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Published on Web 09/03/2003

Resolved Chiral 3,4-Diazaphospholanes and Their Application to Catalytic Asymmetric Allylic Alkylation

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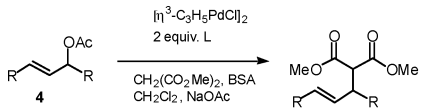
Collections of chiral ligands[1] offer the promise of accelerating the discovery of new catalysts for asymmetric transformations. Because of the ubiquity of phosphine ligands in catalysis by organotransition metal complexes, much effort has been directed toward the synthesis of chiral phosphine libraries. The central problem is rapidly accessing derivatives of a common scaffold that translate into significantly different activity and selectivity patterns (i.e., meaningful diversity). Recently, we reported new methods for synthesizing racemic 3,4 diazaphospholanes[2] that bear structural similarities with the DuPHOS[3] class of phospholanes. Our strategy is to combine the asymmetry of phospholane-like ring structures with the diversity of structures and functionalities available in small peptides. Herein, we report the initial realization of this strategy: the facile synthesis and resolution of a new functionalized diazaphospholane, its elaboration using readily available amino acids, and the discovery of new monophosphine ligands for highly enantioselective catalytic allylic alkylations.

Synthesis of *rac*-*N*,*N*′-phthaloyl-2,3-(2-carboxyphenyl)-phenyl-3,4-diazaphospholane (*rac*-**2**) is performed as a one-pot combination of phenylphosphine, the azine of 2-carboxybenzaldehyde (**1**), and phthaloyl chloride (Scheme 1, see Supporting Information for complete procedures). Reaction scales of tens of grams are convenient and generate 88% yield of the colorless solid *rac*-**2**. Resolution via selective crystallization of diastereomeric α-methylbenzylammonium salts affords both enantiomers of **2** in high yield and >99% ee on multigram scales. The resolved phospholanes (*R*,*R*)-**2** and (*S*,*S*)-**2** are soluble in polar solvents such as methylene chloride and methanol and air stable both as solids and in solution.

Py-BOP mediated[4] coupling of **2** with various primary and secondary amines yields the chiral phosphine ligands shown in Chart 1. The phosphine amide **3l** was converted to the oxazoline **3n** using established procedures.

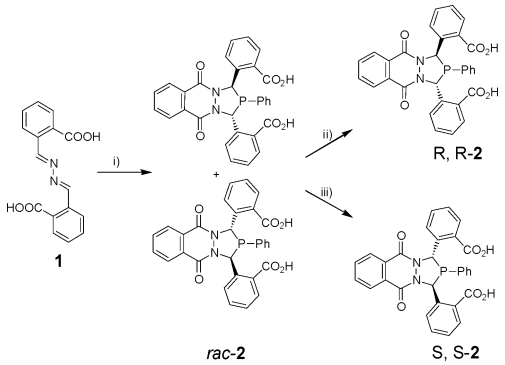


R = CH_3 **(a)**, Ph **(b)**

By virtue of its synthetic utility and the existence of extensive literature, palladium-catalyzed enantioselective allylic alkylation[5] is attractive for testing new chiral phosphines.[6] Whereas the most common test substrate, 1,3-diphenylallyl acetate (**4b**), undergoes highly enantioselective alkylation with dimethyl malonate in the presence of many different ligands, alkylation of 1,3-dimethylallyl acetate (**4a**) is much more challenging. To date, Trost's diphosphine ligand is most effective for palladium-catalyzed alkylation of **4a** with few other phosphine ligands demonstrating useful selectivities and activities. Interestingly, the Trost ligand is rather poor for allyl acetates bearing bulkier groups such as **4b**.[5a]

