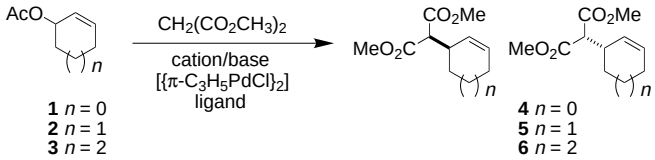
[7] *p*-Nitrophenyl sulfate is available from Sigma Co. (US$ 18.90 per g).
[8] S. G. Ramaswamy, W. B. Jakoby, *Methods Enzymol.* **1987**, *143*, 201 – 7.
[9] [^{35}S]PAPS is available from NEN Life Science Products (US$ 1013 per 100 mCi). The half-life of ^{35}S is 87.1 d. End-point methods of ^{35}S detection on TLC normally involve indirect qualitative determination of radioactivity.
[10] a) A. D. Marshall, J. F. Darbyshire, W. B. Jakoby, *J. Biol. Chem.* **1997**, *272*, 9153; A. D. Marshall, J. F. Darbyshire, W. B. Jakoby, *Chem. Biol. Interact.* **1998**, *109*, 107; b) Y. S. Yang, S. W. Tsai, E. S. Lin, *Chem. Biol. Interact.* **1998**, *109*, 129; c) W.-X. A. Guo, Y.-S. Yang, X. Chen, P. McPhie, W. B. Jakoby, *Chem. Biol. Interact.* **1994**, *92*, 25 – 31; d) Y.-S. Yang, J.-J. Pan, J.-K. Hwang, *Protein Eng.* **1997**, *10*, 70.
[11] Y.-S. Yang, A. D. Marshall, P. McPhie, W.-X. A. Guo, X. Xie, X. Chen, W. B. Jakoby, *Protein Expression Purif.* **1996**, *8*, 423 – 429.
[12] E.-S. Lin, Y.-S. Yang, *Anal. Biochem.* **1998**, *264*, 111 – 117.
[13] X. Chen, Y. S. Yang, Y. Zheng, B. M. Martin, M. W. Duffel, W. B. Jakoby, *Protein Expression Purif.* **1992**, *3*, 421 – 6.
[14] S. Ozawa, K. Nagata, D. Gong, Y. Yamazoe, R. Kato, *Nucleic Acids Res.* **1990**, *18*, 4001.
[15] LineWeaver, a graphical enzyme kinetics program for the Macintosh, was provided by Dr. Ian Ollmann, California Institute of Technology.
[16] The *N*-acetyllactosamine dimer generously provided by Kathryn M. Koeller (Research group of Prof. Wong, Scripps Research Institute).
[17] M. Schultze, C. Staehelin, H. Rohrig, M. John, J. Schmidt, E. Kondorosi, J. Schell, A. Kondorosi, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 2706 – 2709.
[18] P. Lerouge, P. Roche, C. Faucher, F. Maillet, G. Truchet, J. C. Promé, J. Dénarié, *Nature* **1990**, *344*, 781.

Proline-Based P,N Ligands in Palladium-Catalyzed Asymmetric π-Allyl Additions**

Scott R. Gilbertson* and Dejian Xie

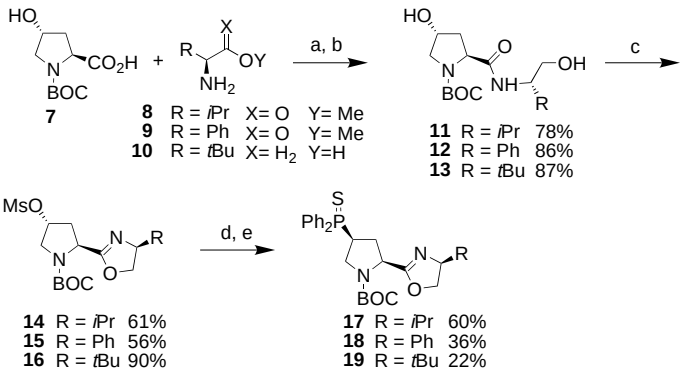
The development of new ligands for use in asymmetric catalysis has undergone incredible growth in the last ten years. One of the reactions that has been investigated extensively is the palladium-catalyzed addition of nucleophiles to allyl acetates.[1, 2] One of the first substrates to yield to catalysis with high selectivity was 1,3-diphenylprop-2-enyl acetate.[3–11] There are now a number of catalysts that have been developed that will catalyze the asymmetric addition of malonate to this substrate in greater than 90 % enantiomeric excess. A type of substrate that has been significantly more difficult to achieve high selectivity with has been the cyclic allyl acetates **1** – **3** (Scheme 1).[12–15] To the best of our knowledge there are currently only two systems that give greater than 95 % *ee* with these types of substrates.[16–22] Herein we report the synthesis of new phosphanyldihydrooxazole ligands that can be used to catalyze this substitution in high enantiomeric excess. The results obtained with these ligands are comparable to the most selective catalysts for the reaction of this substrate. Additionally, these ligands are readily accessible from common amino acids and are proving useful in the catalysis of a number of asymmetric transformations.



