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Asymmetric Rh(II)-Catalyzed Cyclopropanation of Alkenes with Diacceptor Diazo Compounds: *p*-Methoxyphenyl Ketone as a General Stereoselectivity Controlling Group

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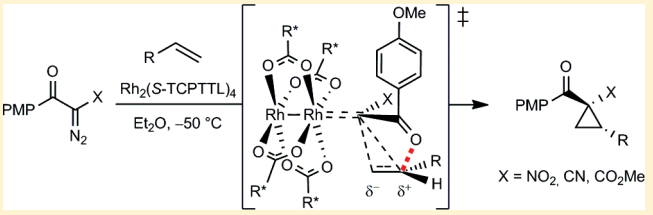
Supporting Information

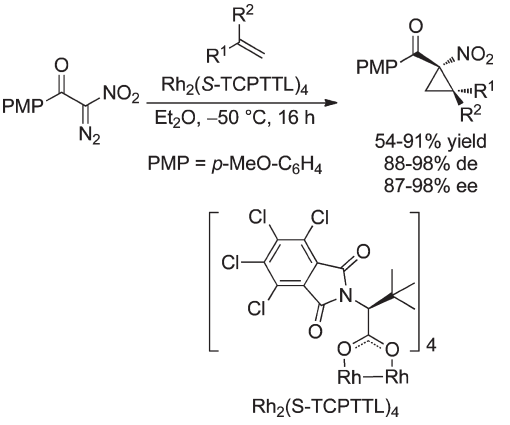
ABSTRACT: Different diacceptor diazo compounds bearing an α-PMP-ketone group were found to be effective carbene precursors for the highly stereoselective Rh_2(*S*-TCPTTL)$_4$-catalyzed cyclopropanation of alkenes (EWG = NO_2, CN, CO_2Me). The resulting products were readily transformed into a variety of biologically relevant enantiopure molecules, such as cyclopropane α- and β-amino acid derivatives. Different mechanistic studies carried out led to a rationale for the high diastereo- and enantioselectivity obtained, where the PMP-ketone moiety was found to play a critical role in the stereoinduction process. Additionally, the use of catalytic amounts of achiral Lewis bases to influence the enantioinduction of the reactions developed is documented.



INTRODUCTION

Cyclopropanes are important subunits commonly found in natural or synthetic products of pharmaceutical interest.[1] In particular, cyclopropanes bearing geminal electron-withdrawing groups are unique synthetic intermediates due in part to their inherent electrophilicity.[2] Numerous reports have been devoted to their use in asymmetric synthesis, mainly involving nucleophilic substitution reactions,[3] formal cycloadditions,[4] or various functional group manipulations with complete preservation of the stereochemical information when enantioenriched cyclopropanes are used. In this regard, the direct enantioselective formation of such motifs using a chiral metal-carbene intermediate bearing two electron-withdrawing groups would, thus, be highly desirable due to its retrosynthetic efficiency. However, success in this field of research has been very limited.[5,6] In the past few years, Zhang et al. have demonstrated that chiral Co(II)-porphyrins complexes are efficient catalysts for such transformation through "carbene radical" intermediates, and their efficiency with acceptor−acceptor carbene equivalents has been recognized.[6d,e] Recently, we have reported a highly enantioselective cyclopropanation of alkenes using α-nitro diazoacetophenones and Hashimoto's complex Rh_2(*S*-TCPTTL)$_4$ (eq 1).[5a] These studies suggest that the *p*-methoxyphenyl ketone (PMP-ketone) moiety of the substrate is playing a dual role, affording good diastereocontrol through a stereoelectronic effect in the transition state, and good enantiocontrol through π-stacking interactions with the catalyst's tetrachlorophthaloyl groups.

Considering this model, which suggests that the nitro group is not crucial in the stereocontrol of the reaction, we were intrigued to verify our hypothesis by replacing it with other electron-withdrawing groups and evaluate the reactivity of these newly designed carbene precursors. Herein we report our recent results



(1)

on the catalytic asymmetric cyclopropanation of alkenes with α-EWG-diazoacetophenones, where EWG = NO_2, CN, CO_2Me, giving access to a wide variety of highly enantioenriched cyclopropane derivatives. In this work, we demonstrate the unique role of the PMP-ketone moiety acting as a highly effective enantio- and diastereoselectivity-control group. The ketone can be transformed into a more versatile PMP-ester following the asymmetric cyclopropanation, permitting further functionalization of these building blocks. The resulting cyclopropanes could readily be obtained in enantiopure form via recrystallization and used as substrates in diverse transformations, providing access to valuable chiral synthons such as cyclopropane α- and β-amino acid derivatives, tetrahydrofurans or α-chiral amines. Considering the efficiency of Rh_2(*S*-TCPTTL)$_4$ in many catalytic asymmetric

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transformations, such as C−H amination reactions,[7] 1,3-dipolar cycloadditions,[8] and aziridinations using metal-nitrene intermediates,[9] the understanding of its stereoinduction mechanism in our system is of broad applicability in future catalyst design.[10]

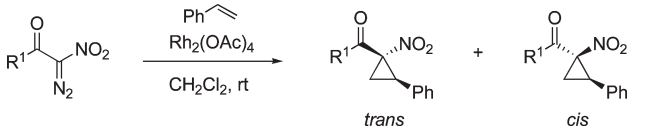
RESULTS AND DISCUSSION

Stereocontrol in Rh(II)-Catalyzed Cyclopropanation Reactions. Over the past few years, our group has studied the reactivity of a variety of metal-carbene precursors bearing two electron-withdrawing substituents in stereoselective cyclopropanation reactions.[5,11] In the Rh(II)-catalyzed reaction between terminal alkenes and *gem*-dicarbonyl diazo compounds, empirical evidence suggests that the diastereoselectivity level of the cyclopropanation not only is a function of the steric properties of the two carbonyl groups but also is highly influenced by their relative Lewis basicity.[5b] This has been attributed to a stereoelectronic effect in the transition state, first proposed by Doyle et al., where the carbonyl's lone pair donates electron density to the LUMO of the approaching alkene, stabilizing the transition state and directing the alkene's substituent position in the final product.[12] The most basic and/or sterically hindered of the two carbonyl functions is, therefore, denoted the *trans*-directing group. For example, the cyclopropanation of alkenes with α-amido diazoacetates or with α-cyano diazoacetamides leads to the cyclopropane derivative where the amide is located *trans* to the alkene's substituent, due to the increased basicity/steric demand of the amide group relative to an ester or a nitrile functionality.[5b,c] Nitrocarbene equivalents bearing an α-carbonyl group are known to somewhat behave in an analogous manner. Indeed, the nature of the carbonyl in those compounds is found to have a profound influence on the diastereoselectivity outcome of the reaction (Table 1).[11d,12e]

