Dynamic Kinetic Asymmetric Transformation of Diene Monoepoxides: A Practical Asymmetric Synthesis of Vinylglycinol, Vigabatrin, and Ethambutol

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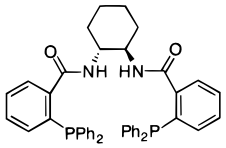
Abstract: The ability to perform a dynamic kinetic asymmetric transformation (DYKAT) using the palladium-catalyzed asymmetric allylic alkylation (AAA) is explored in the context of butadiene monoepoxide. The versatility of this commercially available, but racemic, four-carbon building block becomes significantly enhanced via conversion of both enantiomers into a single enantiomeric product. The concept is explored in the context of a synthesis of vinylglycinol with phthalimide as the nitrogen source. The success of the project required a new design of the ligand for palladium wherein additional conformational restraints were introduced. Thus, the phthalimide derivative of vinylglycinol was obtained in nearly quantitative yield and had an ee of 98% which, upon crystallization, was enhanced to >99%. This one-step synthesis of a protected form of vinylglycinol provided short practical syntheses of the title compounds. Vigabatrin requires only four steps, and ethambutol six. The intermediate to the existing synthesis of ethambutol is available in 87% yield in three steps. *(R)*-Serine derives from oxidative cleavage of the double bond. The reaction of phthalimide and isoprene monoepoxide demonstrates the remarkable ability of the chiral ligands to control both regioselectivity and enantioselectivity and demonstrates the effectiveness of this protocol in creating a quaternary center asymmetrically.

While, in theory, there are many mechanisms for asymmetric induction with transition metal catalysts, in practice, the overwhelming mechanism comes down to the differentiation of enantiotopic faces of prochiral unsaturation (alkenes, carbonyl groups, etc.).[1] The metal-catalyzed allylic alkylation may employ a similar mechanism; however, in most cases, it involves some other enantiodiscriminating events such as discriminating between enantiotopic leaving groups or enantiotopic termini of π-allylmetal interemediates.[2] An unsymmetrical substrate such as **1** (Scheme 1) may lead preferentially to either complex **2** or **3** to give rise to an asymmetric alkylation. On the other hand, it may give a mixture of **2** and **3** which can equilibrate via a σ-complex. In this case, the enantiodiscrimination arises because of a rate differential between the reaction of the two diastereomeric complexes **2** and **3** and the nucleophile to give either enantiomeric product **4** or ***ent*-4**. In this latter scenario, employing the racemate **7** and ***ent*-7** also may lead to asymmetric induction. This type of process, while frequently referred to as a kinetic resolution, is more properly referred to as a dynamic kinetic asymmetric transformation (DYKAT). Using the family of ligands being developed in these laboratories,[3] our mnemonic predicts the complex derived from ligand **5** and Pd(0) should favor path a; whereas, the complex derived from ligand **6** and Pd(0) should favor path b. The major problem with this series is the issue of regioselectivity since attack in such systems is normally favored at the primary carbon which generates an achiral product.[4]



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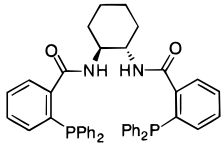

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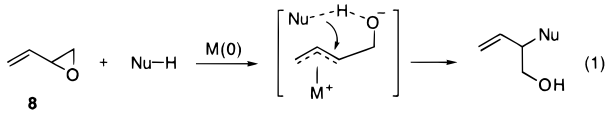
To address the regioselectivity, we chose to examine butadiene monoepoxide (**8**) in a belief that coordination of the pronucleophile to the oxygen leaving group would help deliver the nucleophile to the adjacent carbon (eq 1). The epoxide **8** has



8 (1)

become readily available as a cheap raw material because of the discovery of a silver-catalyzed oxidation of 1,3-butadiene.[5] The utility of vinylglycinol as a chiral building block[6] led us to

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(3) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

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(6) For some recent examples, see: (a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 5263. (b) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 245. (c) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin I* **1998**, 893. (d) Cheung, K. M.; Shoolingin-Jordan, P. M. *Tetrahedron* **1997**, *53*, 15807. (e) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465. (f) Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. I* **1994**, 773.

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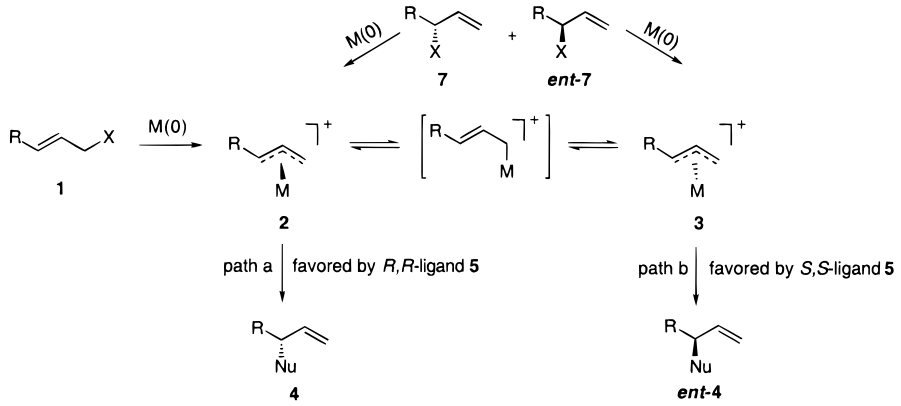
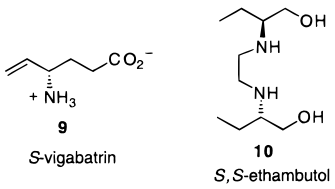
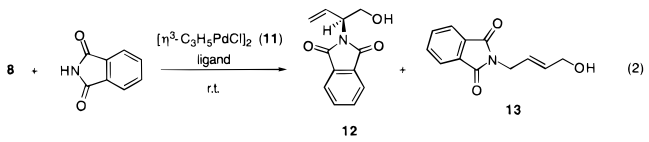
Scheme 1. Asymmetric Induction with Monosubstituted Allyl Systems



focus on phthalimide as the pro-nucleophile. In this paper, we record our studies that led to a practical synthesis of vinylglycinol[7,8a] and the application of this methodology to the asymmetric syntheses of vigabatrin (**9**),[8b] an anti-epileptic drug,[9] and ethambutol, a tuberculostatic drug.[10] The demonstration of the effectiveness of vigabatrin in reducing or abolishing the addictive properties of a variety of drugs including cocaine, nicotine, methamphetamines, and heroin has renewed interest in a practical asymmetric synthesis since all of the activity resides in the *S*-enantiomer.[12] Ethambutol must be enantiomerically pure since its mirror image isomer purportedly causes blindness. All previously reported syntheses[13,14] involve resolution. The effect of substitution on the epoxide, to create a quaternary center asymmetrically, has been examined by extending the study to the use of isoprene monoepoxide.



