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Experimental Evidence for the All-Up Reactive Conformation of Chiral Rhodium(II) Carboxylate Catalysts: Enantioselective Synthesis of *cis*-Cyclopropane α-Amino Acids

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Chiral Rh(II)-carboxylate catalysts have found widespread use in the field of metal carbene transformations, including asymmetric cyclopropanation reactions.¹ Though several enantioselective transformations have been developed to date, little evidence is known on how the chirality is projected near the reaction center by the chiral carboxylates. Davies et al. have suggested that four main possible symmetries have to be considered, from which only two possess equivalent catalyst faces (Figure 1, C_2 and D_2).² It has been postulated that catalysts having two different carbene-formation sites should not be effective in inducing enantioselectivity, since the more kinetically active and accessible face is apparently achiral (C_1 and C_4).^{2b}

However, Fox et al. recently contradicted this concept by reporting the highly efficient asymmetric cyclopropanation of alkenes with α -alkyl- α -diazoesters using such a catalyst, where DFT calculations demonstrated that the all-up conformation of the catalyst plays a prominent role in these reactions.³ Herein, we report our concomitant work that demonstrates strong experimental evidence in favor of the all-up symmetry as the catalyst's reactive conformation in an unprecedented stereoselective cyclopropanation of alkenes with α -nitro diazoacetophenones. Moreover, the products issued from such a process were shown to be valuable intermediates for the expedient synthesis of optically active *cis*-cyclopropane α -amino acids.

Recently, our group has been interested in the synthesis of *trans*cyclopropane α -amino acids via the enantioselective addition of nitrocarbene equivalents to olefins,^{4,5} due to the high potential of such building blocks in drug discovery.⁶ To obtain the corresponding *cis* compound enantioselectively through a similar process, we envisioned that α -nitro diazoacetophenones would be ideal candidates to suit this goal (Scheme 1).^{7,8} Subsequent Baeyer–Villiger oxidation, nitro reduction, and hydrolysis afford an efficient route to optically active *cis*-cyclopropane α -amino acids.⁹

In our early investigations, we identified Hashimoto's amino acid derived catalysts 2a-d and 3a-e, also used in Fox's methodology,³ as promising complexes in our system. We rapidly observed that these two classes of catalysts had very distinct behaviors in terms of enantioinduction, although the only apparent difference is the replacement of aromatic hydrogen atoms by halogen atoms (Table 1).¹⁰

Indeed, modifying the ligand's amino acid side chain had little influence on the stereoselectivity for chlorinated catalysts (entries 5-8), in contrast with their *N*-phthaloyl analogues (entries 1-4). We postulated these observations were due to different reactive conformations in solution. To understand these results better, we first resolved X-ray crystal structures of representative complexes **2c**, **3c**, and **3e**, unraveling the puzzling symmetries of these catalysts (Figure 2).¹¹



Figure 1. Possible symmetries adopted by rhodium(II) carboxylates. *Scheme 1.* Synthesis of *cis*-Cyclopropane α -Amino Acids



Apparently, these three families of catalysts possess similar conformations in the solid state, i.e. all-up (Figure 1), a symmetry that has long been overlooked as non-operative for enantioinduction.² This arrangement of ligands displays two different axial sites on the Rh dimer, suggesting a competition of two mechanisms in the carbene formation step of the reaction and, thus possibly, different stereoinductions in the subsequent [2+1] cycloaddition. Of the four possible symmetries displayed in Figure 1, this is the only one where one axial site is completely shielded from the ligand's amino acid side chains R, i.e. the more accessible top face. For us, the fact that catalysts 3a-d show similar stereoselectivities regardless of this group suggests that this is their reactive conformation, while non-halogenated complexes 2a-d might be less rigid in solution. As highlighted in Figure 2, 3a-e could benefit from halogenbonding interactions to rigidify their all-up conformation, a known bonding event for this specific type of N-protective group.¹² Additionally, VT NMR experiments made on 3d demonstrated the rigid nature of such halogenated complexes in solution.11b

To confirm our hypothesis, we conducted 700 MHz ${}^{1}\text{H}{-}{}^{13}\text{C}$ heteronuclear NOESY experiments on representative catalysts **2d** and **3d**, two complexes that differ only by the replacement of hydrogens by chlorine atoms (eq 1). Indeed, if the all-up symmetry is scrambled in solution, i.e. if at least one phthaloyl group is flipped

Table 1. Influence of the Catalyst's Structure



^a Isolated yield of combined diastereomers. ^b Determined by ¹H NMR analysis of the crude mixture. ^c Determined by SFC on chiral stationary phase. ^d 1 equiv of 4a and 4 equiv of 1a were used. ^e 0.1 mol % of catalyst was used.



Figure 2. X-ray structure of catalysts 3c, 3e, and 2c: side view (left column), top view and halogen-bonding distances in Å (right column); axial solvents were omitted for clarity.

down, one should be able to see an interaction between the side chain's protons and the phthaloyl's aromatic carbons of the adjacent ligand. In the case of chlorinated complex 3d (X = Cl), no interaction is observed with the N-tetrachlorophthaloyl aromatic carbons, between either the *t*-Bu protons or the α -proton, suggesting that the all-up conformation is maintained in solution. In contrast, all aliphatic protons of complex 2d (X = H) display a clear interaction with four N-phthaloyl carbons, highlighting the flexible nature of these non-halogenated catalysts in solution. However, one must recognize that the analysis of these spectroscopic results may be complicated by the different steric and π -stacking properties of the two complexes.



