Dramatic Stereo- and Enantiodivergency in the Intermolecular Asymmetric Heck Reaction Catalyzed by Palladium Complexes with Cyclopropane-Based PHOX Ligands

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Summary: A series of novel chiral phosphanyl-oxazoline (PHOX) ligands possessing a cyclopropyl backbone were synthesized. It was shown that introduction of a strained cyclic fragment in the ligand platform helped restrict conformational fluctuations of the metallacycle and provided the catalyst with marked steric effects. It was demonstrated that insignificant alterations in the ligand structure had a dramatic influence on the stereochemical outcome of the intermolecular asymmetric Heck reaction.

Phosphanyl-oxazoline (PHOX) ligands[1] are a very important class of ligands with a wide array of applications, spanning such cornerstone asymmetric transformations as the Heck reaction,[2] hydrogenation,[3] hydrosilylation,[4] AAA,[5a,b] and the Pauson−Khand reaction.[5c] They are also highly appealing due to their modular design, which permits easy preparation of an analogue series via the same synthetic route.[6] The first-generation of PHOX ligands bearing a flat *ortho*-phenylene tether were introduced by Pfaltz, Helmchen, and Williams[7] (Figure 1). Structural modification of these ligands through the incorporation of sterically demanding chiral elements into the ligand backbone (such as ferrocenyl,[8−10] apobornenyl,[11] and glucosamine-derived[12,13] fragments, Figure 1) allowed for significant improvement of the enantiodiscriminating properties of the corresponding catalysts for a number of transformations. However, the dramatic increase of the ligand's molecular weight and complexity of the system, associated with these modifications, significantly impaired the possibility for in-depth studies of the nature of enantioselection, by either theoretical modeling[14] or SAR methods.[9,15]

In our studies, we decided to implement a different approach widely used in medicinal chemistry, where conformationally constrained cyclic analogues of bioactive molecules are employed to elucidate important mechanisms and identify critical enzyme binding sites.[16] Analogously, we anticipated that tailoring two chelating arms of the ligand to a compact rigid scaffold, such as a three-membered ring, would help restrict the conformational fluctuations of the metallacycle without introducing additional steric demands and overloading the catalyst's structure. This, in turn, would help to accentuate the effect of chelating pendants and more accurately assess their role in controlling the stereochemical outcome of the reactions. Herein we describe the realization of this idea and demonstrate (1) a design of a new type of PHOX ligands featuring a rigid, chiral cyclopropyl backbone,[17] which led to a discovery of a novel, highly efficient catalytic system for the intermolecular asymmetric Heck reaction (AHR);[18] (2) that insignificant alterations in the structure of these ligands result in dramatic

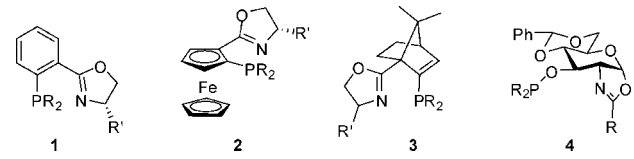

Figure 1. Chiral PHOX-type ligands.

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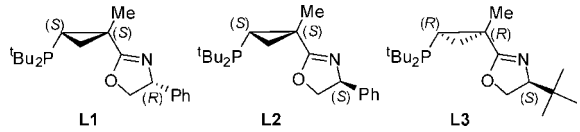


Figure 2. Novel PHOX ligands with a chiral cyclopropyl backbone.

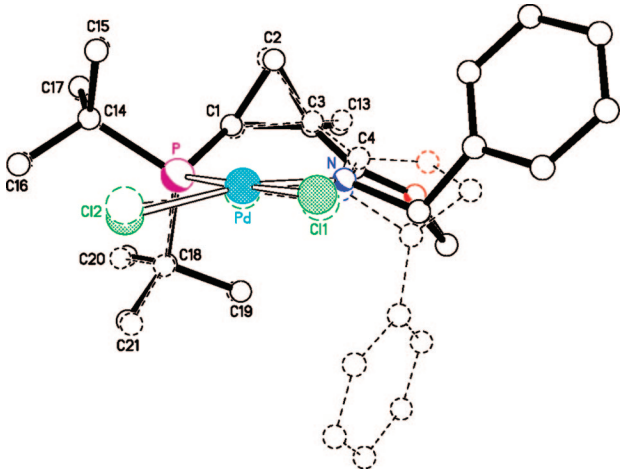
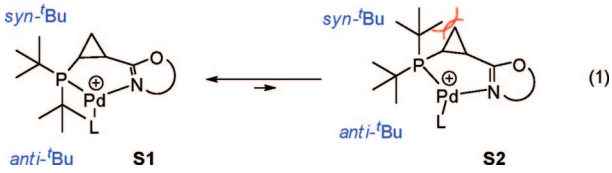


Figure 3. Overlay of X-ray structures of complexes (**L1**)$PdCl_2$ (solid lines) and (**L2**)$PdCl_2$ (dashed lines).

changes in the reaction course; and (3) a lucid rationale for the origins of the enantioselectivity and the factors controlling the rate of the isomerization in the AHR.