In the case of an α-nitroester or of unhindered α-nitroketones, the major product of the $Rh_2(OAc)_4$-catalyzed cyclopropanation with styrene is the *trans* diastereomer, the more basic nitro moiety acting here as the *trans*-directing group (entries 1−3). As the steric demand and/or the basicity of the carbonyl group becomes more important, as is the case with a *t*-Bu-ketone or an acetophenone derivative, the *cis*:*trans* ratio is increased and the *cis*-cyclopropane becomes the major diastereomer (entries 4−6). This is a clear demonstration of the competition between the two proximal electron-withdrawing groups (nitro and carbonyl) for their *trans*-directing ability (Figure 1).

The red dotted lines in the transition states of Figure 1 illustrate the stereoelectronic effect discussed earlier, where electron density is transferred from the *trans*-directing group's lone pair to the alkene's developing positive charge. To maximize this stabilizing interaction and reduce the distance between the alkene LUMO and the basic oxygen, the alkene's substituent (here, Ph) will be oriented *trans* to this basic group in order to minimize unfavorable steric constraints (between Ph and the basic group's oxygen).[12b] This proposed electronic effect is consistent with the tendency observed in Table 1, but one must expect the steric nature of R^1 to *also* impact on the *cis*:*trans* ratio. In order to ultimately prove the presence of this effect, one must be able to dissociate the steric and electronic factors of the transition state. To do so, we envisioned that α-nitro diazoacetophenone derivatives could meet this requirement (Table 2). *Indeed, modifying the* X *or* Y *group on the arylketone moiety should greatly impact on the carbonyl's oxygen basicity without affecting the steric hindrance at the reaction center.* As depicted in Table 2 and Figure 2, the electronic nature of the arylketone has an important effect on the diastereoselectivity level of the reaction, either in the racemic or enantioselective version of the reaction (conditions **A** or **B**).

Table 1. Influence of the Carbonyl's Nature on the Diastereoselectivity of the $Rh_2(OAc)_4$-Catalyzed Cyclopropanation of α-Carbonyl Nitrodiazomethanes with Styrene[11d,12e]



entry	R^1	yield (%)[a]	dr (*cis*:*trans*)[b]
1	OEt	80	12:88
2	O*i*-Pr	78	25:75
3	Me	77	22:78
4	*t*-Bu	55	80:20
5	Ph	74	84:16
6	PMP[c]	71	88:12

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] PMP = *p*-MeO-C_6H_4.

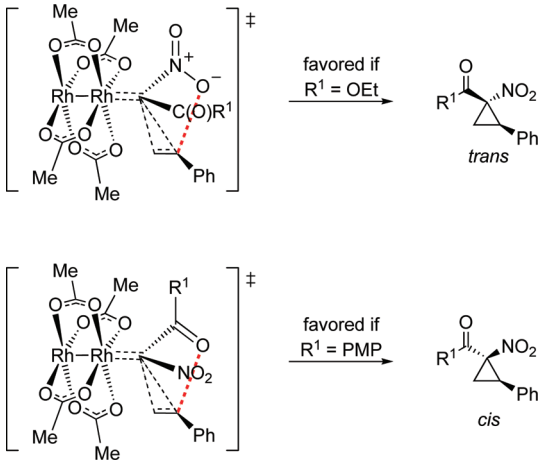


Figure 1. Competitive [2 + 1] cycloaddition transition states showing Doyle's stereoelectronic effect in the cyclopropanation with α-carbonyl nitrodiazomethanes.

The general tendency observed in diastereomeric ratios is as expected from Doyle's stereoelectronic model. Electron-withdrawing substituents such as NO_2 or CF_3 at the *para*-position afford lower ratios due to a weaker basicity of the carbonyl group, whereas electron-rich substituents such as OMe or NMe_2 furnish improved diastereocontrol, with the steric hindrance around the reaction center being similar in each case. Note that the trend in Lewis basicities is shown in Table 2 and Figure 2a as the carbonyl's IR wavenumber of the corresponding acetophenone, data furnishing unambiguous insight onto the polarization of the C═O bond. A Hammett correlation between the diastereoselectivity and the substituents constants also demonstrates the influence of the electronic nature of the aromatic ring (Figure 2b). Furthermore, as noted in our previous work for the $Rh_2(S\text{-TCPTTL})_4$-catalyzed

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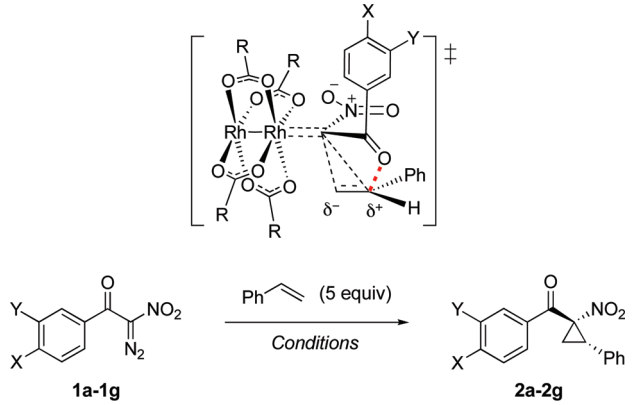
Table 2. Effect of the Arylketone's Electronics on the Stereoselectivity with α-Nitro Diazoacetophenones



entry	diazo	X	Y	ν_{CO} (cm^{-1})[a]	conditions	dr (*cis*:*trans*)[b]	ee (*cis*, %)[c]
1	**1a**	CF_3	H	1695	**A**	4.0:1	
					B	2.3:1	71
2	**1b**	NO_2	H	1693	**A**	4.0:1	
					B	12:1	91
3	**1c**	Cl	H	1685	**A**	4.7:1	
					B	24:1	92
4	**1d**	H	H	1684	**A**	4.9:1	
					B	24:1	94
5	**1e**	H	OMe	1676	**A**	5.7:1	
					B	49:1	96
6	**1f**	OMe	H	1674	**A**	7.0:1	
					B	49:1	93
7	**1g**	NMe_2	H	1657	**A**[d]		
					B	83:1	96

