J|A|C|S COMMUNICATIONS

Published on Web 10/27/2009

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

Vincent N. G. Lindsay, Wei Lin, and André B. Charette*

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

Received June 3, 2009; E-mail: andre.charette@umontreal.ca

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]

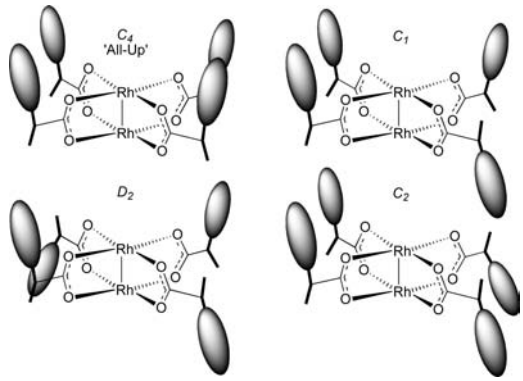
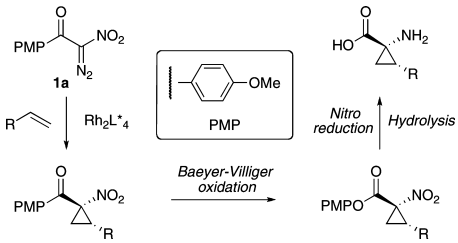


Figure 1. Possible symmetries adopted by rhodium(II) carboxylates.

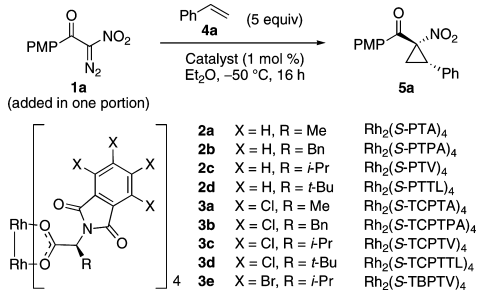
Scheme 1. Synthesis of *cis*-Cyclopropane α-Amino Acids



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 halogen-bonding 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 $^{1}H-^{13}C$ 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



entry	catalyst	yield[a] (%)	dr[b] (*cis*/*trans*)	ee[c] (%, *cis*)
1	**2a**	55	53:47	22
2	**2b**	56	55:45	43
3	**2c**	76	72:28	16
4	**2d**	80	33:67	2
5	**3a**	81	97:3	**92**
6	**3b**	72	94:6	**91**
7	**3c**	82	98:2	**91**
8	**3d**	81	98:2	**93**
9	**3e**	89	96:4	80
10[d]	**3d**	70	99:1	**92**
11[e]	**3d**	80	98:2	**93**

[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. [d] 1 equiv of **4a** and 4 equiv of **1a** were used. [e] 0.1 mol % of catalyst was used.

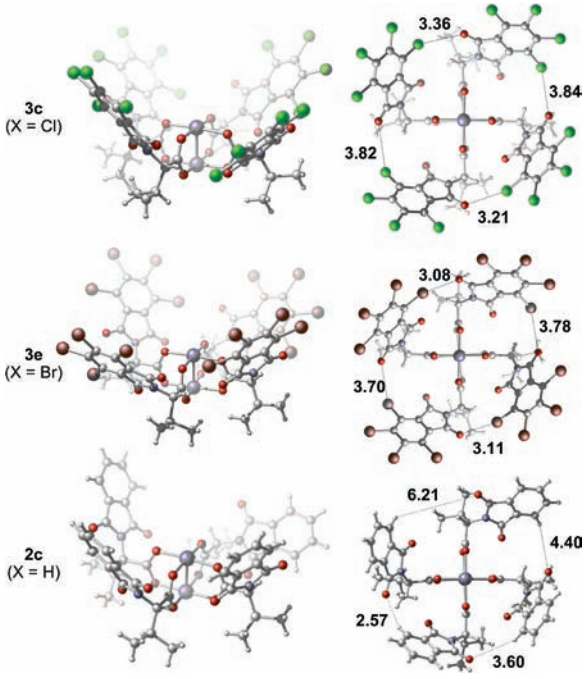


Figure 2. X-ray structure of catalysts **3c**, **3e**, and **2c**: side view (left column), top view and halogen-bonding distances in Å (right column); axial solvents were omitted for clarity.

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.

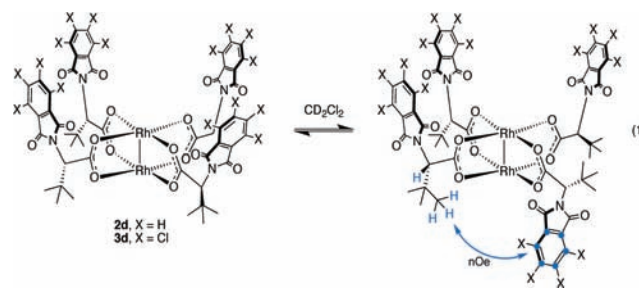
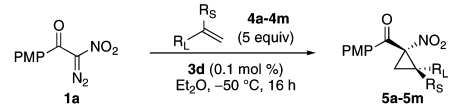