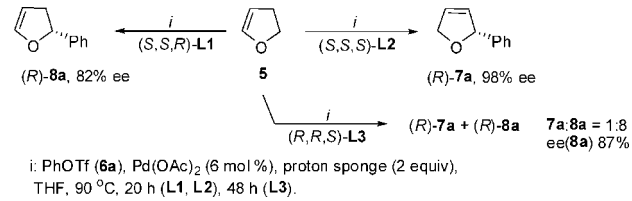
We began our studies by synthesizing two cyclopropyl analogues of ligand **1** (Figure 1), (*S,S,R*)-**L1** and (*S,S,S*)-**L2**,[19] possessing bulky *t*Bu_2P pendants and oxazoline moieties derived from (*R*)- and (*S*)-phenyl glycinol, respectively (Figure 2). This ligand topology was envisioned to be particularly beneficial for producing a conformationally rigid metallacycle. Thus, simple molecular modeling of the putative conformational equilibrium **S1** ⇆ **S2** suggested the strong preference of conformation **S1**, with a pseudoequatorial *syn*-*t*Bu group (eq 1). The alternative conformation **S2** appears to be highly disfavored due to significant repulsion between the pseudoaxial *syn*-*t*Bu substituent and the methylene group of cyclopropane, which is positioned nearly orthogonally to the plane of the palladacycle (eq 1). The X-ray analysis of the obtained palladium complexes (**L1**)$PdCl_2$ and (**L2**)$PdCl_2$ confirmed the predicted very high stability of the palladacycle conformation **S1**, which was independent of the absolute configuration of the chiral center at the dihydrooxazolyl moiety (Figure 3).



The dramatic difference between the new cyclopropane-based ligands and the previously reported PHOX analogues was revealed in comparative experiments on the asymmetric arylation of dihydrofuran **5**. It was found that employment of **L1** and **L2** provided very selectively two different products, (*R*)-**8a** and (*R*)-**7a**, respectively (Scheme 1). Close monitoring of the reaction catalyzed by Pd(**L1**) using chiral GC suggested the reaction begins with formation of product **7a**; however, at the time of complete consumption of the starting material **5**, the entire amount of **7a**

(19) See Supporting Information for details.

Scheme 1



i: PhOTf (**6a**), $Pd(OAc)_2$ (6 mol %), proton sponge (2 equiv), THF, 90 °C, 20 h (**L1**, **L2**), 48 h (**L3**).

produced was converted into **8a**. Furthermore, all through the reaction course, the absolute configuration of the stereogenic center at C2 remained the same, and the optical purity of both products **7a** and **8a** did not change significantly.[20] The obtained results were in striking contrast with the existing paradigm that (a) P,N-ligands always produce 2,5-dihydrofurans **7** with very high selectivity[2,18] and (b) enantioselectivity of the reaction carried out in the presence of PHOX ligands is generally governed by the configuration of the C4 in the oxazoline moiety.[21] An even more remarkable result was obtained when the analogous reaction was performed in the presence of ligand **L3**, which represents a pseudoenantiomer[22] of **L1** (Figure 2). Unexpectedly, a subtle change of the substituent size at C4 in the oxazoline ring resulted in a complete switch of the enantioselectivity of the reaction.[23] Similarly to the reaction catalyzed by the Pd(**L1**) complex, the isomerized product **8a** was obtained selectively; however, both the arylation reaction and the isomerization proceeded much slower in this case (Scheme 1).