[a] ν_{CO} of the corresponding acetophenone. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase. [d] No desired product was observed under these conditions.

transformation, the enantioselectivity also increases with the electron-donating character of the substituents. It is noteworthy that this latter observation is proposed to be attributed to a different effect dependent on the catalyst structure, i.e., the improved favorable catalyst−substrate π-stacking interactions for electron-rich arylketones.[5a]

For both effects, one could argue that the increased stereocontrol can be due to a lower electrophilicity of the carbene, leading to a later transition state. DFT calculations and X-ray structures of metal-carbenes bearing at least one carbonyl group fail to support this hypothesis.[13] Indeed, the carbonyl group in these systems is believed to be out of the plane of the metal-carbene in the transition state, offering minimal orbital overlap between the Rh═C and the C═O bonds (Figure 3b).

The two situations illustrated in Figure 3 represent extreme cases, where the *in-plane* conformations (φ = 0° or 180°) are uphill, while the *out-of-plane* conformations (φ = 90° or −90°) represent the ground state of the metal-carbene species. It is believed, through DFT calculations, that the carbene reacts in a

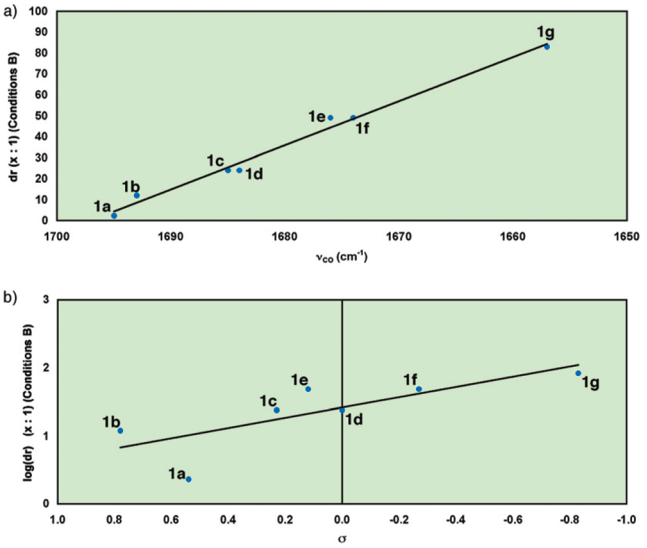


Figure 2. (a) Relationship between the carbonyl's basicity and the diastereoselectivity obtained. (b) Hammett correlation between the diastereoselectivity and the substituents constants.

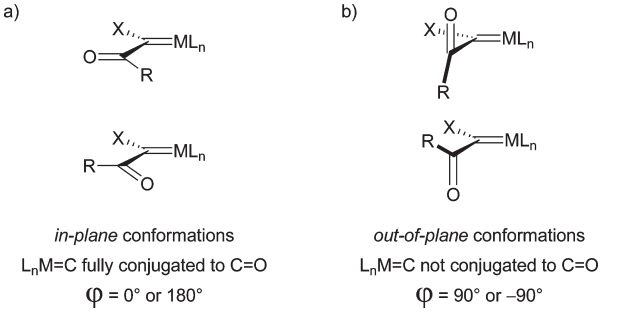


Figure 3. Possible conformations of metal-carbenes derived from α-diazocarbonyl compounds.

conformation very similar to the case of Figure 3b.[13a,d] This carbene thus receives only little electronic influence of the substituents on the aromatic ring (inductive effects only), and the global impact on the carbene's electrophilicity is expected to be negligible. Moreover, in entry 5, where the *meta*-substituent effect of diazo **1e** should be minimal on the carbene but significant in increasing the aromatic ring's HOMO, we observe an increase in enantioselectivity, in accordance with our catalyst-substrate π-stacking hypothesis.

Stereoselective Rh_2(*S*-TCPTTL)$_4$-Catalyzed Cyclopropanations. Since the aromatic ketone controls the diastereoselectivity *and* the enantioselectivity in our model, we wished to explore the reactivity of different α-EWG-diazoacetophenones in asymmetric cyclopropanation. The results displayed in Table 3 show that substituting the nitro group with a nitrile or a methyl ester also leads to high stereocontrol, under very similar conditions. In fact, complete reoptimization of the solvent and catalyst's structure provided Rh_2(*S*-TCPTTL)$_4$ as catalyst in Et_2O as the optimal conditions for the three transformations. In the case of substrate **1f** or **1h**, the diazo compound could be added in one portion in the solid state under air, without the requirement of syringe-pump techniques, while a slow addition was performed (over 15 min) in the case of diazo **1i**. The optimal temperature had to

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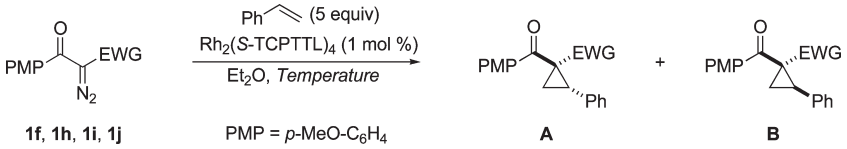
Table 3. Influence of the Nature of the Electron-Withdrawing Group (EWG) in the Rh_2(*S*-TCPTTL)$_4$-Catalyzed Cyclopropanation of α-EWG-Diazoacetophenones with Styrene



1f, **1h**, **1i**, **1j** PMP = *p*-MeO-C_6H_4 **A** **B**

entry	substrate	EWG	temp (° C)	yield (%)[a]	dr (**A**:**B**)[b]	ee (%)[c]
1	**1f**	NO_2	−50	81	98:2	93
2	**1h**	CN	−35	98	95:5	84
3	**1i**	CO_2Me	−40	60	99:1	88
4	**1j**	Ph	−50	9	>95:5	98

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] ee of major diastereomer determined by SFC on chiral stationary phase.

