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High Enantiocontrol in the Intramolecular Cyclopropanation of Diazo Ketones Catalyzed by Dirhodium(II) Complexes with *Ortho*-Metalated Aryl Phosphine Ligands

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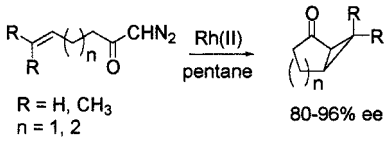
ABSTRACT



Chiral dirhodium(II) complexes, $Rh_2(O_2CCF_3)_2(PC)_2$, [PCH = (*p*-$CH_3C_6H_4)_3P$, (*m*-$CH_3C_6H_4)_3P$], provide an excellent yield and a high enantiocontrol in the cyclopropanation of α-diazo ketones with γ and δ double bonds. The ee values are significantly dependent on the solvent used; the best results are obtained using pentane.

The achievements in asymmetric catalytic metal carbene transformations are impressive, but they are by no means complete.[1] The dirhodium(II) carboxamidate catalysts have proven to be the most selective catalysts for intramolecular cyclopropanation reactions of diazoacetates and diazoacetamidates.[1a,c] However, these catalysts fail to induce even moderate levels of enantioselectivities with diazo ketones.[2] This observation has been explained by conformational control of carbonyl alignment (*syn* or *anti* to the metal) of the metal carbene intermediate.[2] Also, the oxocarbenes derived from diazo esters and diazo amides are less electron-deficient (more selective) than the carbenes derived from diazo ketones due to the resonance interactions between the heteroatoms and the carbonyl group in oxycarbonyl carbenes and amides.[3]

In 1995, Pfaltz et al.[4] showed that semicorrin-copper catalysts led to cyclopropanation of diazo ketones with a moderate yield (less than 60%) (Tables 1−4). Until now, these copper(I) compounds were the most efficient catalysts to induce enantiocontrol in the cyclization of the mentioned substrates. However, their selectivity strongly depended on the substrate structure. Thus, homologous substrates having the same substitution pattern at the olefinic C=C bond reacted with quite different enantioselectivities (Tables 3 and 4). Later, new chiral catalysts were unsuccessfully sought for improving the enantioselectivity in the intramolecular

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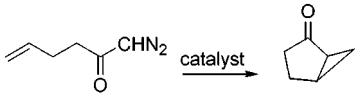
Table 1. Cyclopropanation of Diazo Ketone **2**



2 **3**

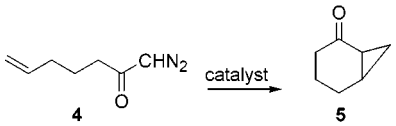
		3	
catalyst	solvent	% yield[a]	% ee[b]
1a[c]	pentane	90	74
1a[c]	CH_2Cl_2	96	65
1b[c]	pentane	96	87
1b[c]	CH_2Cl_2	98	64
Cu(I)[d]	$ClCH_2CH_2Cl$	50	75
Cu(I)[e]	CH_2Cl_2		25
Rh(II)[f]	CH_2Cl_2	85	23
Ru(II)[g]	$CHCl_3$	84	5

[a] Cyclopropanation yield based on diazo ketone. [b] ee values calculated in this report were based on GC analysis with a 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-CDX column. [c] The reaction mixture was refluxed in the indicated solvent for 1 h. [d] Copper semicorrin complexes (see ref 4). [e] Biferrocene-based bis(oxazoline) copper complex (see ref 6). [f] Rh_2(4*S*-IPOX)$_4$ (see ref 2). [g] Ru(II) with chiral diphenyl phosphino(oxazolinyl)quinoline ligands (see ref 5).

cyclopropanation of diazo ketones (Tables 1−4). Apart from the failed attempt with dirhodium(II) carboxamide catalysts, chiral Ru(II) and Cu(I) complexes did not prove satisfactory (Tables 1−4). Thus, Ru(II) with chiral diphenyl phosphino(oxazolinyl)quinoline ligands provided high yields in the cyclization, albeit with less enantiocontrol compared to Pfaltz catalytic systems.[5] Chiral biferrocene-based bis(oxazoline) Cu(I) complexes catalyzed the intramolecular cyclization of diazo ketones with low to moderate enantioselectivities and low reactivity.[6]

Our efforts have been focused on the use of dirhodium(II) catalysts of the general formula $Rh_2(O_2CR)_2(PC)_2$, containing two *ortho*-metalated aryl phosphines (PCH) in a head to tail arrangement,[7] (Figure 1). These compounds have backbone chirality and they can be isolated as pure enantiomers by conventional resolution methods.[8] The racemic

Table 2. Cyclopropanation of Diazo Ketone **4**

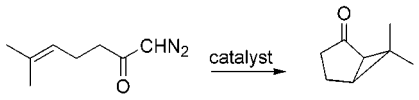


4 **5**

		5	
catalyst	solvent	% yield	% ee
1a	pentane	96	90
1a	CH_2Cl_2	85	87
1b	pentane	90	95
1b	CH_2Cl_2	92	89
Cu(I)[a]	$ClCH_2CH_2Cl$	57	95
Rh(II)[b]	CH_2Cl_2	58	6

[a] Copper semicorrin complexes (see ref 4). [b] Rh_2(5*S*-MEPY)$_4$ (see ref 2).