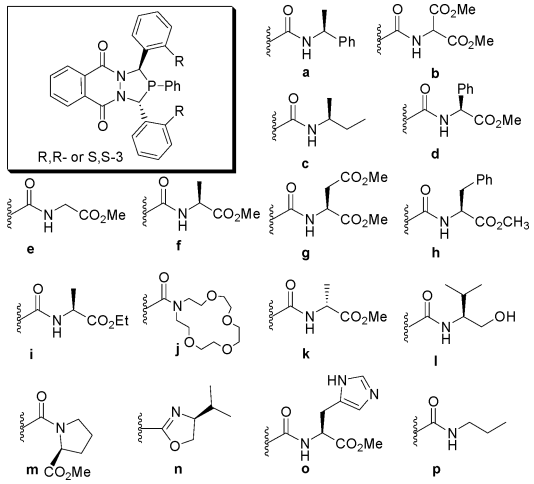
As shown by the data in Table 1, Pd-catalyzed allylic alkylation of both **4a** and **4b** with monophosphine ligands derived from **2** exhibits (1) selectivity on par with the state-of-the-art catalysts, (2) strong sensitivity to the nature of the amino acid, and (3) variable response to the presence of PF_6^- salts.

Scheme 1. Synthesis and Resolution of Diazaphospholane[a]



[a] (i) (a) Phthaloyl dichloride, phenyl phosphine, THF; (b) 10% aq. K_2CO_3; (c) 3 M HCl. (ii) (a) (*S*)-α-methylbenzylamine, THF; (b) 10% aq. K_2CO_3; (c) 3 M HCl. (iii) (a) (*R*)-α-methylbenzylamine, THF; (b) 10% aq. K_2CO_3; (c) 3 M HCl.

Chart 1. Ligand Collection



Both the enantioselectivity (92% ee) and the yield (ca. 92%) for the asymmetric allylic alkylation of **4a** with *R*,*R*-**3f** and *R*,*R*-**3i** rival the best results to date for this notoriously difficult substrate. To the best of our knowledge, ligand **3f** is unique among previously reported ligands in being highly effective for both substrates **4a** and **4b** under common conditions. Comparisons of matched and "mismatched" diastereomers (e.g., *R*,*R*-**3a** and *S*,*S*-**3a**) indicate that the product stereochemistry is determined predominately by the phospholane ring stereochemistry, rather than that of the amino acid. Most significant is the exquisite (and unpredictable) sensitivity of the catalyst to subtle changes in ligand structure as illustrated by the series: glycine (**3e**, 46% ee), phenylglycine (**3d**, 51% ee),