We propose the following simple rationale for the observed phenomena (Schemes 2, 3). First, we envision that coordination of the soft π-ligand dihydrofuran should take place predominantly *trans* to the soft phosphorus,[24] whereas the σ-aryl ligand should reside *trans* to the hard N-donor atom.[13] The axial P-*t*Bu group and a bulky substituent at C4 in the dihydrooxazolyl moiety in the Pd((*S,S,S*)-**L2**) complex act synergistically to provide efficient blocking of both bottom quadrants, thereby completely preventing the *re*-face attack (**S5**, Scheme 2A). As a result, the reaction proceeds highly selectively via the *si*-face attack, producing (*R*)-**7** (**S4**, Scheme 2A). In the case of (*S,S,R*)-**L1**-derived complex **S6**, the pseudoaxial P-*t*Bu group and the *syn*-phenyl substituent encumber the *re*-face (**S8**) and the *si*-face approach (**S7**), respectively. Still, the former interaction (**S8**) is dominating (as judged by simple docking modeling); accordingly, the (*R*)-enantiomer of the product **7** is formed predominantly, albeit with lower enantioselectivity (Scheme 2B). Similar considerations were used to account for the observed reversal of enantioselectivity in the reaction carried out in the presence of *ent*-**L3** (Scheme 2C).[25] Thus, ample sterics caused by a bulky *tert*-butyl group in the top right quadrant counterbalances the effect of the pseudoaxial P-*t*Bu substituent. This leads to (a) a significant decrease of the reaction

(20) This is in contrast to the isomerization catalyzed by palladium complexes with diphosphine ligands, in which the normal (**7a**) and the isomerized product (**8a**) had opposite absolute configurations. See: Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

(21) It should be mentioned, however, that in the reactions using PHOX ligands bearing a very bulky backbone, the enantiomeric outcome is controlled by the absolute configuration of the backbone rather than that of the oxazoline ring. For discussion, see ref 8b.

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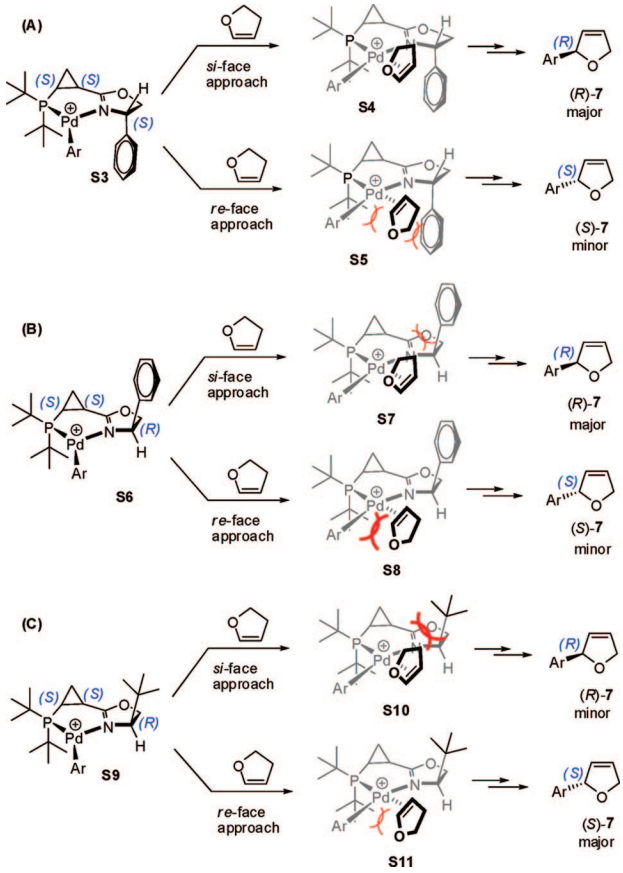
(23) During preparation of the manuscript, an example of enantioselectivity switch in the AHR catalyzed by seven-membered N-Pd-P complexes was reported. See ref 14a.

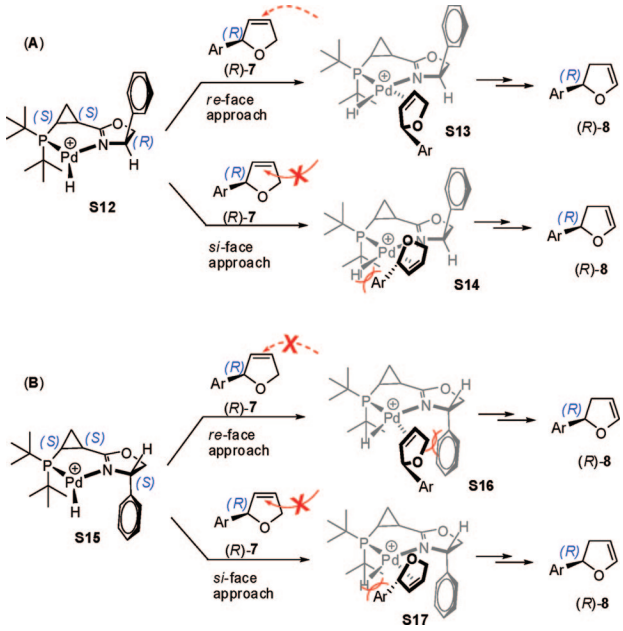
(24) For *trans*-effect in Pd complexes with P-N ligands, see for example: (a) Lee, S.; Lim, C. W.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445. (b) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031. (c) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *23*, 566.