Initial Experiments. Exposing an approximately equimolar mixture of butadiene monoepoxide and phthalimide to a catalyst formed in situ from π-allylpalladium chloride dimer (**11**) and a ligand led to a smooth reaction as summarized in eq 2. Using



triphenylphosphine as ligand in THF solvent, a 4:1 ratio of **12**:**13** was obtained in 71% yield. Performing the reaction in THF with ligand **5**[15] gave a significantly improved regioselectivity, favoring attack at the more substituted allyl terminus (**12**:**13**, 16:1) and a reasonable ee 77% (er 88.5:11.5). The ee may be established by NMR and/or HPLC methods. Converting the primary alcohol to the (*S*)-*o*-methylmandelate ester **14**[16] allowed the de to be determined by both ^{1}H NMR and HPLC. The doublet of doublets for the methylene group appears clearly separated at δ 4.387 for **14** and δ 4.515 for the *R*,*S*-diastereomer. HPLC analysis (Dynamax, 15% ethyl acetate in hexane) elutes the *R*,*S*-diastereomer before the *S*,*S*-isomer. Chiral HPLC (Chiracel OD, 90:10 heptane:2-propanol) also resolves the two enantiomers of **12**.

Varying the reaction conditions did not improve the selectivity. For example, switching to methylene chloride which dramatically improved the ee with symmetrically 1,3-disubstituted substrates led to a slight decline to 68% ee (er 84:16). On the other hand, changing the ligand to the diphenyl system **15**[15] improved both the regioselectivity (**12**:**13**, 19:1) and enantioselectivity (83% ee, er 91.5:8.5).

New Ligand Design. With our first generation of ligands, we reached a plateau in the selectivity. There are two explanations. In the first instance, the equilibration between the two

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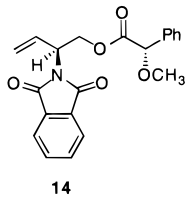

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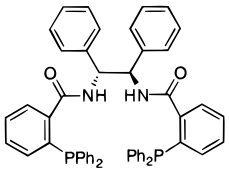

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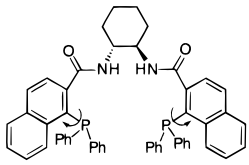
diastereomeric complexes corresponding to **2** and **3** is not fast enough compared to the rate of nucleophilic attack. In the second instance, the rate difference between path a and path b is not large enough. To address both of these issues, we considered ways to create a tighter chiral pocket by restricting conformations. Introduction of a benzo ring as in **16** restricts the degrees of freedom of the diphenylphosphino moiety; whereas, annulation of a benzo ring in **17** restricts the conformational freedom of the amide carbonyl. For completeness and to ascertain any role associated with a naphtho versus a benzo linker, the third possible orientation as in **18** was also considered.



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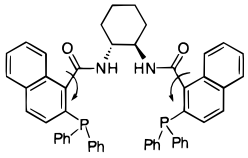

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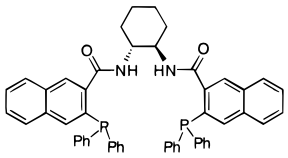

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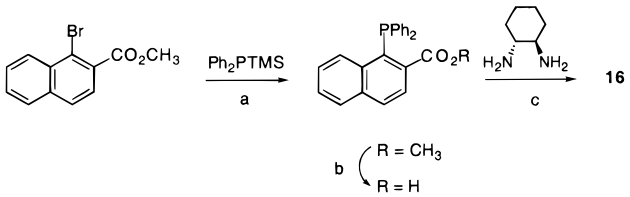
Schemes 2−4 show the syntheses of the three ligands. Either the bromoester[17] (Scheme 2) or the triflates of the salicyclic esters[18,19] (Schemes 3 and 4) participate well in Pd-catalyzed cross-coupling to introduce the diphenylphosphino moiety without the need to protect the phosphine functionality.[20,21] Hydrolyses of the methyl esters were straightforward in the cases of Schemes 2 and 4. On the other hand, the very hindered methyl ester of Scheme 3 failed to hydrolyze under standard conditions. However, employing barium hydroxide provided the desired acid in good yield.

Activation of the carboxylic acid sufficient for amide bond formation while avoiding intramolecular Friedel−Crafts acylations of the electron-rich diphenylphosphino moiety proves tricky. DCC promoted amide bond formation did proceed well to form ligand **16** (Scheme 2) but failed in the preparation of ligand **18** (Scheme 4). A more convenient procedure employs diphenylchlorophosphate as the coupling agent since the byproduct is readily removed in the aqueous washes. This method, which has been employed for the preparation of **17** (Scheme 3) and **18** (Scheme 4), has become our method of choice.

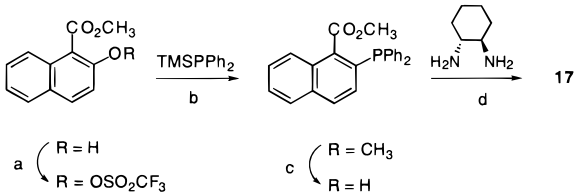
An X-ray structure of the naphtho ligand **17** was obtained (see Figure 1). As expected, the plane of the acyl moiety lies perpendicular to the plane of the naphthalene ring. The triarylphosphino moieties also adopt propellor-like arrangements.