Table 3. Cyclopropanation of Diazo Ketone **6**



6 **7**

		7	
catalyst	solvent	% yield	% ee
1a	pentane	99	80
1a	CH_2Cl_2	99	52
1b	pentane	99	70
1b	CH_2Cl_2	99	58
Cu(I)[a]	$ClCH_2CH_2Cl$	58	85
Cu(I)[b]	CH_2Cl_2	51	63
Rh(II)[c]	CH_2Cl_2	80	27
Ru(II)[d]	$CHCl_3$	91	75

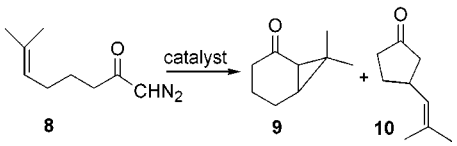
[a] Copper semicorrin complexes (see ref 4). [b] Biferrocene-based bis(oxazoline) copper complex (see ref 6). [c] Rh_2(4*S*-MEOX)$_4$ (see ref 2). [d] Ru(II) with chiral diphenylphosphino(oxazolinyl)quinoline ligands (see ref 5).

$Rh_2(O_2CR)_2(PC)_2$ compounds have been used in intramolecular processes, and they produce a high level of regio- and chemoselectivity in the cyclization of α-diazo ketones.[9,10] Those with highly electron-withdrawing carboxylate groups (CF_3CO_2) and basic phosphines [such as triphenylphosphine and tris(methylphenyl)phosphine] have shown the best selectivity values, and they are able to induce high enantiocontrol in the intermolecular cyclopropanation of styrenes.[11]

We now report the results obtained with $Rh_2(O_2CCF_3)_2(PC)_2$ [PCH = (*p*-$CH_3C_6H_4)_3$P, (*m*-$CH_3C_6H_4)_3$P] catalysts (**1a** and **1b**) in the intramolecular cyclization of α-diazo ketones. Catalytic reactions were performed by addition of the diazocompound to a 1.0 mol % of dirhodium(II) complex in the refluxing solvent. Use of catalysts **1a** and **1b** for cyclopropanation of diazo ketones **2**, **4**, **6**, and **8** gave the results reported in Tables 1−4.

In all the cases the cyclopropanation of the diazo compound gave a high yield. On the other hand, the ee values

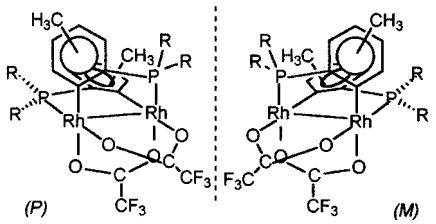
Table 4. Cyclopropanation of Diazo Ketone **8**



8 **9** **10**

catalyst	yield (%)	solvent	**9**, % (ee)	**10**, % (ee)
1a	87	pentane	93 (80)	7 (91)
1a	74	CH_2Cl_2	67 (63)	33 (93)
1b	92	pentane	69 (80)	31 (94)
1b	93	CH_2Cl_2	51 (63)	49 (92)
Cu(I)[a]	50	$ClCH_2CH_2Cl$	50 (14)	
Cu(I)[b]	12	CH_2Cl_2	12 (64)	
Rh(II)[c]	67	CH_2Cl_2	76 (17)	24 (1)

[a] Copper semicorrin complexes (see ref 4). [b] Biferrocene-based bis(oxazoline) copper complex (see ref 6). [c] Rh_2(5*S*-MEPY)$_4$ (see ref 2).



R = *p*-$CH_3C_6H_4$ **1a**

R = *m*-$CH_3C_6H_4$ **1b**

Figure 1. Rh(II) catalysts with *ortho*-metalated aryl phosphine ligands.

were significantly dependent on the solvent used; the best results in the cyclopropanation of all the substrates were obtained using pentane.

In the case of diazo ketone **8** the C−H insertion reaction to compound **10** competed with cyclopropanation to compound **9**. Interestingly, the C−H insertion product was obtained with high ee values in both solvents, dichloromethane and pentane.

Both (*M*) and (*P*) enantiomers were used as catalysts and as expected, they induced identical enantiocontrol in the cyclization of the diazo ketones, but with the opposite configuration. Once again these results confirm the generally accepted idea that catalytic reactions of this type occur via dirhodium-carbenoid species, and they also confirm that degradation to an achiral rhodium catalyst is not a major competing pathway.

The configurations of ketones **3**,[5,12] **5**,[12] **7**[5,12] and **9**[13] were determined by correlation of the sign of polarized light with that of the known enantiomer. The absolute stereochemistry of compound **3**, formed from the reaction of diazo ketone **2** with **(*P*)-1a** and **(*P*)-1b** catalysts, was established as (1*S*,5*R*); however, in the same conditions, the homologous diazo compound **4** led to ketone **5** with the (1*R*,6*S*) configuration. The same behavior has been previously observed for the reaction of diazo compounds **2** and **4** with Aratani catalysts. The reason for this reversal in conformational preference has been explained by the fact that the preferred configuration could be determined by the chirality of the catalyst; also, the orientation of the carbon−carbon double bond with respect to the *p*-orbital of the metal carbene could determine the preferred configuration. The size of the ring being formed could play an important role in the method of the addition of the carbene to the carbon−carbon double bond, occurring from one of the two enantiotopic faces. An additional example was found with diazo compounds **6** and **8**; ketones **7** and **9** were also obtained with the opposite configuration, (1*R*,5*S*) and (1*S*,6*R*), respectively, when using the (*P*)-catalysts.

In conclusion, the high ee values provided by chiral dirhodium(II) complexes with *ortho*-metalated phosphine in the cyclopropanation of the diazo ketones compare very favorably with the values obtained using other chiral catalysts. Diazo ketones have found a large number of successful applications in racemic synthesis;[15,16] by far they have not met the spectacular success in asymmetric synthesis encountered with diazo esters and diazo amides. The data reported here demonstrate the suitability of dirhodium(II) catalysts with phosphine ligands to overcome this deficiency, since an excellent yield and a high enantiocontrol in the cyclization of all the tested diazo ketones were obtained.

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