Table 2. Scope of the Cyclopropanation

e

9

	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	4a-4m 5 equiv) nol %) °C, 16 h	PMP 5a-5m	
entry	alkene	yield ^a (%)	dr ^b (<i>cis/trans</i>)	ee ^c (%, <i>cis</i>)
1	PhCH= CH_2 (4a)	80	98:2	93
2	4-MePhCH= CH_2 (4b)	75	97:3	92
3	$4-tBuPhCH=CH_2$ (4c)	65	94:6	87
4	4-ClPhCH=CH ₂ (4d)	91	98:2	93
5	4-FPhCH= CH_2 (4e)	88	98:2	92
6	$4-NO_2PhCH=CH_2$ (4f)	74	99:1	95
7	$4\text{-}CF_3PhCH=CH_2$ (4g)	75	98:2	91
8^d	$3-MeOPhCH=CH_2$ (4h)	85	97:3	92

10^e	2-ClPhCH= CH_2 (4j)	68	96:4	92			
11	2-FPhCH= CH_2 (4k)	54	97:3	93			
12^{d}	1-naphthylCH= CH_2 (41)	81	98:2	95			
13 ^f	$PhC(Me) = CH_2 (4m)$	88	99:1	98			
^a Isolated yield of combined diastereomers. ^b Determined by ¹ H NMR							
nalysis of the crude mixture. ^c Determined by SFC on chiral stationary							

68

96:4

94

a phase. ^d 1 mol % 3d was used. ^e Reaction was run at -40 °C. ^f Results after recrystallization.

Scheme 2. Derivatization of Compound 5a

 $3-CF_3PhCH=CH_2$ (4i)



Our reaction was shown to be efficient for a wide range of styrene derivatives, using only 0.1 mol % of catalyst 3d (Table 2). It should be noted that diazoketones bearing an α -EWG such as 1a are usually well-known to afford low enantioselectivities in Rh(II)catalyzed cyclopropanation reactions.13

Gratifyingly, the reaction could be carried out on a multigram scale with similar efficiency, and the high crystalline nature of these compounds permitted isolation of 5a as a single stereoisomer in good overall yield (Scheme 2). After extensive optimization, appropriate Baeyer-Villiger oxidation conditions provided the corresponding cis-a-nitroester in 82% isolated yield. Furthermore,



x x		4a (5 3d (1 Et ₂ O, -{	equiv) mol %) 50°C, 16h	Y X 53.8b.80	NO : ′Př
entry (diazo)	х	Y	yield ^a (%)	dr ^b (<i>cis/trans</i>)	ee ^c (%, <i>cis</i>)
1 (1b)	CF ₃	Н	80	70:30	71
2 (1c)	Cl	Н	82	96:4	92
3 (1a)	OMe	Н	81	98:2	93
4 (1d)	NMe_2	Н	38	99:1	96
5 (1e)	Н	OMe	72	98:2	96

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

reduction of the nitro group using In/HCl in THF furnished the *cis*- α -amino ester 6, a *C*-protected amino acid, with a minimum loss of stereochemical information.¹⁴ Compound 6 can then be transformed into the known N-Boc amino acid 7 through elemental steps.^{2a}

To gain further insight into the enantioinduction process of our reaction, we synthesized five electronically different α -nitro diazoacetophenones 1a-1e and submitted them to our reaction conditions. As depicted in Table 3, electron-deficient analogue 1b furnished decreased levels of enantioselectivity compared to our model substrate 1a, while the more electron-rich diazo 1d afforded superior asymmetric induction. Our working hypothesis is that the tetrachlorophthaloyl moieties of the ellipsoidal chiral pocket induced by the all-up symmetry of catalyst 3d (top face) could permit π -stacking interactions with the arylketone group on the substrate, fixing it in a conformation where one of the prochiral faces of the carbene is blocked. With these chlorinated groups being electrondeficient, such interactions would be more important for electronrich arylketones, thus providing enhanced enantioselectivity for substrates like 1d or 1e. In addition, we noticed during our optimization that running the reaction in aromatic solvents like benzene led to a drastic decrease in enantioselectivity (20% ee compared to 87% ee in Et₂O), suggesting the presence of π -stacking as a key element in the enantiodiscriminating step of the reaction.

It is noteworthy that the diastereoselectivity was also found to be dependent on the arylketone's electronics, confirming the presence of Doyle's stereoelectronic effect in our system.^{1b,15} Indeed, α-nitro diazoacetophenones can permit dissociation of steric and electronic factors in the transition state, since the X group is away from the reaction center but still strongly influences the ketone's oxygen basicity.

In summary, we report the first catalytic enantioselective cyclopropanation of alkenes with α -nitro diazoacetophenones and the corresponding products obtained from this reaction have been shown to be practical precursors of optically active cis-cyclopropane α -amino acids. All our experiments suggest that the halogenated rhodium carboxylate catalysts used in this process react through an all-up conformation, which is consistent with Fox's DFT calculations made on non-halogenated analogues. Additional insights into the mechanism of related reactions will be reported in due course.

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Supporting Information Available: X-ray crystal structure of 3d, experimental procedure for the preparation of compounds, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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