Scheme 2. Synthesis of (*R,R*)-1,2-(1-Diphenylphosphino-2-naphthalene-carboxamido)cyclohexane (**16**)



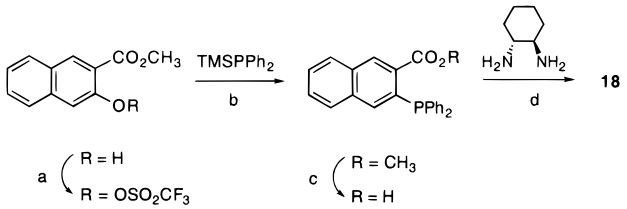
[a] (a)$(PhCN)_2PdCl_2$, $PhCH_3$, 120°, 66%. (b) $LiOH{\cdot}H_2O$, C_2H_5OH, H_2O, reflux, 92%. (c) DCC, DMAP, CH_2Cl_2, −25°, 85%.

Scheme 3. Synthesis of *(R,R)*-1,2-(2-Diphenylphosphino-1-naphthalenecarboxamido)cyclohexane (**17**)



[a] (a)$(CF_3SO_2)_2O$, C_5H_5N, CH_2Cl_2, −78−0°, 89%. (b) $(PhCN)_2PdCl_2$, $PhCH_3$, reflux, 95%. (c) $Ba(OH)_2{\cdot}8H_2O$, CH_3OH, reflux, 88%. (d) $(PhO)_2P(O)Cl$, $(C_2H_5)_3N$, CH_2Cl_2, 0°, 51%.

Scheme 4. Synthesis of *(R,R)*-1,2-(3-Diphenylphosphino-2-(naphthalenecarboxamido)cyclohexane (**18**)



[a] (a)$(CF_3SO_2)_2O$, C_5H_5N, CH_2Cl_2, −78−0°, 78%. (b)$(PhCN)_2PdCl_2$, $PhCH_3$, reflux, 55%. (c) $LiOH{\cdot}H_2O$, C_2H_5OH reflux, 94%. (d) $(PhO)_2P(0)Cl$, $(C_2H_5)_3N$, CH_2Cl_2, 0°, 51%.

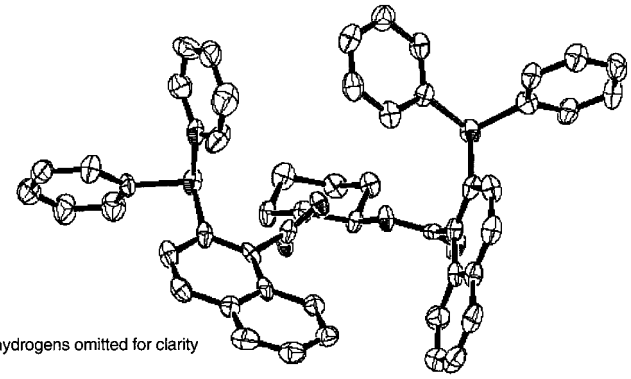


Figure 1. X-ray Structure of ligand **17**.

Reaction Optimization. A standard set of operating conditions that employed 2.5 mol % palladium complex **11**, 7.5 mol % ligand (P:Pd 3:1), and 5% sodium carbonate was adopted. The sodium carbonate serves as an initiator of the catalytic cycle. Table 1 summarizes the results. Ligand **16** generally gave low ee in all of its reactions, so it was not pursued in this case. The conformationally rigidified ligand **17** did not show any improvement in ee in THF (entry 4). On the other hand, switching the solvent to methylene chloride dramatically enhanced the reaction whereby a nearly perfect reaction occurred in terms of regioselectivity (75:1), enantioselectivity (98% ee, 99:1 er), and yield

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(19) Cohen, J. B.; Dudlay, H. W. *J. Chem. Soc. (London)* **1910**, 748.
(20) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748.
(21) For a subsequently developed alternative using Ni-catalyzed cross-coupling, see: Ager, D. J.; East, M. B.; Eisenstadt, A.; Laneman, S. A. *Chem. Commun.* **1997**, 2359.

Table 1. Amination of Butadiene Monoepoxide

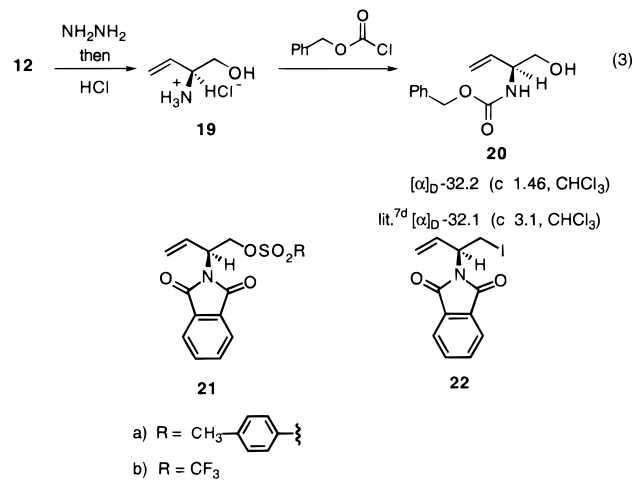
entry	ligand	solvent	**12:13**	yield (%)	ee (%)
1	Ph_3P	THF	4:1	71	N.A
2	**5**	THF	16:1	87	77
3	**5**	CH_2Cl_2	–	83	68
4	**17**	THF	–	86	67
5	**17**	CH_2Cl_2	75:1	99	98
6	**18**	THF	–	94	66
7	**18**	CH_2Cl_2	–	99	55

(99%) (entry 5). This solvent trend has been previously observed in other asymmetric allylic alkylations with the standard ligand.[22]

Further optimization focused on catalyst load. Dropping the loading to 0.4 mol % from 2.5 mol % gave a 98% yield of phthalimide **12** of 96% ee. Lowering the catalyst further significantly decreased the ee. Recrystallization of product of 96% ee from di-isopropyl ether increased the ee to ≥99%.

To examine whether the source of the enhanced selectivity with ligand **17** was associated with the naphthalene fragment per se or the conformational constraints imposed by ligand **17**, the 2,3-disubstituted ligand **18** was also examined. As shown in entries 6 and 7 of Table 1, the results directly mirrored the behavior of the catalyst derived from the standard ligand. In fact, the slightly lower ee's with ligand **18** compared to those with **5** suggest a detrimental effect, if any, of a larger naphthalene unit.