Scheme 1. Asymmetric addition of dimethylmalonate to cyclic allyl acetates **1** – **3**.

The design of this system was founded on the observation that ligands based on proline often result in reasonably high stereodifferenation. There have been a number of examples of proline-based bisphosphane systems that have resulted in selective catalysis.[23–27] For this reason a series of proline-based phosphanyldihydrooxazole ligands was synthesized.

The synthesis of this class of ligand begins with commercially available *tert*-butoxycarbonyl (BOC)-protected *trans* 4-hydroxy-L-proline (**7**) which could be coupled to either an amino acid ester or an amino alcohol (Scheme 2). The dihydrooxazole was formed through reduction of the ester



Scheme 2. Synthesis of the dihydrooxazole ligands **17** – **19**. EDC/HOBt, RT, CH_2Cl_2; b) when X = O, $LiBH_4$, THF, 0 °C to RT; c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, RT; d) $Ph_2P^-Na^+$, THF, – 78 °C to RT; e) S_8 or $Na_2S_2O_2$, CH_3OH/H_2O, 45 °C. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole. Ms = mesyl.

to an alcohol and formation of a bis-mesylate by reaction with methanesulfonyl chloride. The primary mesylate then underwent cyclization to form the dihydrooxazole ring (**14** – **16**). After this reaction, the secondary mesylate was subjected to substitution by sodium diphenylphosphide. Following substitution the phosphane is protected as the phosphane sulfide. The ligands are purified as the phosphane sulfides and then converted to phosphanes (**20** – **25**) by reduction with Raney

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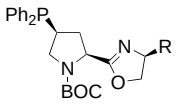
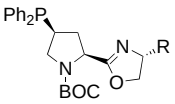
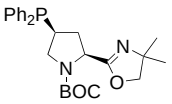


20 R = *i*Pr
21 R = Ph
22 R = *t*Bu



23 R = *i*Pr
24 R = Ph

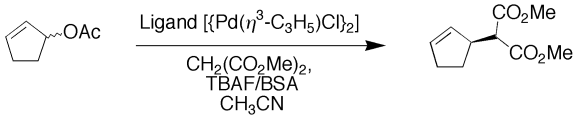


25

nickel before coordination to palladium. This route is appealing because it allows the synthesis of a wide variety of analogues. The R group on the dihydrooxazole ring is easily changed by simply coupling a different amino acid ester to *trans*-hydroxyproline. Another point of differentiation in this ligand system is at the nitrogen of the proline ring. Our inital studies have been with the nitrogen protected with a BOC group but there is clearly the possibility to make systematic changes to this portion of the molecule.

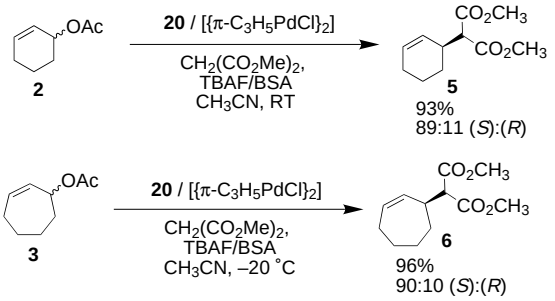
The reaction with cyclopent-2-enyl acetate (**1**) and dimethyl malonate, at 0 °C, using ligand **20** provided the desired substitution product in 94% yield and 90% *ee* (Table 1, entry 1). Reduction of the temperature to −20 °C resulted in an increase in selectivity to 94% *ee*. At −35 °C the selectivity improves to 96% *ee*. It was felt that modification of the R group next to the dihydrooxazole nitrogen atom would result in an increase in the selectivity. In the phosphanyldihydrooxazole systems reported previously it has been shown that changing the stereochemistry of the group next to the nitrogen alters the selectivity of the catalysts in favor of the other enantiomer. In the proline-based system reported here this is not the case. Catalysis with the ligand where L-valine (**20**) was replaced with D-valine (**23**) resulted in a significant decrease in the rate of the reaction as well as a decrease in the reaction's selectivity (entry 6); however, the major product is the same enantiomer in both cases. Catalysis by a variety of complexes with different R groups next to nitrogen resulted in variable results. Substitution of L-phenylalanine (**21**) for L-valine gives lower selectivity (76% *ee*, entry 7). Use of ligand **22** in the same stoichiometry as ligand **20** resulted in a decrease in selectivity (entry 10). Ligand **25**, which does not possess a chiral center next to the dihydrooxazole nitrogen, gives the product in 90% yield and 80% *ee* (entry 9). The effect of solvent on the reaction was also probed. It was found that acetonitrile gives the highest selectivity with DMF and methylene chloride giving selectivities above 80% *ee* (entries 13 and 11, respectively). When the reaction conditions found for cyclopent-2-enyl acetate (**1**) were used with cyclohex-2-enyl acetate (**2**) the reaction proceeded in high yield and with good selectivity. Catalysis of the addition to the cyclohept-2-enyl allyl acetate (**3**) proceeded in good selectivity and at a faster rate than for **2** (Scheme 3).

