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Following an ISES Lead: The First Examples of Asymmetric Ni(0)-Mediated Allylic Amination

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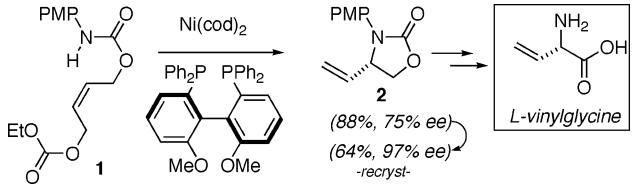
ABSTRACT



An ISES (in situ enzymatic screening) lead pointed to conditions (PMP N-protecting group, Ni(cod)$_2$ catalyst precursor) under which chiral, bidentate phosphines could promote Ni(0)-mediated allylic amination. Therefore, bidentate phosphines bearing central, axial, and planar chirality were examined with two model substrates of interest for PLP-enzyme inhibitor synthesis. In the best case, with (*R*)-MeO-BIPHEP, vinylglycinol derivative 2 was obtained in 75% ee (97% ee, one recrystallization) from 1. Further manipulation provided a Ni(0)-mediated entry into L-vinylglycine.

α-Vinyl amino acids are potential inactivators of pyridoxal phosphate (PLP) enzymes.[1] "Suicide substrates" bearing this vinylic trigger include the natural product L-vinylglycine[2] and the anti-epileptic drug (*S*)-vigabatrin (γ-vinyl-GABA),[3] which may also have potential to treat substance abuse.[4] This has led to considerable synthetic activity toward these targets.[5−7] Among the most efficient and stereocontrolled approaches to appear are transition-metal-mediated allylic amination routes by Hayashi,[8] Alper,[9] Trost,[10] and Overman.[11] Heretofore, such ventures have been focused on palladium.

In developing an in situ enzymatic screening (ISES) method for evaluating catalysts, we chose an intramolecular allylic amination route to a protected vinylglycinol (**1** → **2**) as a model reaction. Our initial findings demonstrated that, among non-Pd metals screened, Ni(0) showed particular promise for this transformation.[12] Furthermore, the PMP nitrogen-protecting group and bidentate phosphine ligands were found to promote this chemistry.

As can be seen in Figure 1, ISES reveals that the combination of Ni(cod)$_2$ with *chiral*, bidentate phosphines also gives this chemistry. As before, relative ISES rates track well with relative rates of product formation under standard reaction conditions, as judged by NMR at short times (Table 1).

In our earlier studies, dppb had shown the fastest initial rates by ISES, and so it was retained as a standard here. Similarly, SKEWPHOS, a chiral, acyclic three-carbon bridged bidentate P,P-ligand, gives relatively rapid formation of **2**. The initial ISES screen also pointed to slower, yet potentially

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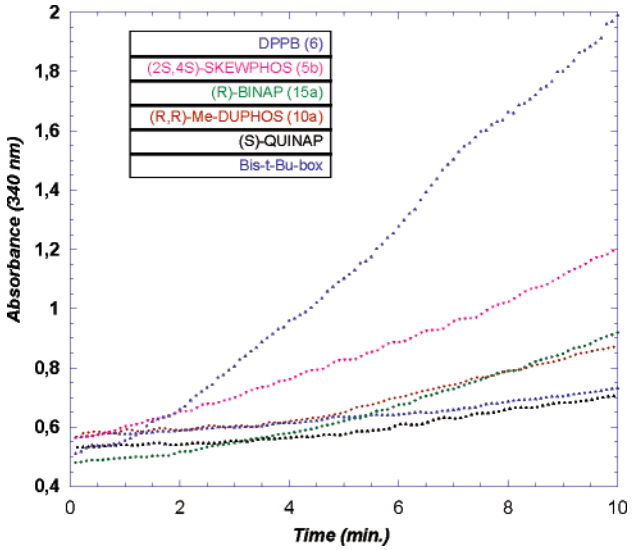
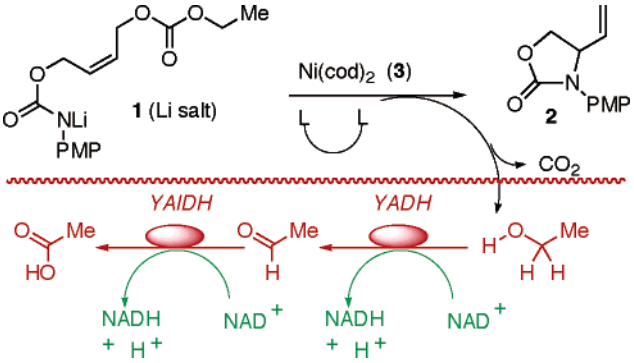