Absolute Configuration. The absolute stereochemistry of the amination product was established by correlation to a known compound. Standard removal of the phthalimide from **12** derived from a reaction with the *R,R*-ligand **17** by reaction with hydrazine in ethanol at reflux followed by addition of 6 N aqueous hydrochloric acid followed by further heating at reflux gave the vinylglycinol hydrochloride (**19**, eq 3). The product



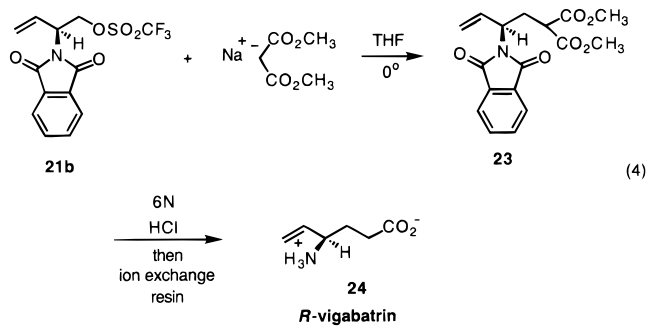
was directly subjected to benzyl chlorocarbonate $(C_2H_5)_3N$, CH_2Cl_2, 0°, 1 h) to give the known carbamate **20**[7d] in 62% overall yield for the two steps. The observed optical rotation agreed very well in magnitude to that reported, and the sign of the rotation indicated that the absolute configuration was *S* as depicted.

Synthesis of Vigabatrin. The synthesis of vigabatrin requires a two-carbon chain extension from vinylglycinol. In the ideal situation, this modification can be performed directly with the phthalimide **12**. The alcohol was readily converted to the corresponding sulfonate esters **21a** and **21b** in standard fashion[23] in 62 and 97% yield, respectively. In light of subsequent events, it is quite interesting that the iodide **22** formed in standard fashion[24] (I_2, Ph_3P, imidazole, CH_3CN, ether, room temperature) in 85% yield. One advantage of the phthalimido group is that it imparts crystallinity to all of these derivatives. While the tosylate **21a** and iodide **22** were stable and readily handled, the triflate **21b** did not store well and should be used within a few days of its preparation.

Attempts to effect displacements with the lithium enolate of *tert*-butyl acetate using the tosylate or iodide led to no substitution. In the case of the tosylate, products derived from addition to one of the carbonyl groups of the phthalimide, cleavage of the tosylate, and elimination were observed. To reduce the susceptibility for carbonyl addition, malonate nucleophiles were employed. While carbonyl addition was not observed, neither was alkylation with **21a** or **22**. Either starting material was recovered, or if more forcing conditions were employed, elimination was observed.

The inability to observe any displacement product was surprising in light of the facility with which the iodide **22** formed since an S_N2 displacement was involved. Since the leaving group in this case was a phosphineoxide, we briefly examined Mitsunobu conditions[25] but again unsuccessfully.

In complete contrast to the disappointing behavior of the tosylate and iodide toward displacement, the triflate behaved quite well (eq 4). Dimethyl sodiomalonate, generated in situ,



effected displacement at 0° in THF to give the alkylated product **23** in 64% yield. Global deprotection with 6N aqueous hydrochloric acid gave a 96% yield of the hydrochloride salt of *(R)*-vigabatrin from which *(R)*-vigabatrin **24** was liberated using a basic ion-exchange column. Both the rotation (obsd $[\alpha]_D = -12.1$ (*c* 2.35, H_2O), lit.[12] $[\alpha]_D = -12.0$ (*c* 2.5, H_2O)) and mp (obsd 165 °C, lit.[12] 164−165 °C) agree with those reported in the literature. The synthesis of the biologically active *S*-enantiomer simply requires a change in the ligand of the initial palladium-catalyzed alkylation.

Synthesis of Ethambutol. Ethambutol has been synthesized in modest yield by the direct alkylation of (+)-2-amino-1-butanol, the latter obtained by resolution.[13] It has also been reported that the reductive alkylation using glyoxal and sodium borohydride succeeds.[13a] Thus, simple reduction (10% Pd/C, 1 atm H_2, C_2H_5OH, 96%) of the double bond and cleavage (ethylenediamine, C_2H_5OH, reflux, 92%) of the phthalimide to form enantiomerically pure 2-amino-1-butanol constitutes a

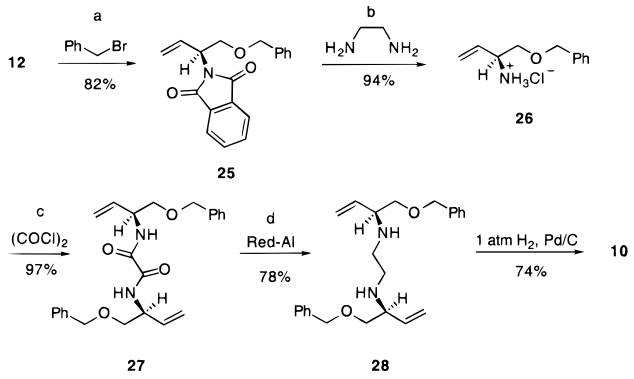
(22) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

(23) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. V. R.; Effenberger, F.; Kunz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099.

(24) Garegg, P. J.; Samielsson, B. *J. Chem. Soc., Perkin Trans. I* **1980**, 2866.

(25) Cf. Yu, J.; Cho, H. S.; Falck, J. R. *J. Org. Chem.* **1993**, *58*, 5892.

Scheme 5. Asymmetric Synthesis of (+)-Ethambutol

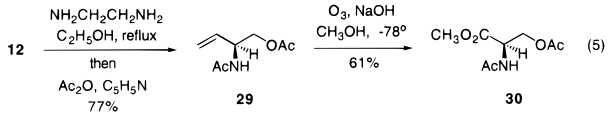


[a] (a) NaH, DMF, 0°. (b) C_2H_5OH, reflux, then 6 N aqueous HCl. (c) C_5H_5N, CH_2Cl_2, 0°. (d) $PhCH_3$, 45°. (e) CH_3OH, rt; add 1.2 N HCl; ion-exchange resin.

formal synthesis of ethambutol (*vide infra*). Our inability to reproduce these two literature procedures led us to an alternative strategy.

