol%.

Satisfactory results were also obtained in MeCN with a catalyst load of only 1 mol% (Table 3). For example, the yield of **5a** increased from 21% in CH_2Cl_2 with 1 mol% of catalyst to 81%, and the ee from 43% in CH_2Cl_2 to 59% in MeCN. THF was also efficient with 48% yield and 52% ee in the presence of 1 mol% of catalyst. Solvents such as benzene and trifluorotoluene were ineffective, however.

Table 3 Optimization of Reaction Conditions with Styrene (**4a**) and $[Rh_2[(S)\text{-nttl}\}_4]$[a]

Entry	Solvent	[Catalyst] (mol%)	Yield of **5a** (%)	ee (%)
1	CH_2Cl_2	5	90	43
2	CH_2Cl_2	4	72	37
3	CH_2Cl_2	3	54	36
4	CH_2Cl_2	2	32	35
5	CH_2Cl_2	1	20	39
6	$C_6H_5CF_3$	1	0	–
7	MeCN	1	81	59
8	C_6H_6	1	0	–
9	THF	1	48	52

[a] ReactionConditions: 10 mL of solvent, at 30 °C, 10 mmol of **1**, 1.4 equivalents of $PhI(OAc)_2$, 2.3 equivalents of Al_2O_3, MS 4 Å (250 mg).

Table 4 Asymmetric Cycloproanation of Olefins with $[Rh_2\{(S)\text{-nttl}\}_4$[a]

Compound	Olefin	Method	Yield (%)	ee (%)
4a	styrene	A	90	43[b]
4a	styrene	B	84	37
4a	styrene	C	79	57[c]
4b	pent-1-ene	A	56	70
4b	pent-1-ene	B	97	59
4b	pent-1-ene	C	55	59
4d	*cis*-penta-1,3-diene	A	50	33
4d	*cis*-penta-1,3-diene	C	61	30
4e	*cis*-pent-2-ene	A	47	33
4e	*cis*-pent-2-ene	C	50	54

[a] Method A: In situ procedure, in CH_2Cl_2, 5 mol% of catalyst. Method B: With isolated ylide **2**.[7] Method C: In situ procedure, in MeCN, 1 mol% of catalyst.

Table 4 compares yields and enantioselectivities for olefin cyclopropanation of several olefins under the in situ conditions in CH_2Cl_2 (Method A),[15] MeCN (Method C) with isolated ylide (Method B). The yields resulting from the in situ procedure are generally lower than those resulting from Method B as was the case with $[Rh_2(OAc)_4]$ (Table 2). On the other hand, the enantioselectivity of the in situ method compares well with those of Method B.

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(14) For characterization of the cyclopropanes **5a**–**f**, see ref.[7]

(15) Representative procedure (Method A): CH_2Cl_2 (10 mL) was added through syringe into a 50 mL round bottom flask containing a mixture of Meldrum's acid (**1**, 10 mmol, 1 equiv), $PhI(OAc)_2$ (1.4 equiv), $[Rh_2(OAc)_4]$ or $[Rh_2\{(S)\text{-nttl}\}_4]$ (5 mol%), Al_2O_3 (2.3 equiv) and molecular sieves 4 Å (250 mg), followed by the addition of the olefin (10 equiv). The reaction mixture was thermostated in an oil bath to 30 °C and stirred under Ar. 100 μL Samples were taken after several time intervals. The samples were filtered using a syringe filter holder (0.2 μm pore size) and the organic layer was diluted with 100 μL of CH_2Cl_2 and analyzed by GC. The reaction progress was monitored qualitatively by TLC using pentane–EtOAc (2:1) as eluent. An aliquot of the supernatant was used for GC. When maximum conversion was reached, the reaction was terminated by filtration through celite. The residue on the celite was washed twice with CH_2Cl_2. Evaporation of the combined filtrates under reduced pressure followed by chromatography on silica gel column with pentane–EtOAc (2:1) as eluent afforded the desired cyclopropane derivatives.