Figure 1. UV/vis traces for the ISES data in Table 1.

useful conversions with chiral P,P-ligands of the DUPHOS and BINAP variety (Figure 1). On the contrary, neither QUINAP (P,N-BINAP analog) nor a prototypical bis-(oxazoline) (N,N-ligand) gave significant ISES rates. Next, it was noted that although unconstrained ligands such as SKEWPHOS gave both very good rates and conversions, better ee's could be obtained with BINAP or DUPHOS. Clearly, we were not seeing a direct correlation between rate and ee here. On the basis of these observations, it was decided to explore broadly relatively electron-rich chiral bidentate phosphines. The ligand array chosen includes elements of central, planar and axial chirality (Figure 2).

Table 1. ISES Evaluation of Bidentate Ligands for Ni(0)-Mediated Allylic Substitution



no.[a]	bidentate ligand	ΔO.D.$_{340}$/time (mAbs/min)[b]	% conv[c]
1	DPPB (**6**)	132 ± 16	71
2	(*S*,*S*)-SKEWPHOS (**5b**)	64 ± 12	39
3	(*R*)-BINAP (**15a**)	45 ± 10	28
4	(*R*,*R*)-Me-DUPHOS (**10a**)	30 ± 1	22
5	(*S*)-QUINAP[d]	18	f
6	(*S*,*S*)-Di-*t*-Bu-box[e]	15 ± 2	f

[a] Conditions for the biphasic ISES screen (YADH = yeast alcohol dehydrogenase and YAlDH = yeast aldehyde dehydrogenase) as described in the Supporting Information. [b] Observed rates (10 min) of NADH formation in units of ΔO.D.$_{340}$ min^{-1}. Unless otherwise indicated, ISES slopes are reported as mean ± SD (duplicate runs). [c] Reaction conditions: 200 mM **1**, 10 mol % of Ni(cod)$_2$, 20 mol % of ligand, LiHMDS (1 equiv), THF, rt, 15 min. Product/educt ratio estimated by NMR following workup. [d] Ligand is (*S*)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline. [e] Ligand is 2,2′-methylenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]. [f] Trace product (crude NMR).

Table 2. Cyclizations of Allylic Amination Substrate **1**[a]

no.	ligand	yield[b] (%)	ee[c] (%)	config[d]
1	(*R*,*R*)-NORPHOS (**4**)	80	28	*R*
2[e]	(*S*,*S*)-CHIRAPHOS (**5a**)	75	0	
3[f]	(*2S*,*4S*)-SKEWPHOS (**5b**)	94	13	*S*
4[g]	(*2S*,*4S*)-BPPM (**7**)	87	6	*R*
5	(*S*,*S*)-DIOP (**8**)	79	0	
6	Trost ligand (**9**)	37	4	*S*
7[h]	Trost ligand (**9**)	nr		
8[g]	(*R*,*R*)-Me-DUPHOS (**10a**)	89	48	*S*
9	(*S*,*S*)-*i*-Pr-DUPHOS (**10b**)	86	24	*S*
10[g]	**(*S*,*S*)-Me-en-DUPHOS (10c)**	**78**	**46**	***R***
11	(*S*,*S*)-Et-FerroTANE (**11**)	60	7	*R*
12	**JOSIPHOS-type (12a)**	**65**	**56**	***S***
13	**JOSIPHOS-type (12b)**	**17**	**82**	***S***
14	JOSIPHOS-type (**12c**)	31	22	*S*
15	JOSIPHOS-type (**12d**)	38	0	
16	JOSIPHOS-type (**12f**)	79	43	*S*
17	WALPHOS-type (**13a**)	nr		
18	(S_p)-PHANEPHOS-type (**14**)	nr		
19	(*R*)-BINAP (15a)	90	46	*S*
20	**(*R*)-Tol-BINAP (15b)**	**94**	**59**	***S***
21	**(*R*)-MeO-BIPHEP (16a)**	**86**	**72**	***S***
22[h]	**(*R*)-MeO-BIPHEP (16a)**	**88**	**75**	***S***
23	(*R*)- Me$_2$-OMe-BIPHEP (**16b**)	32	38	*S*
24	(*R*)-^{i}Pr$_2$-OMe-BIPHEP (**16c**)	74	44	*S*
25	(*R*)-^{t}Bu$_2$-OMe-BIPHEP (**16d**)	nr		