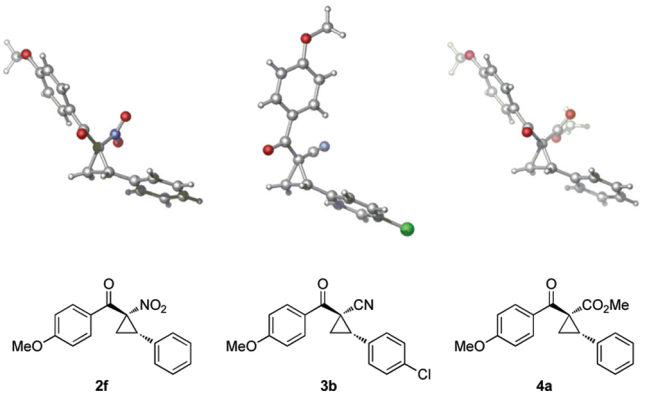


Figure 4. X-ray structures of cyclopropanation products from the reaction of styrenes with α-EWG-diazoacetophenones (EWG = NO_2 (left), CN (middle), CO_2Me (right)).

be slightly increased for substrates **1h** and **1i** to −35 and −40 °C, respectively, due to their lower reactivity. As expected, X-ray analysis of the resulting cyclopropanic derivatives shows that the PMP-ketone is *trans* to the alkene's substituent in all cases in the major product (Figure 4), and the absolute configuration of the major enantiomer was found to be the same for the three classes of cyclopropanic derivatives. It is noteworthy that the introduction of other EWGs at the α position of the substrate, such as sulfones, phosphonates or ketones, led only to minimal amounts of the desired product in the Rh_2(*S*-TCPTTL)$_4$-catalyzed process. Also, replacing the EWG with a hydrogen atom afforded good yields of the product but only poor stereocontrol (75% yield, 60:40 dr, 45% ee), whereas the use of a α-alkyl-diazoketone analog (EWG = Bu) led only to undesired *β*-hydride elimination. Interestingly, donor−acceptor diazo **1j** (EWG = Ph) afforded the cyclopropane in poor yield but in outstanding stereocontrol, confirming the importance of the PMP-ketone as the stereoselectivity controlling group (entry 4).

In previous work, we have provided significant evidence that Rh_2(*S*-TCPTTL)$_4$, the optimal catalyst for these transformations, is reacting through an "all-up" conformation (also designated "chiral crown").[5a] In such a system, the two axial sites where the metal carbene can be formed (top face or bottom face) are considerably different in space, leading to distinct enantioinduction mechanisms (Figure 5). Through experimental studies

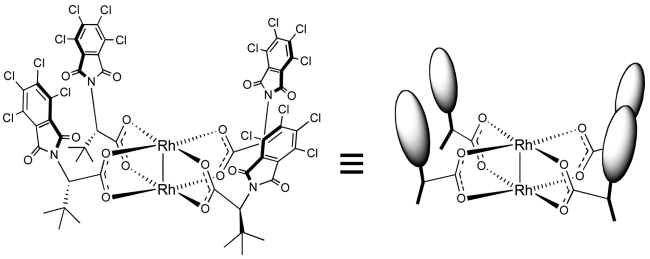


Figure 5. Representation of the all-up reactive conformation of Rh_2(*S*-TCPTTL)$_4$.[5a]

of the catalyst's structure, we have reasoned that in our system, the carbene-formation step of the reaction with **1f** is occurring on the more accessible top face, i.e., on the side of the tetrachlorophthaloyl groups.[5a]

We sought to further explore the potential of such structural asymmetry by studying the effect of achiral Lewis basic additives. Indeed, assuming that this symmetry is kept in solution, such additives could selectively block one side of the rhodium dimer and/or impact on its electronical properties, ultimately affecting the global stereoinduction of the reaction. Whereas weaker Lewis bases such as sulfides, phosphonamides, or ureas had no significant effect on the reaction's outcome in the case of α-nitro diazoacetophenones (Table 4, entries 3−5), pyridine derivatives and, more precisely, DMAP had a beneficial impact on the enantioselectivity level obtained (entry 1 vs 10).[14a] It should be noted that this effect was not observed at higher temperatures (i.e., 0 °C), indicating the reversible nature of such axial complexation on the rhodium dimer.[14b] The pink complex immediately formed by addition of 1 mol % DMAP (1 equiv relative to the catalyst), a more electron-rich catalyst, proved to be considerably less active than Rh_2(*S*-TCPTTL)$_4$. Indeed, the reaction was significantly slower, and lowering the catalyst loading to less than 1 mol % furnished only partial conversions. Using larger amounts of DMAP led to a decreased yield, with similar enantiomeric excess (95% ee). This observed effect on enantioselectivity might be due to a selective complexation of DMAP on the less enantiodiscriminative side of the rhodium dimer. Since we have already concluded that the carbene formation occurs exclusively on the top face, a second rationalization for the increment of enantioinduction should be taken into account (Figure 6).