Table 1. Reactions of cyclic allyl acetate **1** with dimethylmalonate catalyzed by palladium complexes of ligands **20**–**25**.



Entry[a,b]	Ligand	T [°C]	solvent	Yield [%]	Ratio S:R[c]
1	**20**	0	CH_3CN	94	95:5
2	**20**	−20	CH_3CN	99	97:3
3	**20**	−35	CH_3CN	79	98:2
4[d]	**20**	0	CH_3CN	96	93:7
5	**20**	20	CH_3CN	95	93:7
6	**23**	0	CH_3CN	93	84:16
7	**21**	0	CH_3CN	99	88:12
8	**24**	0	CH_3CN	91	88:12
9	**25**	0	CH_3CN	90	90:10
10[e]	**22**	0	CH_3CN	92	84:16
11	**20**	0	CH_2Cl_2	99	91:9
12	**20**	25	C_6H_6	30	86:14
13	**20**	0	DMF	90	93:7
14	**20**	0	THF	86	90:10

[a] The phosphane ligand is generated by reduction of the phosphane sulfide with Raney nickel. [b] Reactions were run with 2 mol% Pd to 3 mol% ligand. [c] Enantiomeric ratios were determined by NMR spectroscopy using the [Eu(hfbc)] shift reagent (hfbc = 3-(heptafluorobutyryl)-D-camphorate). The absolute stereochemistry was determined by comparison of optical rotations with the literature. [d] The ratio of Pd/ligand of 1/1 was used. [e] 2 mol% Pd was used.



Scheme 3. Asymmetric addition of dimethylmalonate to cyclohex-2-enyl acetate **2** and cycloheptyl-2-enyl acetate **3** by using palladium complexes of the new phosphanyldihydrooxazole ligand **20**.

Figure 1 shows a model of the metal complex with an allyl group attached. It has been shown in other phosphanyldihydrooxazole systems that addition of the nucleophile to the allyl group takes place at the carbon that is *trans* to the phosphane on the metal center.[4–7, 9, 28–30] To obtain the products observed with our catalyst the two methylenes of the five-membered ring must point down toward the BOC group. It is not obvious from this model what structural features are responsible for this preference in orientation, but given the high selectivity it is clearly favored. It is interesting that the configuration of the carbon center next to dihydrooxazole nitrogen does not have a stronger effect on the selectivity of the catalysis; the same enantiomer is obtained as the major product regardless of its stereochemistry.

Ligand **20** has proven to be very effective in the control of the addition of dimethyl malonate to allyl acetates **1**–**3**. This system differs from other phosphanyldihydrooxazole ligands in that the dominating chirality is not the chiral center next to the dihydrooxazole nitrogen but rather the chirality of the two hydroxyproline-derived chiral centers. We are currently looking at catalysis of the addition of other nucleophiles with this system. Derivatives of this ligand are also being developed for use in other transition metal catalyzed reactions.

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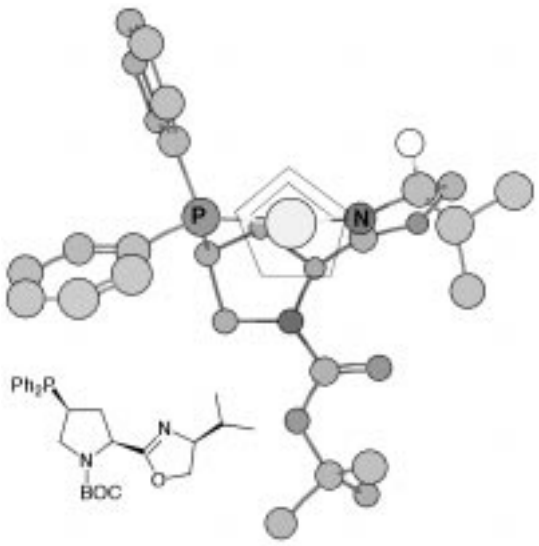

Figure 1. Model of the metal complex with an allyl group attached.