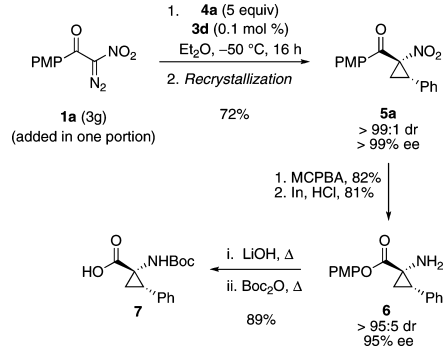
Table 2. Scope of the Cyclopropanation



entry	alkene	yield[a] (%)	dr[b] (*cis*/*trans*)	ee[c] (%, *cis*)
1	PhCH=CH$_2$ (**4a**)	80	98:2	93
2	4-MePhCH=CH$_2$ (**4b**)	75	97:3	92
3	4-*t*BuPhCH=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$_2$PhCH=CH$_2$ (**4f**)	74	99:1	95
7	4-CF$_3$PhCH=CH$_2$ (**4g**)	75	98:2	91
8[d]	3-MeOPhCH=CH$_2$ (**4h**)	85	97:3	92
9	3-CF$_3$PhCH=CH$_2$ (**4i**)	68	96:4	94
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$_2$ (**4l**)	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 analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase. [d] 1 mol % **3d** was used. [e] Reaction was run at −40 °C. [f] Results after recrystallization.

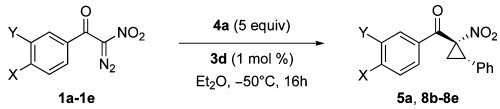
Scheme 2. Derivatization of Compound **5a**



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*-α-nitroester in 82% isolated yield. Furthermore,

Table 3. Effect of the Arylketone's Electronics on Stereoselectivity



entry (diazo)	X	Y	yield[a] (%)	dr[b] (*cis*/*trans*)	ee[c] (%, *cis*)
1 (**1b**)	CF_3	H	80	70:30	71
2 (**1c**)	Cl	H	82	96:4	92
3 (**1a**)	OMe	H	81	98:2	93
4 (**1d**)	NMe_2	H	38	99:1	96
5 (**1e**)	H	OMe	72	98:2	96

[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.

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 electron-deficient, such interactions would be more important for electron-rich 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 Et_2O), 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.

Acknowledgment. This work was supported by NSERC (Canada), Merck Frosst Canada & Co., Boehringer Ingelheim (Canada) Ltd., and the Université de Montréal. We are grateful to F. Bélanger-Gariépy and CYLView for X-ray analysis; J. Tannous for SFC analysis; and M. T. Phan Viet and S. Bilodeau for NMR analysis. V.N.G.L. is grateful to NSERC (PGS D) and the Université de Montréal for postgraduate fellowships.

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.

References

(1) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (c) Davies, H. M. L.; Antoulinakis, E. G. *Org. React. (N.Y.)* **2001**, *57*, 1.
(2) (a) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (b) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545.
(3) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230.
(4) (a) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327. (c) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262.
(5) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493.
(6) (a) Beaulieu, P. L.; Gillard, J.; Bailey, M. D.; Boucher, C.; Duceppe, J. S.; Simoneau, B.; Wang, X. J.; Zhang, L.; Grozinger, K.; Houpis, I.; Farina, V.; Heimroth, H.; Krueger, T.; Schnaubelt, J. *J. Org. Chem.* **2005**, *70*, 5869. (b) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838. (c) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (d) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313.
(7) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468.
(8) For selected examples of rhodium-catalyzed enantioselective cyclopropanation of diazo compounds bearing two electron-withdrawing groups, see: (a) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155. (b) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970. (c) Lin, W.; Charette, A. B. *Adv. Synth. Catal.* **2005**, *347*, 1547. (d) Wurz, R.; Charette, A. B. *J. Mol. Catal. A* **2003**, *196*, 83.
(9) For other examples of catalytic asymmetric synthesis of *cis*-cyclopropane amino acids, see ref 2a and: Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460.
(10) For examples of other types of asymmetric reactions using these catalysts, see: (a) Anada, M.; Kitagaki, S.; Hashimoto, S. *Heterocycles* **2000**, *52*, 875. (b) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109. (c) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559. (d) Shimada, N.; Anada, M.; Nakamura, S.; Nambu, H.; Tsutsui, H.; Hashimoto, S. *Org. Lett.* **2008**, *10*, 3603.
(11) (a) The structure of **3d** was also solved, and it displays a similar conformation. (b) See Supporting Information for details.
(12) Borowiak, T.; Wolska, I.; Brycki, B.; Zieliński, A.; Kowalczyk, I. *J. Mol. Struct.* **2007**, *833*, 197.
(13) (a) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145. (b) Charette, A. B.; Wurz, R. *J. Mol. Catal. A: Chem.* **2003**, *196*, 83. (c) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253.
(14) He, L.; Srikanth, G. S. C.; Castle, S. L. *J. Org. Chem.* **2005**, *70*, 8140.
(15) (a) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. (b) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinkler, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906. (c) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341.

JA9044955