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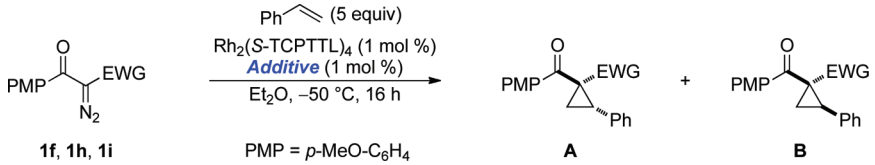
Table 4. Influence of Achiral Additives in the Rh_2(*S*-TCPTTL)$_4$-Catalyzed Cyclopropanation of α-EWG-Diazoacetophenones with Styrene



entry	substrate	EWG	additive	dr (A:B)[a]	ee (%)[b]
1	**1f**	NO_2	none	98:2	**93**
2	**1f**	NO_2	DMSO	98:2	93
3	**1f**	NO_2	HMPA	98:2	93
4	**1f**	NO_2	DMPU	98:2	93
5	**1f**	NO_2	PhSMe	98:2	93
6	**1f**	NO_2	pyrazine	ND	78
7	**1f**	NO_2	PBu_3	98:2	94
8	**1f**	NO_2	NMI	97:3	94
9	**1f**	NO_2	pyridine	97:3	94
10	**1f**	NO_2	DMAP	97:3	**95**
11[c]	**1h**	CN	none	95:5	**84**
12[c]	**1h**	CN	DMAP	95:5	**72**
13[d]	**1i**	CO_2Me	none	99:1	**88**
14[d]	**1i**	CO_2Me	DMAP	99:1	**79**

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] ee of major diastereomer determined by SFC on chiral stationary phase. [c] Reaction perfomed at −35 °C. [d] Reaction perfomed at −40 °C.

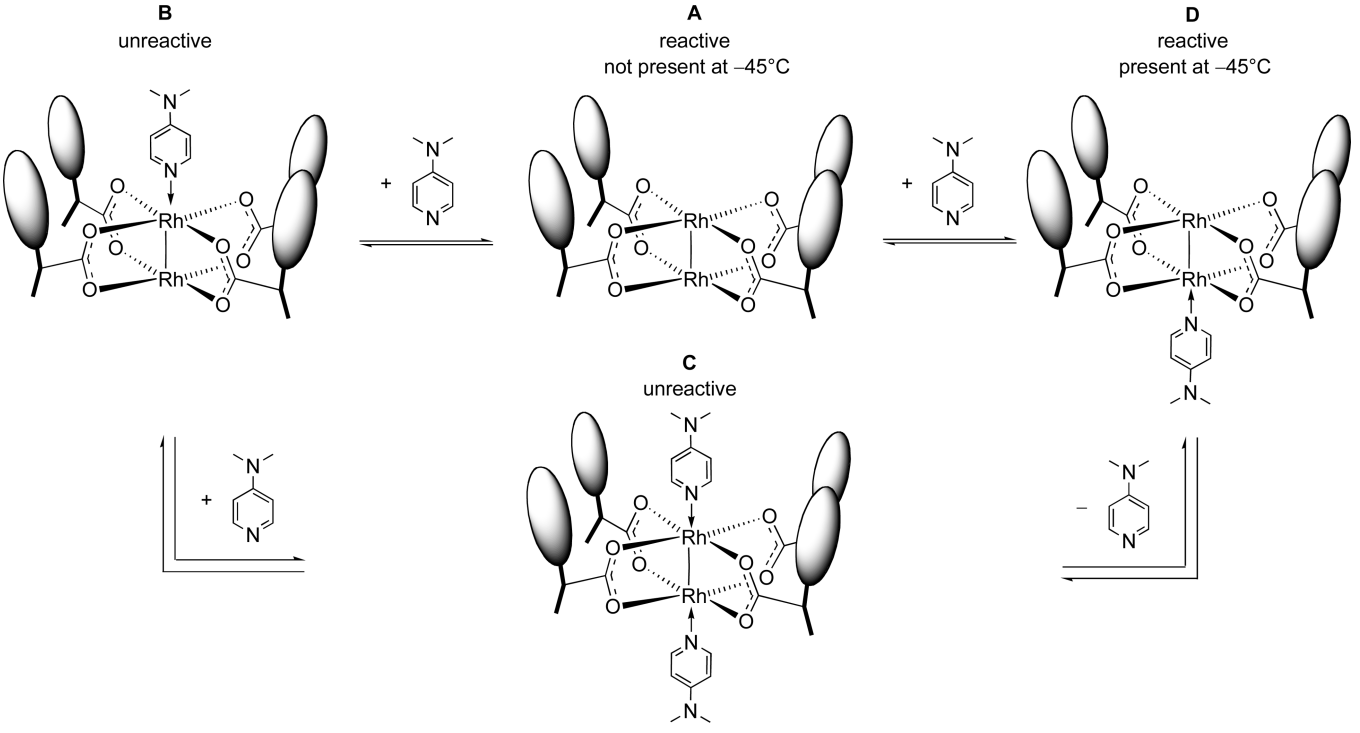


Figure 6. Rationalization for the increment of enantioselectivity with DMAP as catalytic additive.

As the carbene formation does not occur on the bottom face, complexes such as **B** or **C** are considered to be unreactive in this system. The DMAP-catalyst complex **D** can be formed either directly from **A** or through the intermediacy of **B** and **C**. This reactive complex may give rise to a later transition-state for the asynchronous 2 + 1 cycloaddition step of the mechanism as compared to the native catalyst **A**, due to a lower electrophilicity of the resulting carbene, globally leading to an improved

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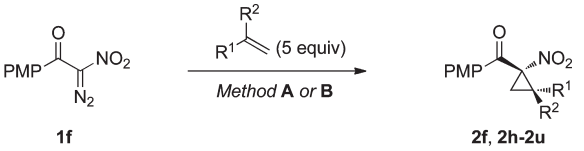
Table 5. Scope of Alkenes with α-Nitro Diazoacetophenones: Effect of DMAP as Catalytic Additive