Believing the difficulties encountered with the amino alcohol stemmed from the involvement of the free alcohol led us to protect the alcohol as the benzyl ether **25** as shown in Scheme 5. Cleavage of the phthalimide with hydrazine gave the product of double bond reduction, the saturated amino alcohol, in addition to the unsaturated product. On the other hand, clean deprotection occurred by the use of ethylenediamine in refluxing ethanol which then became our normal method of choice.[26] Oxalamide formation to give **27** occurs nearly quantitatively. Reduction with Red-Al proceeds uneventfully to give the bis-benzyl ether of bis-dehydroethambutol **28**. The straightforward nature of this sequence contrasts sharply with the difficulties of the reductive alkylation of the free amino alcohol with glyoxal. Completion of the synthesis requires saturation of the double bond and hydrogenolysis of the benzyl ethers. The former occurs readily with 1 atm of hydrogen in methanol at neutral pH. To effect hydrogenolysis of the benzyl ethers, 1.2 N methanolic hydrochloric acid was added and the reduction continued at room temperature. Purification utilizing an ion-exchange resin gave (+)-ethambutol whose mp (obsd 84−5 °C; lit.[10a] mp 87.5−88.5 °C) and rotation (obsd $[\alpha]_D = +13.5$ (*c* 3.31, H_2O, lit.[13a] $[\alpha]_D = 13.7$ (*c* 2, H_2O) agree well with the literature.

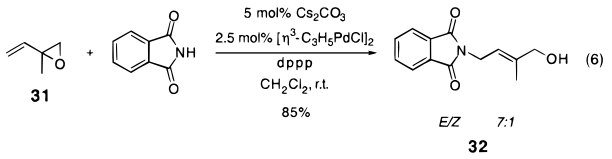
Synthesis of Serine. The juxtaposition of a double bond and alcohol flanking a carbon bearing an amino group makes vinylglycinol a good building block for the asymmetric synthesis of amino acids by two routes. The most obvious derives from the ability of generating either enantiomer of vinylglycinol by simply switching the catalyst. An alternative starts from one enantiomer and then utilizes either the alcohol or the alkene to become the carboxylic acid which then provides either enantiomer of the amino acid from one chiral intermediate. A simple synthesis of a *(R)*-serine derivative illustrates the point (eq 5).



Removal of the phthalimide was followed directly by acetylation to give the diacetate **29**. Ozonolysis in basic methanol provided the methyl ester of the diacetate of *(R)*-serine **30**.

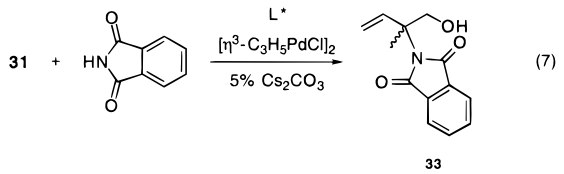
(26) Kanie, O.; Crawley, S. C.; Palcic, M. M.; Hindgaul, O. *Carbohydr. Res.* **1993**, *243*, 139.

Reaction with Isoprene Monoepoxide. The success of the butadiene monoepoxide led to our examination of isoprene monoepoxide (**31**) in which a quaternary center will be created. The notion that a tight pocket is required for good ee suggests that the reaction will be sensitive to such steric effects. The initial reaction examined the addition of phthalimide to epoxide **31**, using an achiral ligand as shown in eq 7. In contrast to

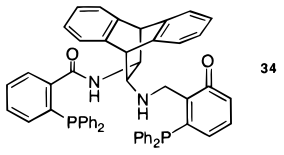


butadiene monoepoxide **8**, the 1,4-substitution product **32**, as a 7:1 *E/Z* mixture of olefin isomers, was obtained. Thus, the chiral ligand must invert the regioselectivity as well as control enantioselectivity.

Utilizing the "standard" ligand **5**, the regioselectivity virtually completely reversed to produce a 58% yield of the vicinal alkylation product **33** albeit very slowly (2 days) in THF at room temperature with only trace amounts of **32** detectable by TLC (see eq 8). Enantiomeric purity was determined by chiral



HPLC using a Chiracel OD column eluting with heptane/isopropyl alcohol to be 83% ee. Running the reaction at 55 °C decreased the reaction time to 5.5 h but decreased the ee to 71% although the yield improved to 78%. Notably, no decrease in regioselectivity occurred. The anthracene-derived ligand **34** is believed to possess a more rigid pocket stemming from a larger P−Pd−P bite angle because of the large dihedral angle between the amide groups in the rigid framework and the benzo rings.[2,3] Nevertheless, no significant change in ee was observed running the reaction at 55° compared to ligand **5**.



Given the success of the naphthalene-based ligand **17**, we examined the use of this ligand in detail. Table 2 summarizes the data. Using the preferred solvent for butadiene monoepoxide as our starting point (entries 1−6), it is immediately apparent that this reaction is considerably slower, consistent with the tight pocket of the catalyst and the increased steric demand of the substrate. Increasing the amount of base did appear to enhance the rate of the reaction (entry 3), whereas no base led to a poor yield but the best ee thus far (entry 6). Most effective, with respect to yield and rate, was increasing temperature (entry 4) although the ee declined somewhat.

Switching to toluene (entry 7) led to the formation of both regioisomeric products because of the long time required (vide infra) and poor ee. Dioxane proved even poorer. On the other hand, initial results with THF gave the most promising results (entry 9). Increasing time (entry 10) but, better, increasing temperature (entries 11−13) led to the optimum result of 72%

Table 2. Amination of Isoprene Monoepoxide Utilizing Naphthalene Ligand **17**[a]

entry	mol % Pd	mol % base	solvent	temp (°C)	time (h)	isolate yield **33** (%)	ee **33** (%)
1	2.5	5	CH_2Cl_2	rt	5	22	79
2	2.5	5	CH_2Cl_2	rt	16	29	N.D.
3	2.5	50	CH_2Cl_2	rt	29	52	75
4	2.5	50	CH_2Cl_2	55	4	89	62
5	2.5	50	CH_2Cl_2	55	7	60	70
6	2.5	0	CH_2Cl_2	55	5.5	18	85
7	2.5	5	$PhCH_3$	55	24	51[b]	18
8	2.5	5	dioxane	55	24	11	N.D.
9	2.5	5	THF	rt	21.5	36	84
10	2.5	5	THF	rt	72	44	87
11	1.25	5	THF	40	7	54[d]	84
12	2.5	5	THF	55	3	34	82
13	2.5	5	THF	55	7	72	87
14	2.5	5	THF[e]	55	24	0[f]	–
15	2.5	50	THF	55	7	78	80
16	2.5	0	THF	55	5.5	32	86
17	2.5	5[g]	THF	55	24	66	71
18	2.5	5+50[h]	THF	55	24	31[i]	60
19	2.5	5	THF[j]	55	24	0	–
20	2.5	5	CH_3CN	55	24	62[k]	>90