10.1021/ja036359f CCC: $25.00

Table 1. Pd-Catalyzed Allylic Alkylation Results

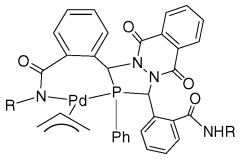
		with $AgPF_6$		without $AgPF_6$	
substrate	ligand	ee (%)	yield[b] (%)	ee (%)	yield[b] (%)
4a	*R,R*-**3a**	52(16) (*S*)[a]	87(9)	57(4) (*S*)	78(10)
4a	*R,R*-**3b**	73(2) (*S*)[a]	20(2)	47(10) (*S*)	8(2)
4a	*R,R*-**3c**	53(10) (*S*)[a]	88(4)	49(5) (*S*)	68(16)
4a	*R,R*-**3d**	51(4) (*S*)[a]	48(11)	48(4) (*S*)	26(7)
4a	*R,R*-**3e**	46(6) (*S*)[a]	66(11)	29(3) (*S*)	30(9)
4a	*R,R*-**3f**	92(1) (*S*)[a]	92(1)	53(4) (*S*)	71(7)
4a	*R,R*-**3g**	89(1) (*S*)[a]	94(4)	89(1) (*S*)	84(3)
4a	*R,R*-**3h**	83(1) (*S*)[a]	84(5)	46(1) (*S*)	29(5)
4a	*R,R*-**3i**	92(1) (*S*)[a]	86(10)	47(1) (*S*)	65(3)
4a	*R,R*-**3j**	56(9) (*R*)[a]	19(8)	9(2) (*R*)	4(1)
4a	*R,R*-**3k**	84(1) (*S*)[a]	77(16)	32(1) (*S*)	23(9)
4a	*R,R*-**3m**	11(4) (*S*)[a]	32(3)	20(1) (*S*)	8(2)
4a	*R,R*-**3n**	38(4) (*S*)[a]	26(5)		
4a	*S,S*-**3a**	59(4) (*R*)[a]	87(5)	50(3) (*R*)	100(2)
4a	*S,S*-**3o**	55(6) (*S*)[a]	5(2)	44(4) (*S*)	88(4)
4a	*S,S*-**3p**	40(1) (*R*)[a]	16(5)	30(6) (*R*)	38(15)
4a	*S,S*-**3m**	54(3) (*S*)[a]	14(3)	34(2) (*S*)	2(1)
4a	*S,S*-**3n**	64(1) (*R*)[a]	92(7)	60(*R*)	18
4b	*R,R*-**2**	71(1) (*S*)[c]	32(8)	50(1) (*S*)	13(1)
4b	*R,R*-**3f**	92(1) (*S*)[c]	61(5)	97(1) (*S*)	92(6)
4b	*R,R*-**3m**	56(*R*)[c]	26	19(2) (*R*)	36(4)
4b	*S,S*-**3a**	91(6) (*R*)[c]	>95	75(1) (*R*)	88(1)
4b	*S,S*-**3o**	9(1) (*R*)[c]	8(1)	97(1) (*S*)	99(2)
4b	*S,S*-**3p**	64(2) (*R*)[c]	34(1)	67(1) (*R*)	78(10)

[a] Determined by GC (β-DEX 120). [b] Isolated yields for ligand **4b** and GC yields for **4a**. [c] Determined by HPLC (ChiralCel OD).

and alanine (**3f**, 92% ee). We attribute this sensitivity to the close proximity of the amino acid side chains with the substrate-binding pocket.

During initial screens of asymmetric allylic alkylation reactions, we observed large salt effects on the catalytic reaction rates and enantioselectivities (see Table 1). In general, addition of chloride scavengers such as $AgPF_6$ leads to increased enantioselectivities. For all cases examined, $NaPF_6$ is as effective as the silver salt. Strong halide effects in Pd-catalyzed allylic alkylations are well established[7] and, due to recent, incisive studies by Lloyd-Jones and co-workers,[7a,b] becoming better understood.

Our working model ascribes the most active and selective catalysts to monophosphine Pd-allyl complexes, possibly bidentate[8] via coordination of an amidate[9] (see below) or amide carbonyl.[10] Support for coordination of a single phosphine to palladium in the active species comes from the observation that allylic alkylations with 1:1, 2:1, and higher phosphine:palladium ratios give identical ee's and similar initial rates as measured by ^{1}H NMR for ligand **3f**. The poor activities and selectivities of *N,N*-disubstituted amides may reflect poor bidentate binding.



In summary, the 3,4-diazaphospholanes comprise readily accessible and versatile ligands for asymmetric catalysis. In this work, we demonstrate that resolution of **2** combined with simple coupling chemistry provides access to ligands with meaningful diversity, at least with respect to catalytic allylic alkylation. We currently are pursuing clarification of mechanistic issues that have arisen from this work, application of these ligands to other catalytic transformations, and further extension of mono- and bis-3,4-diazaphospholanes through coupling to small peptides and peptoids.

Acknowledgment. The Department of Energy and Dow Chemical Co. provided support for this work. We kindly thank Prof. Sam Gellman for access to HPLC equipment, Prof. Helen Blackwell for stimulating discussions, and Dr. Ilia Guzei for the crystallographic work.

Supporting Information Available: Synthetic and catalytic procedures, characterization data, and crystallographic coordinates for *R,R*-**2** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA036359F