[a] Reaction conditions: 10 mol % of Ni(cod)$_2$, 20 mol % of ligand, LiHMDS (1 equiv), THF, rt, overnight (unless otherwise indicated). [b] All yields are isolated yields of pure products. nr = no reaction observed. [c] ee's were determined by chiral HPLC (Chiralcel OD, hexane/*i*-PrOH 80/20). [d] Configuration assigned by correlation with L-vinylglycine (Scheme 2). [e] t = 8 h. [f] t = 4 h. [g] t = 6 h. [h] Reaction carried out without exogenous base (i.e., no LiHMDS); t = 6 h.

The results for the transformation **1** → **2** are collected in Table 2. A few patterns emerge. Indeed, all bis(diphe-

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(11) Overman uses a Pd(II) catalyst and invokes an intramolecular, aminopalladation mechanism that preserves the Pd(II) oxidation state throughout the catalytic cycle: Overman, L. O.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12−13.

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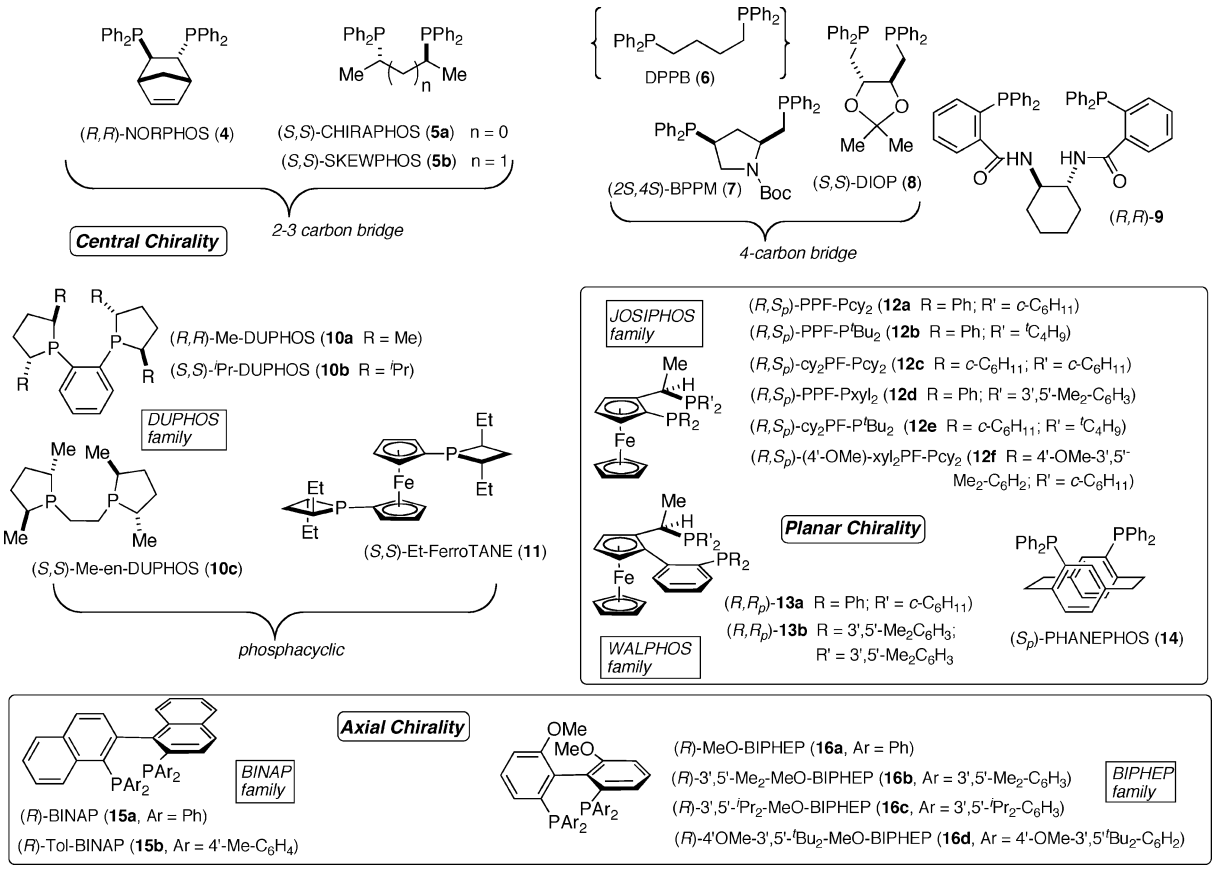


Figure 2. Array of chiral bidentate phosphine ligands examined.