[a] All reactions were run utilizing 1 equiv of **31**, 1.1 equiv of phthalimide, $[\eta^3\text{-}C_3H_5PdCl]_2$as the Pd source and Cs_2CO_3 as base at 0.1 M in the stated solvent except as indicated otherwise. [b] 18% of **32** also isolated. [c] Reaction run at 0.03 M. [d] 5% of **32** also isolated. [e] Reaction run at 0.03 M. [f] Only **32** isolated in 85% yield. [g] Na_2CO_3 used as base. [h] 50 mol % pyridine also used. [i] 29% of **32** also isolated. [j] 10 mol % water added. [k] 10% of **32** also isolated.

yield of vinylglycinol derivative **33** of 87% ee (entry 13). Using the *R,R*-ligand **17**, the absolute configuration is assigned as *S*. The reaction time is significant since prolonged reaction led to formation of the 1,4-product **32** instead of the 1,2-product **33** (entry 14). This result strongly suggests that the initial alkylation product **33** can be ionized under the reaction conditions at 55 °C. The thermodynamic ratio favors the formation of the distal adduct **32**. Most importantly, the ee was not too sensitive to temperature since we obtained the same ee at room temperature (87%, entry 10) as at 55 °C (87%, entry 13). Under these conditions, increasing the base from 5 to 50 mol % had no significant effect on yield although it decreased the ee slightly (entry 15). We suggest the small loss in ee may result in more rapid trapping of the organometallic intermediate because of a higher concentration of nucleophile which then does not permit complete equilibration of the diastereomeric π-allylpalladium complexes. On the other hand, the absence of base did not increase the ee but did see a drop in yield (entry 16). Changing the base from cesium carbonate to sodium carbonate saw a decrease in ee (entry 17) which also may relate to the rate of trapping by a sodium versus cesium salt. Other work in these laboratories suggest that cesium salts may react more slowly with π-allylpalladium complexes than sodium salts[27]—a feature that is desirable to ensure full equilibration of the diastereomeric complexes. Adding pyridine as a more soluble base proved considerably less effective (entry 18). We had previously noted that sometimes addition of water was beneficial to the rate of the palladium reactions of vinyl epoxides.[28] That proved not to be the case here (entry 19). On the other hand, use of a more polar solvent, acetonitrile, led to the best ee (>90%) but suffered from the formation of some 1,4-product **32**. It should be noted that the formation of the undesired regioisomer may result from an equilibration of the initial product as a result of the long reaction time.

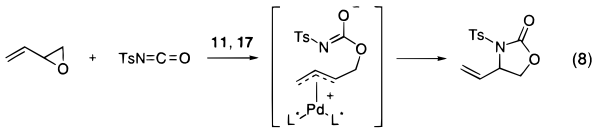
(27) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.
(28) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.

Discussion

A dynamic kinetic asymmetric transformation has a potential advantage over a resolution (kinetic or dynamic kinetic)—fewer synthetic steps. If the act of converting a racemic mixture into a single enantiomeric series is combined with one of the required structural transformations, the dynamic resolution is not an additional step in the synthesis and thereby saves a step. Palladium-catalyzed asymmetric allylic alkylation (AAA) offers much promise in this area.

Butadiene monoepoxide, which derives from butadiene and oxygen, is now commercially available on large scale. The functional versatility of this four-carbon building block makes it an interesting synthon if the racemic starting material can be directly converted into enantiomerically pure products. Enantiomerically pure vinylglycinol is an especially valuable building block that normally derives from amino acids.[7] Methionine, via a sulfoxide elimination, provides the amino alcohol in five steps. The use of serine as a precursor also requires five steps. A more direct synthesis enhances the utility of this chiral building block.

The palladium-catalyzed cyclization of the bis-urethane of 2-butene-1,4-diol using a ferrocenyl-based ligand provides a vinylglycinol derivative in a maximum 73% ee.[29] More relevant to the current work are the AAA reactions of butadiene moneopoxide with isocyanates and carbodiimides. We examined the reaction of the epoxide with tosylisocyanate[30] using the naphthalene ligand **17** which nicely provided the *N*-tosyloxazolin-2-one in 98% yield (eq 8). Unfortunately, it was virtually



racemic. We presume the covalent tethering of the nucleophile as depicted enhances the rate of the cyclization at the expense of the racemization. On the other hand, BINAP analogues have been shown to give good ee's in an analogous reaction with carbodiimides but not isocyanates.[31] However, unmasking of the derivatives of vinylglycinol produced in both cases to the parent is not trivial.

The classic Gabriel synthesis is one of the most reliable syntheses of primary amines; however, unlike the above cases, the lack of covalent tethering of the nucleophile to the substrate raises the issue of regioselectivity. On the other hand, this feature might permit racemization of the π-allylpalladium intermediate to compete more effectively with nucleophilic attack. Interestingly, the regioselectivity with the chiral ligands was significantly increased relative to triphenylphosphine. Thus, the regioselectivity presumably does not stem from the templating effect depicted in eq 1 alone; the chiral ligands are also helping to control the regioselectivity to direct the nucleophile to the more hindered position.[4] Furthermore, the regioselectivity paralleled the enantioselectivity. Figure 1 depicts the nature of the reactive complex according to our working model.[3] Placing the hydroxymethyl substituent in the right front quadrant as in I minimizes steric strain with the "walls" (the phenyl rings which are close to the π-allyl fragment) of the chiral space compared to II. Minimizing any steric interactions between the approaching nucleophile and the chiral ligand also directs it to approach from

(29) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99.
(30) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.
(31) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709; *idem. J. Org. Chem.* **1998**, *63*, 6229.