Method **A**: Rh_2(*S*-TCPTTL)$_4$ (0.1 mol %), Et_2O, –50 °C, 16 h

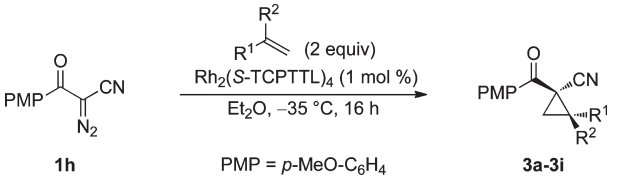
Method **B**: Rh_2(*S*-TCPTTL)$_4$ (1 mol %), **DMAP (1.2 mol %)**, Et_2O, –45 °C, 16 h

entry	R^1	R^2	product	method	yield (%)[a]	dr (*cis*:*trans*)[b]	ee (*cis*, %)[c]
1	Ph	H	**2f**	**A**[d]	81	98:2	93
				A[e]	80	98:2	93
				A[f]	80	98:2	92.9 ± 0.1
				B[f]	78	97:3	95.0 ± 0.2
2	4-Me-C_6H_4	H	**2h**	**A**[f]	76	98:2	92.4 ± 0.5
				B[f]	81	97:3	94.2 ± 0.2
3	4-*t*-Bu-C_6H_4	H	**2i**	**A**[f]	65	95:5	87.8 ± 0.5
				B[f]	70	91:9	89.1 ± 0.2
4	4-Cl-C_6H_4	H	**2j**	**A**[f]	91	98:2	93.2 ± 0.1
				B[f]	84	97:3	95.0 ± 0.5
5	4-F-C_6H_4	H	**2k**	**A**	88	98:2	92
				B	85	96:4	95
6	4-O_2N-C_6H_4	H	**2l**	**A**	74	99:1	95
				B	87	99:1	97
7	4-F_3C-C_6H_4	H	**2m**	**A**	75	98:2	91
				B	75	96:4	95
8	3-MeO-C_6H_4	H	**2n**	**A**[d]	85	97:3	92
				B	61	94:6	94
9	3-O_2N-C_6H_4	H	**2o**	**A**[d]	54	95:5	91
10	3-F_3C-C_6H_4	H	**2p**	**A**	68	96:4	94
				B	60	95:5	96
11	2-Cl-C_6H_4	H	**2q**	**A**[g]	68	96:4	92
				B	53	96:4	94
12	2-F-C_6H_4	H	**2r**	**A**	54	97:3	93
				B	36	98:2	94
13	1-naphthyl	H	**2s**	**A**[d]	81	98:2	95
				B	78	96:4	94
14	Ph	Me	**2t**	**A**[h]	88	99:1	98
15	*n*-Bu	H	**2u**	**A**	5	54:46	42

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase (ee of major diastereoisomer). [d] 1 mol % of catalyst was used. [e] 0.5 mol % of catalyst was used. [f] Reaction was performed three times and results are reported as the mean values, with standard deviation for the ee. [g] Reaction perfomed at −40 °C. [h] Results shown are after recrystallization.

enantioinduction.[14a] It is interesting that using DMAP as additive with our two analogous substrates **1h** and **1i** had an opposite effect, leading to a drastic decrease in enantioselectivity (entries 11−14). These results illustrate the complexity of this system, and the fact that other factors, such as structural and/or conformational changes of the catalyst, might also be involved in this DMAP effect.

Table 6. Scope of Alkenes with α-Cyano Diazoacetophenones



entry	R^1	R^2	product	yield (%)[a]	dr (*trans*:*cis*)[b]	ee (*trans*, %)[c]
1	Ph	H	**3a**	92	95:5	84
2	4-Cl-C_6H_4	H	**3b**	94	97:3	88
3	4-O_2N-C_6H_4	H	**3c**	90	99:1	91
4	3-MeO-C_6H_4	H	**3d**	92	95:5	79
5	2-Cl-C_6H_4	H	**3e**	88	98:2	81
6	1-naphthyl	H	**3f**	99	96:4	73
7	*n*-Bu	H	**3g**	75	81:19	73
8	Ph	Me	**3h**	97	84:16	75
9[d]	OBz	H	**3i**	82	97:3	94

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase (ee of major diastereoisomer). [d] 10 equiv alkene was used.

These results convinced us to undertake a two-method scope of alkenes with α-nitro diazoacetophenones (Table 5). Method **A** furnishes the product with decreased enantioselectivity but uses 10 times less catalyst than method **B**, which in turn provides better enantiomeric excesses. The results summarized in Table 5 demonstrate that both methods gave rise to similar trends in term of enantioselectivity obtained, although method **B** generally furnished a 2−3% ee increase, showing that this DMAP effect is not dependent on the structure of the alkene. This selectivity increment roughly represents a non-negligible 0.15−0.22 kcal/mol increase in energy difference between the competing diastereomeric transition states in play. The yield and diastereoselectivity observed generally remain similar for both methods. Styrene derivatives bearing substituents at the *ortho*, *meta*, or *para* position are all tolerated under the reaction conditions. It is noteworthy that styrenes bearing electron-donating groups (e.g., OMe) at the *para* position only gave rise to ring-opened or unidentified products, due to the strong electrophilic nature of such cyclopropane bearing two electron-withdrawing groups. Importantly, α-methylstyrene reacted smoothly under our conditions with excellent stereoselectivity, giving access to the corresponding highly strained *cis*-cyclopropane α-amino acid derivative (entry 14). Unfortunately, alkyl-substituted alkenes did not provide the corresponding cyclopropane in useful yields (entry 15), and dienes afforded only Cope-rearranged achiral products.

α-Cyano diazoacetophenone **1h** is also a good substrate for the asymmetric cyclopropanation with a wide variety of olefins (Table 6). This method usually provides very high yields of the corresponding cyclopropanes in excellent diastereoselectivity and good enantioselectivity, using only 2 equiv of the alkene. Various styrene derivatives, aliphatic alkenes, and enol esters are tolerated as substrates, with a considerable degree of variability with respect to the electronic nature of the double bond. It is noteworthy that dienes and electron-rich styrene derivatives were also reactive in this process but afforded only poor stereocontrol.