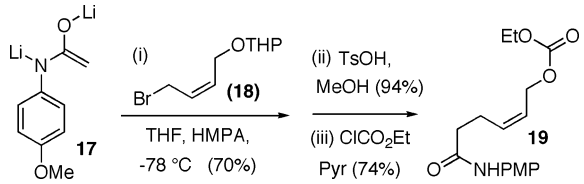
nylphosphino) L's with two to four sp^3-carbon spacers (**4**, **5a**,**b**, **7**, **8**) give excellent conversions, but low ee's. The phospholane-based DUPHOS ligands all give excellent conversion, but only the methyl-substituted ones (**10a**,**c**) lead to ee's of some note, approaching 50%. The JOSIPHOS ligand family incorporates both central chirality and planar chirality. Best results, in terms of both catalysis and enantioselection, are seen with ligands bearing a (diarylphosphino)ferrocene in tandem with a (dialkylphosphino)ethyl moiety (i.e., **12a**,**b**,**f**). A similar structure/activity observation has been made with JOSIPHOS ligands in a model Pd-mediated allylic alkylation reaction.[13] Interestingly, in comparing **12a** and **12b**, one sees that subtle changes in sterics can have significant consequences in ee and rate (Tables 2 and 3). Thus, **12a** (R′ = cy), gives higher yields (55−65% vs 17−23%) with both substrates **1** and **19** (vide infra), but **12b** (R′ = ^{t}Bu) gives higher ee's (74−82%), indeed among the highest seen here.

The most practical results were obtained with ligands possessing axial chirality. Enantioselection steadily increases from BINAP (**15a**, 46% ee) to tol-BINAP (**15b**, 59% ee) to MeO-BIPHEP (**16a**, 72−75% ee),[14−16] while yields are outstanding (86−94%) across the series. More sterically hindered BIPHEP ligands (**16b**−**d**) provided less satisfactory results.

Given the importance of vigabatrin,[4,6] we next set out to examine the Ni(0)-mediated transformation **19** → **20**, which would serve as a formal synthesis of the drug. Note that substitution of a CH_2 for the bridging O means that an N-PMP amidate replaces the N-PMP carbamate as the formal nitrogen nucleophile.

Pleasingly, it was found that the requisite substrate **19** could be efficiently assembled via C-alkylation of the dianion derived from N-PMP-acetamide (Scheme 1). The ligand survey (Table 3) revealed decreased enantioselection for the

Scheme 1. Synthesis of the Vigabatrin Precursor



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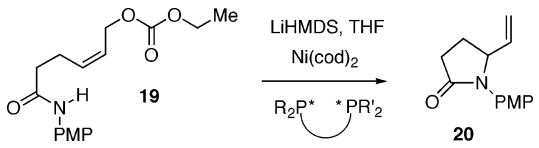
(14) Schmid, R.; Foricher, J.; Cereghetti, M.; Schoenholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370−389.
(15) BIPHEP ligands have been utilized mostly for asymmetric Ru-mediated ketone reductions. For a leading reference, see: Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320−325.

Table 3. Allylic Aminations to Vigabatrin Derivative 20[a]