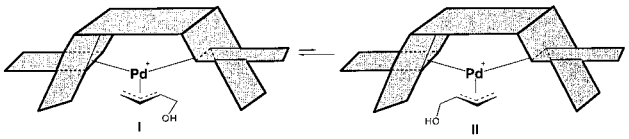


Figure 2. Cartoon depiction of chiral space.

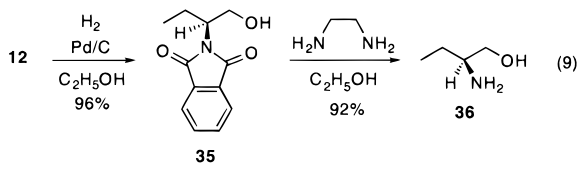
the front right quadrant. Thus, the model nicely rationalizes both the regio- and enantioselectivity.

The model of Figure 2 depicts the more reactive (and probably more stable) π-allylpalladium complex. All other π-allyl complexes formed must equilibrate to that depicted faster than nucleophilic attack to achieve a dynamic kinetic asymmetric transformation. With the standard ligand, the greater flexibility of the chiral space allows for nucleophilic attack on one of the other complexes to compete—a rationalization of both the lower regio- and enantioselectivity. Increasing the steric demands of the tether of the chiral scaffold as in **15** increases both selectivities; however, still not to a satisfactory level. The greatest success arises by rigidifying the linker between the chiral scaffold (the diamine or diols) and the diacylphosphino units. Indeed, rigidifying the carboxylate conformation as in ligand **17** gives nearly a perfect result in methylene chloride but not THF. The dramatic solvent effect can be best ascribed to one of two explanations. In the first, the rate of nucleophilic attack in THF may be faster than in methylene chloride. If so, nucleophilic attack may compete more effectively with equilibration of the diastereomeric complexes lowering the ee. In the second, the nature of the chiral space may change because of the differing solvation abilities of the two solvents. The fact that the complexes are cationic, which should be more strongly solvated by THF, may decrease the rate difference between reaction of the two diastereomeric complexes I and II. While other explanations do exist, we believe these two represent the more likely ones. At this time, we cannot differentiate between them.

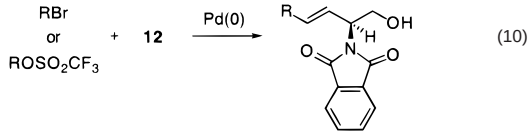
Decreasing the conformational freedom of the diphenylphosphino fragment as in ligand **16** has a strong deleterious effect on the chiral recognition. This observation is consistent with our model which proposes the induced conformational chirality of the triarylphosphino portion is responsible for the chiral recognition.

It is interesting to note that there was an effect of the catalyst load on the enantioselectivity. In trying to minimize the amount of palladium, it was successfully reduced to 0.4 mol %. As the amount of catalyst was further reduced, the ee began to drop precipitously. This dependence of ee on concentration of palladium is surprising if the mechanism of Scheme 1 is fully correct. None of the steps should show such a dependence. Further, the only step that one can envision a mechanism for such a dependence is the interconversion of the diastereomeric π-allylpalladium complexes **2** and **3**. The mechanism depicted is first order in palladium. However, the transformation involves movement of palladium from one face of the π-allyl moiety to the other which might be envisioned to occur via a Pd−Pd substitution. Such substitutions are known.[32] We deemed such substitutions to be inconsequential with such bulky palladium complexes. Nevertheless, there appears to be no viable alternative.

Of all the routes to vinylglycinol, this one is the shortest starting from two commodity chemicals, butadienemonoepoxide and phthalimide. Numerous syntheses reported in the literature can be significantly shortened by the availability of either enantiomer of **12**. The synthesis from methionine requires seven steps (although two are performed on crude material) and proceeds in 15−34% overall yield.[12c] The synthesis reported herein requires four steps from racemic starting materials employing a DYKAT process and proceeds in 58% overall yield. The synthesis of ethambutol also illustrates the power of this approach. The current synthesis employs *(S)*-2-amino-1-butanol (**36**) which is obtained enantiomerically pure by resolution. One of the existing racemic syntheses also starts with butadiene monoepoxide and converts it to the chlorohydrin in order to develop a strategy to control regioselectivity.[13b] This key intermediate (**36**) is available enantiomerically pure in three steps and 87% overall yield from butadiene monoepoxide and phthalimide via **12** followed by hydrogenation to **35** and phthalimide cleavage as shown in eq 9. Furthermore, a more



controlled alternative synthesis of ethambutol also was devised. This new synthesis proceeds in 42% overall yield in six steps from the two commodity chemicals. This represents the first catalytic asymmetric synthesis of ethambutol. The known oxidation of the primary alcohol[33] provides vinylglycine which has been employed in the synthesis of the antitumor antimetabolite acivicin. Heck type reactions provide access to more substituted vinylglycinols according to eq 10.[6e] These can also



provide access to more substituted vinylglycine derivatives. Finally, oxidative cleavage of the double bond also provides amino acids as illustrated in the synthesis of *(R)*-serine. Elaboration of the alcohol prior to cleavage of the double bond provides another route to unusual amino acids.

The ability to extend the reaction to isoprene monoepoxide demonstrates the effectiveness of this catalytic system to create quaternary centers asymmetrically. Furthermore, it demonstrates the power of the ligands to control regioselectivity wherein the chiral ligands totally reverses the regioselectivity despite the steric hindrance associated with forming a quaternary center compared to a primary center. Thus, this method holds promise to be reasonably general for the 3,4-epoxides derived from 3-substituted-1,3-dienes.

Experimental Section

Preparation of 1-Carbomethoxy-2-naphthyl Trifluoromethanesulfonate. To 17.2 g (85 mmol) of methyl 2-hydroxyl-1-naphthoate was added 17.2 mL of pyridine and 100 mL of dichloromethane. The reaction was cooled to −78 °C, and a solution of 28.2 g (100 mmol) of trifluoromethanesulfonyl anhydride in 55 mL of dichloromethane was added over 1 h. The reaction was warmed to 0 °C and then stirred for 14 h while warming to room temperature. The reaction was diluted with 500 mL of diethyl ether and filtered through a sintered glass funnel

(32) MacKenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046; Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292; Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.; Granberg, K. L.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.