(25) For a clear -cut comparison, *ent*-**L3** with the (*S,S,R*)-configuration is used in the discussion of mechanistic rationale.

Scheme 2. Rationale for the Observed Enantioselectivity in the Reactions Catalyzed by Pd(L2) (A), Pd(L1) (B), and Pd(L3) (C)



Scheme 3. Rationale for the Observed Isomerization Aptitude in the Reactions Catalyzed by Pd(L1) (A) and Pd(L2) (B)

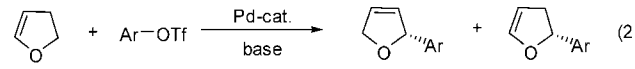


rates and (b) the *si*-face approach becoming considerably less favorable, which results in the reaction proceeding via the *re*-face attack to give (*S*)-**7** (Scheme 2C).

The different tendencies of Pd(**L1**) and Pd(**L2**) catalysts to promote isomerization of product **7** into **8** can be rationalized as follows (Scheme 3). Thus, we argue that the *si*-face approach of species **S12** to the double bond of **7** cannot be realized due to severe steric clashes between the di(*tert*-butyl)phospanyl group of the ligand and the aryl substituent in **7** (**S14**, Scheme 3A).

However, the alternative *re*-face approach is not associated with any significant steric hindrance, making this mechanistic channel available for isomerization (**S13**, Scheme 3A).[26] In contrast, both potential pathways for hydropalladation of **7** by the diastereomeric Pd(**L2**) hydride species **S15** are hampered due to unfavorable steric interactions of the substrate either with the aryl substituent in the heterocyclic pendant (**S16**) or with the tBu$_2$P moiety of the ligand (**S17**) (Scheme 3B). As a result, both mechanistic channels for isomerization of compound **7** into **8** are suppressed in this case.

Table 1. Asymmetric Arylation of Dihydrofuran with Aryl Triflates



5 **6** (*R*)-**7** (*R*)-**8**

no.	aryl[a]		time, h	**7**:**8**	ee (**7**), %	conv, %[b]	yield, %[c]
1	Ph	**6a**	48	16:1	98	97	73
2	*p*-Me-C_6H_4	**6b**	36	16:1	99	96	85
3	*p*-MeO-C_6H_4	**6c**	20	17:1	98	98	92
4	*p*-CF_3-C_6H_4	**6d**	48	>50:1	98	58	52
5	1-Nphth	**6e**	48	18:1	98	70	70

[a] Conditions: $Pd(OAc)_2$ (6 mol %), **L2** (6 mol %), **5** (4 equiv), iPr$_2$NEt (2 equiv), THF, 90 °C. [b] Conversion by GC. [c] Isolated yields.

In contrast to a number of previously reported examples showing a significant dependence of both ee and regioselectivity on the electronic and steric properties of the aryl triflate.[27]

In conclusion, by lowering the degrees of freedom in the catalyst structure through the introduction of a rigid cyclopropyl fragment in the ligand backbone, we have created a conformationally constrained yet lightweight system with marked steric effects and distinct catalytic activity. Dramatic stereo- and enantiodivergent effects resulting from subtle modifications to the ligand structure have been observed in the intermolecular asymmetric Heck arylation reaction. These studies resulted in the development of an efficient catalyst demonstrating excellent enantioselectivities in the asymmetric arylation of dihydrofuran with various aryl triflates.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Similarly, isomerization of (*S*)-**7a** into (*S*)-**8a** in the presence of Pd(**L3**) catalyst can be explained.

(27) See, for example: (a) Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611. (b) Kang, J.; Lee, J. H.; Im, K. S. *J. Mol. Catal. A* **2003**, *196*, 55. (c) Dai, W.-M.; Yeung, K. K. Y.; Wang, Y. *Tetrahedron* **2004**, *60*, 4425. (d) Hou, X.-L.; Dong, D. X.; Yuan, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2189. See also refs 12b and 15.