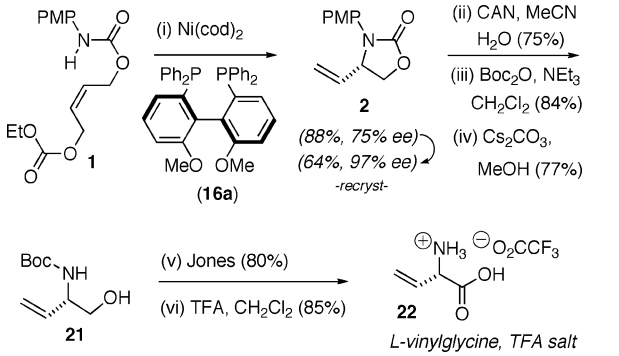
no.	ligand	yield[b] (%)	ee[c] (%)	config[d]
1	**(*R,R*)-Me-DUPHOS (10a)**	**93**	**66**	***R***
2	(*S,S*)-^{i}Pr-DUPHOS (**10b**)	90	47	*R*
3	(*S,S*)-Et-FerroTANE (**11**)	28	8	*S*
4	JOSIPHOS-type (**12a**)	55	31	*R*
5	**JOSIPHOS-type (12b)**	**28**	**74**	***R***
6	JOSIPHOS-type (**12c**)	23	22	*S*
7	JOSIPHOS-type (**12d**)	73	5	*S*
8	JOSIPHOS-type (**12e**)	nr		
9	JOSIPHOS-type (**12f**)	46	36	*R*
10	WALPHOS-type (**13a**)	8	32	*S*
11	**WALPHOS-type (13b)**	**60**	**53**	***S***
12	(*R*)-BINAP (**15a**)	70	43	*R*
13	(*R*)-Tol-BINAP (**15b**)	84	44	*R*
14[e]	**(S)-MeO-BIPHEP (16a)**	**97**	**53**	***S***
15	**(*R*)-Me$_2$-OMe-BIPHEP (16b)**	**65**	**54**	***R***
16	(*R*)-^{t}Bu$_2$-OMe-BIPHEP **(16d)**	60	23	*R*

[a] Reaction conditions: 67 mM **19**, 10 mol % of Ni(cod)$_2$, 20 mol % of ligand, LiHMDS (1 equiv), THF, rt, overnight. [b] Isolated yields of pure products. nr = no reaction observed. [c] ee's determined by chiral HPLC (Chiralcel OD, hexane/*i*-PrOH 73/27). [d] Configuration assigned by correlation with the known γ-lactam, following PMP deprotection (CAN, MeCN, H_2O): $[\alpha]^{23}_D$ (66% ee-chiral HPLC; see the Supporting Information) −23.7 (EtOH, *c* 2.0) [lit.[6e] $[\alpha]^{23}_D$ (*S*)-isomer) +50.4 (EtOH, *c* 2.2)]. [e] No exogenous base used (i.e., no LiHMDS).

axially chiral ligands, with the exception of **16b**. But, these ligands were eclipsed by DUPHOS ligand **10a** (66% ee) and the P^{t}Bu$_2$-bearing JOSIPHOS ligand **12b** (74% ee), again, albeit with low conversion for **12b**. Interestingly, one of the WALPHOS ligands (**13b**, 60%, 53% ee) also appears to show promise.

While isolated examples of Ni(0)-mediated allylic amination have been reported,[17] *to our knowledge, these represent the first asymmetric examples.* At this juncture, we chose to examine the best case more closely, namely the (*R*)-MeO-BIPHEP-Ni(0)-promoted synthesis of **2** (Table 2, entry 21). Unfortunately, additives found to be beneficial in other late transition metal-mediated allylic substitutions[18] such as NEt_3,[18a] HOAc,[18a] NBu_4OAc,[17a] LiCl[18b] (<5% conversion), LiF[18c] (60%, 73% ee), NBu_4F[18d] (60%, 57% ee), NBu_4PF_6[17b] (83%, 70% ee), and NBu_4BH_4[18d] (51%, 26% ee-*R*) were deleterious here. Changing the N-protecting group from PMP to OMP[19] (46%, 64% ee) or TMP[19] (83%, 67% ee) was not beneficial. The (*E*)-isomer of **1** gave the same sense of induction, though at lower ee (65%) and yield (69%). This result is reminiscent of Hayashi's observations with Pd[8] and may be evidence of rapidly equilibrating π-allylmetal intermediates.

Scheme 2. Ni(0)-Mediated Synthesis of L-Vinylglycine



However, whereas all of the initial screens had employed 10 mol % Ni(cod)$_2$, 20 mol % L, and a full equivalent of base (LiHMDS), *it was found that, at least in this case, base could be completely eliminated and MeO-BIPHEP reduced to 10 mol % with essentially no consequence (83%, 75% ee). Gratifyingly, we also found that with a single recrystallization, the ee of the product could be increased from 75% to 97% with 64% overall yield.* This refinement then allowed for a practical entry into L-vinylglycine, centered around this new asymmetric Ni(0)-mediated intramolecular allylic amination (Scheme 2). Studies to further delineate the scope and limitations of this asymmetric Ni(0)-chemistry are in progress and will be described in due course.

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Supporting Information Available: Experimental procedures, representative chiral HPLC traces, and ^{1}H NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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