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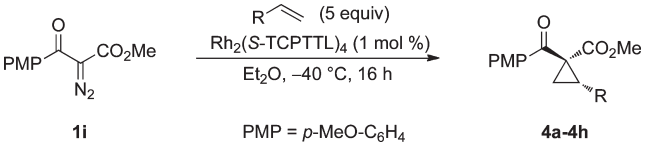
The β-keto α-diazoester analogue **1i** furnishes the corresponding *gem*-dicarbonyl cyclopropanes in excellent stereoselectivity, although generally with lower yields (Table 7). The reaction offers optimal stereoselectivity at −40 °C with the use of 1 mol % of Rh_2(*S*-TCPTTL)$_4$ as catalyst, affording the highest selectivities with electron-poor styrene derivatives (entries 2−4).

Table 7. Scope of Alkenes with β-Keto α-Diazoester



1i **4a-4h**

entry	R	product	yield (%)[a]	dr (*cis*:*trans*)[b]	ee (*cis*, %)[c]
1	Ph	**4a**	60	99:1	88
2	4-Cl-C_6H_4	**4b**	31	99:1	94
3	4-F_3C-C_6H_4	**4c**	60	99:1	93
4	4-O_2N-C_6H_4	**4d**	10	99:1	94
5	4-Me-C_6H_4	**4e**	70	99:1	84
6	3-Me-C_6H_4	**4f**	54	99:1	86
7	2-Cl-C_6H_4	**4g**	33	>97:3	90
8	1-naphthyl	**4h**	52	99:1	85

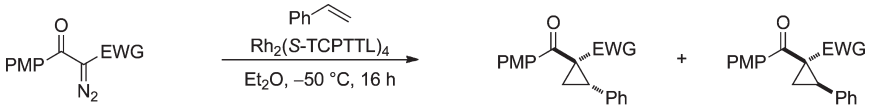
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase.

Applications of the Enantioenriched Cyclopropanes. With these methods in hand, a wide variety of cyclopropane derivatives bearing an α-PMP ketone group can be efficiently synthesized in high stereoselectivity. Much to our delight, this ketone moiety was found to control not only the selectivity but also the crystallinity of the final product. Indeed, in almost all cases, the major diastereoisomer was a white crystalline solid, while the minor isomer was a colorless oil. As shown in Table 8, the three methods could be applied on a 2−3 g scale (10−14 mmol) with comparable results of yield, dr and ee, and the products' crystallinity permitted access to enantiopure material when desired, in good overall yields.

The PMP group on the ketone directs the regioselectivity of a subsequent Baeyer−Villiger oxidation to form activated esters (Table 9). The optimized procedure proceeded smoothly in the case of α-nitro acetophenone **2f**[5a] and α-cyano acetophenone **3a**, affording high yields of the corresponding esters, with total retention of the stereochemical information. The β-ketoester **4a** proved to be significantly less reactive, and only 18% of the corresponding *gem*-diester could be obtained in these conditions, while the use of stronger peroxidation agents provoked decomposition of the acid-sensitive starting material. This observation is presumably due to the increased steric demand and decreased electron-withdrawing character of the methyl ester as compared with a nitro group or a nitrile. The regioselectivity of the transformation was found to be complete in all three cases.

Schemes 1−3 furnish a global picture of the array of transformations that can be applied to the three types of cyclopropane derivatives possessing geminal electron-withdrawing groups obtained from our method. In the case of the α-nitro and α-cyano

Table 8. Cyclopropanation on Larger Scale to Access Enantiopure Material



10-14 mmol PMP = *p*-MeO-C_6H_4 **A** **B**

entry	substrate	EWG	yield (%)[a,b]	dr (**A**:**B**)[a,c]	ee (%)[a,d]
1	**1f**	NO_2	82 (72)	98:2 (>99:1)	93 (>99)
2[e]	**1h**	CN	93 (66)	95:5 (>99:1)	83 (98)
3[f]	**1i**	CO_2Me	57 (41)	99:1 (>99:1)	87 (>99)

[a] Results in parentheses are after recrystallization. [b] Isolated yield of combined diastereomers. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] ee of major diastereomer determined by SFC on chiral stationary phase. [e] Reaction perfomed at −35 °C. [f] Reaction perfomed at −40 °C.

Table 9. Baeyer−Villiger Oxidation of the Resulting α-EWG Acetophenones

PMP = *p*-MeO-C_6H_4 **A** **B**

entry	EWG	substrate	product	yield (%)[a]	dr (**A**:**B**)[b,c]	ee (%)[d,e]
1[5a]	NO_2	**2f**	**5a**	82	>99:1 (>99:1)	>99 (>99)
2	CN	**3a**	**5b**	89	>99:1 (>99:1)	98 (98)
3	CO_2Me	**4a**	**5c**	18	>99:1 (>99:1)	>99 (>99)

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] dr of starting material in parentheses. [d] ee of major diastereomer determined by SFC on chiral stationary phase. [e] ee of starting material in parentheses.