Experimental Section

Procedure for π-allyl alkylation: The phosphanyldihydrooxazole ligand was mixed with $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ in degassed solvent, followed by addition of the cyclic allylic acetate. To this mixture a solution containing dimethyl malonate (3 equiv), tetrabutylammonium fluoride (TBAF) (3 equiv) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) was added slowly through a addition funnel (30 min). After the reaction was complete, water was added to quench the reaction and the organic solvent was removed by evaporation. The water layer was then extracted with diethyl ether twice and the ether solution was washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. Evaporation of solvent gave a residue that was chromatographed by using EtOAc/*n*-hexanes (10/90, v/v) as an eluant to afford a colorless oil.

The enantiomeric purity was determined by integration of the NMR signals of the methyl residues on the dimethyl malonate, upon titration with europium chiral shift reagent $[Eu(hfbc)_3]$.

The ligand with the opposite configuration can be synthesized from D-hydroxyproline, which is accessible from L-hydroxyproline.[30]

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[1] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422.
[2] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089 – 1122.
[3] S. R. Gilbertson, C.-W. Chang, *Chem. Commun.* **1997**, 975 – 976.
[4] P. von Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614 – 615; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566 – 568.
[5] J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsolnai, *Tetrahedron Lett.* **1994**, *35*, 1523 – 1526.
[6] H. Steinhagen, M. Reggelin, G. Helmchen, *Angew. Chem.* **1997**, *109*, 2199 – 2202; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2108 – 2110.
[7] A. Togni, U. Burckhardt, V. Gramlich, P. S. Pregosin, R. Salzmann, *J. Am. Chem. Soc.* **1996**, *118*, 1031 – 1037.
[8] M. Bovens, A. Togni, L. M. Venanzi, *J. Organomet. Chem.* **1993**, *451*, C28 – C31.
[9] J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin, J. M. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2065 – 2071.
[10] M. Yamaguchi, T. Shima, T. Yamagishi, M. Hida, *Tetrahedron Lett.* **1990**, *31*, 5049 – 5052.
[11] S. R. Gilbertson, C.-W. Chang, *J. Org. Chem.* **1998**, *63*, 8424 – 8431.
[12] T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Am. Chem. Soc.* **1998**, *120*, 1681 – 1687.
[13] T. Minami, Y. Okada, T. Otaguro, S. Tawaraya, T. Furuichi, T. Okauchi, *Tetrahedron: Asymmetry* **1995**, *6*, 2469 – 2474.
[14] Y. Okada, T. Minami, Y. Umezu, S. Nishikawa, R. Mori, Y. Nakayama, *Tetrahedron: Asymmetry* **1991**, *2*, 667 – 682.
[15] U. Nettekoven, M. Widhalm, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1997**, *8*, 3185 – 3188.
[16] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1996**, *118*, 235 – 236.
[17] B. M. Trost, R. C. Bunt, *Angew. Chem.* **1996**, *108*, 70 – 73; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99 – 102.
[18] B. M. Trost, M. G. Organ, G. A. O'Doherty, *J. Am. Chem. Soc.* **1995**, *117*, 9662 – 9670.
[19] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089 – 4090.
[20] G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1997**, *69*, 513 – 518.
[21] G. Knühl, P. Sennhenn, G. Helmchen, *J. Chem. Soc. Chem. Commun.* **1995**, 1845 – 1846.
[22] S. Kudis, G. Helmchen, *Angew. Chem.* **1998**, *110*, 3210 – 3212; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047 – 3050.
[23] G. Parrinello, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 7122 – 7127.
[24] M. Hodgson, D. Parker, *J. Organomet. Chem.* **1987**, *325*, C27-C30.
[25] K. Tani, K. Suwa, E. Tanigawa, T. Ise, T. Yamagata, Y. Tatsuno, S. Otsuka, *J. Organomet. Chem.* **1989**, *370*, 203 – 221.
[26] H. Brunner, E. Graf, W. Leitner, K. Wutz, *Synthesis* **1989**, 743 – 745.
[27] H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 367 – 370.
[28] G. J. Dawson, J. M. J. Williams, *Tetrahedron: Asymmetry* **1995**, *6*, 2535 – 2546.
[29] H. Kubota, K. Koga, *Tetrahedron Lett.* **1994**, *35*, 6689 – 6692.
[30] G. L. Baker, S. J. Fritschel, J. R. Stille, J. K. Stille, *J. Org. Chem.* **1981**, *46*, 2954 – 2960.

DNA Responds to Ionizing Radiation as an Insulator, Not as a "Molecular Wire"**

Michael G. Debije, Michael T. Milano, and William A. Bernhard*

The understanding of electron and hole transfer in DNA is critical to predicting the biological consequences of exposure to ionizing radiation. These processes are biologically relevant since about 50 % of the consequential damage is produced by direct-type events,[1] that is, from one-electron loss (holes) and one-electron gain directly by the DNA[2] or by fast transfer of holes and electrons to the DNA from adjacent solvent.[3] Transfer processes are chemically relevant since the distribu-

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