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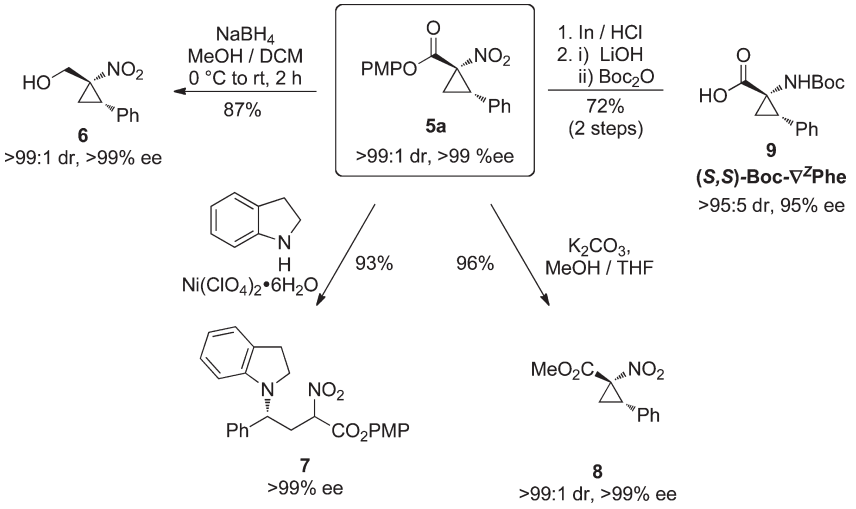
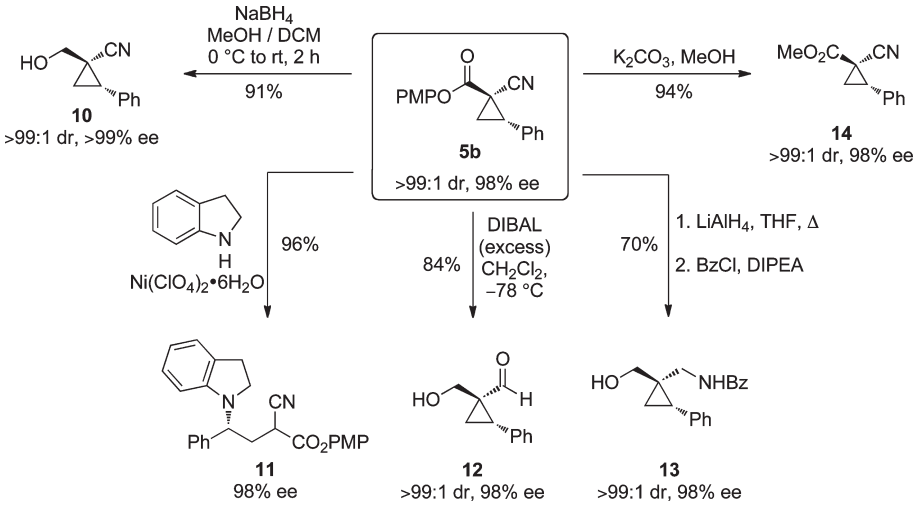
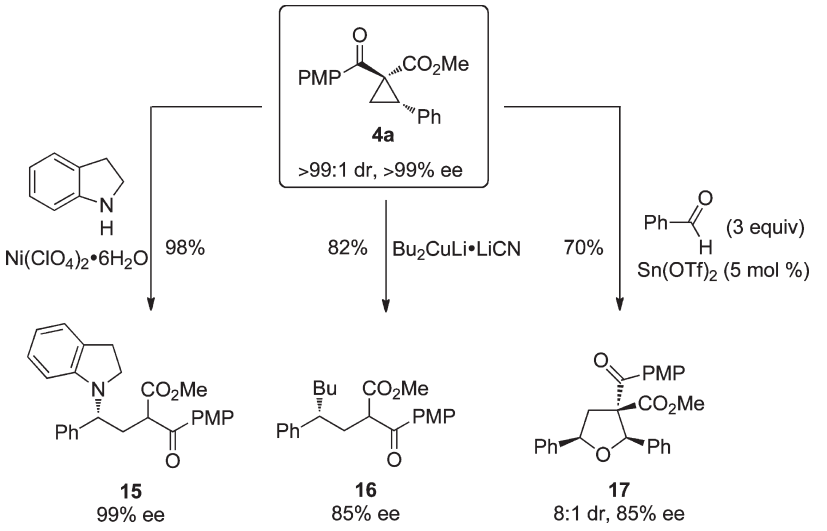
Scheme 1. Applications of α-Nitro PMP-Ester 5a



Scheme 2. Applications of α-Cyano PMP-Ester 5b



Scheme 3. Applications of *β*-Ketoester 4a



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PMP-esters **5a** and **5b**, chemoselective reductions of either of the geminal functionalities can be efficiently performed (Schemes 1 and 2). The PMP-ester is cleanly reduced to the primary alcohols **6** and **10** using $NaBH_4$ at 0 °C with retention of the stereochemical information. In the case of α-nitroester **5a**, selective reduction of the nitro group is achieved using In/HCl, and the resulting α-aminoester is shown to be a suitable precursor of the *cis*-cyclopropane α-amino acid derivative (*S*,*S*)-Boc-∇^ZPhe (**9**). α-Cyanoester **5b** can be fully reduced to the corresponding γ-amino alcohol **13** using an excess of $LiAlH_4$ under reflux, the product obtained from such transformation being an obvious precursor of the cyclopropane β-amino acid. Using an excess of DIBAL instead leads to the formation of the *cis*-β-hydroxyaldehyde **12** in high yield. For both substrates, simple transesterification is efficient under K_2CO_3/MeOH conditions in excellent yields (**8** and **14**). Moreover, the stereospecific addition of an aniline under $Ni(ClO_4)_2 \cdot 6H_2O$ catalysis, previously shown to be efficient on methylnitroacetate derivatives,[3c] affords outstanding yields of the ring-opened product in all three cases (**7**, **11**, and **15**), with full conservation of the initial enantioselectivity level. The analogous nucleophilic substitution of a cuprate is also possible in the case of **4a**, affording ring-opened product **16** in 82% yield. In addition, **4a** is demonstrated to be a suitable substrate in a formal cycloaddition with benzaldehyde under Johnson's conditions to form chiral tetrahydrofuran **17**, although with a slight loss of stereochemical information in this case.[4b]

CONCLUSION

In summary, on the basis of our experimental evidence concerning the stereoinduction mechanism in Rh_2(*S*-TCPTTL)$_4$-catalyzed cyclopropanations, we have designed and developed a highly stereoselective cyclopropanation of alkenes with α-EWG-diazoacetophenones, where EWG = NO_2, CN, or CO_2Me. The methods feature the use of a PMP-ketone as diastereo- and enantioselectivity control group, which can be transformed to activated esters following the cyclopropanation for further functionalization. The efficient access to enantiopure material is demonstrated, along with a myriad of transformations for which these cyclopropanes are useful substrates. For instance, the synthesis of highly enantioenriched cyclopropane α- and β-amino acid derivatives, α-chiral amines, and tetrahydrofurans was successfully achieved.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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