(33) Vygas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037.

to remove the pyridinium trifluoromethanesulfonate. The organic phase was washed with 2 × 100 mL of 2 N hydrochloric acid, 2 × 100 mL of water, and 1 × 100 mL of saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and concentrated in vacuo. The product was purified by flash chromatography on silica gel (5 cm × 12 cm, 10% ethyl acetate in hexanes) to give 25.3 g (89%) of a yellow oil, $R_f = 0.62$ (1:1 hexanes/ethyl acetate). IR (neat 1583, 1512, 1425, 966, 833, 617 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (m, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.89 (m, 1H), 7.68−7.54 (m, 2H), 7.40 (d, $J = 9.2$ Hz, 1H), 7.89 (m, 1H), 7.68−7.54 (m, 2H), 7.40 (d, $J = 9.2$ Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 144.7, 133.1, 132.3, 130.6, 128.7, 128.3, 127.6, 125.6, 123.6, 119.0, 118.7 (q, $J_{CF} = 321$ Hz), 52.6. HRMS: Calcd for $C_{20}H_9F_3O_5S$: 334.0123. Found: 334.0122.

Preparation of Methyl 2-diphenylphosphino-1-naphthoate. To 3.34 g (10 mmol) of 1-carbomethoxy-2-naphthyl trifluoromethanesulfonate was added 91 mg (0.25 mmol) of bis(benzonitrile)palladium dichloride, 25 mL of toluene, and 4.39 g (17 mmol) of trimethylsilyldiphenylphosphine.[20] The reaction was heated at reflux for 26 h. After cooling to room temperature, the reaction was diluted with 80 mL of chloroform. The organic phase was washed with 1 × 40 mL of saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The product was absorbed onto 8 g of silica gel and purified by flash chromatography on silica gel (5 cm × 11 cm, 10% ethyl acetate in hexanes) to give 3.5 g (95%) of the phosphine as a waxy solid, mp 107−108 °C, $R_f = 0.33$ (9:1 hexanes/ethyl acetate). IR ($CDCl_3$): 1729, 1434, 743, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (m, 1H), 7.83 (m, 1H), 7.79 (d, $J = 9.1$ Hz, 1H), 7.59−7.53 (m, 2H), 7.38−7.34 (m, 10H), 7.20 (dd, $J = 8.5$, 3.3 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (d, $J = 2.5$ Hz), 139.0 (d, $J = 34.7$ Hz), 137.0 (d, $J = 10.6$ Hz), 133.7 (d, $J = 20.0$ Hz), 133.5 (d, $J = 18.2$ Hz), 133.4, 130.0, 129.9 (d, $J = 7.5$ Hz), 129.7, 128.8, 128.7 (d, $J = 6.8$ Hz), 128.3, 127.6, 127.4, 125.5, 51.9. Anal. Calcd for $C_{24}H_{19}O_2P$: C, 77.83; H, 5.17; P, 8.36; MW, 370.1123. Found: C, 77.87; H, 5.34; P, 8.33; MW, 370.1113.

Preparation of 2-Diphenylphosphino-1-naphthoic Acid. A solution of 2.85 g (7.7 mmol) of methyl 2-diphenylphosphino-1-naphthoate and 14.8 g (47.0 mmol) of barium hydroxide octahydrate in 47 mL of methanol was heated at reflux for 25 h. After cooling to room temperature, the reaction mixture was neutralized with 200 mL of 1 N sodium bisulfate. The aqueous phase was extracted with 4 × 100 mL dichloromethane, and the combined organic phases were dried over sodium sulfate and concentrated in vacuo. The product was absorbed onto 8 g silica gel and filtered through a short column of silica gel (4 cm × 6 cm, 100% ethyl acetate) to give 2.42 g (88%) of the acid as a yellow solid (mp 190 °C decomposes) which was used without further purification. $R_f = 0.56$ (100% ethyl acetate). IR (KBr): 3414, 1685, 1434, 1287, 1252 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.0 (d, $J = 8.2$ Hz, 1H), 7.8 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.5−7.6 (m, 2H), 7.25 (m, 10H), 7.15 (dd, $J = 8.3$, 2.8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.4 (d, $J = 3.4$ Hz), 141.6 (d, $J = 38.0$ Hz), 137.0 (d, $J = 10.7$ Hz), 133.1 (d, $J = 19.1$ Hz), 132.1, 131.9, 130.7 (d, $J = 17.0$ Hz), 129.6, 129.3, 129.2, 128.9 (d, $J = 6.9$ Hz), 128.7, 128.5, 127.8, 125.5. Anal. Calcd for $C_{23}H_{17}O_2P$: C, 77.52; H, 4.81; P, 8.69. Found: C, 77.38; H, 5.00; P, 8.51.

Preparation of (−)-(1*R*,2*R*)-Diamino-1*N*,2*N*-bis(2′-diphenylphosphino-1′naphthoyl)cyclohexane 17. To a solution of 1.90 g (5.33 mmol) of 2-diphenylphosphino-1-naphthoic acid in 42 mL of dichloromethane at 0 °C was added 1.78 g (17.6 mmol) of triethylamine followed by 1.58 g (5.87 mmol) of diphenylchlorophosphite added over 2−3 min. After warming to room temperature over 5 h, the mixture was transferred via cannula to a solution of 304 mg (2.66 mmol) of (1*R*,2*R*)-diaminocyclohexane and 30.5 mg (0.25 mmol) of DMAP in 11 mL of dichloromethane and stirred at 25 °C for 12 h. The reaction mixture was then diluted with 50 mL of dichloromethane, washed with 1 × 50 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo. The product was purified by flash chromatography on silica gel (4.5 cm × 11 cm, 25% ethyl acetate in hexanes) to give 1.07 g (51%) of a white solid which was crystallized from 5 mL of 1:1 chloroform: hexanes as a white powder (mp 148−150 °C), $[\alpha]_D = +13.9°$ (*c* 1.19, CH_2Cl_2), $R_f = 0.64$ (50% ethyl acetate in hexanes). IR ($CDCl_3$): 3412, 1648, 1602, 1510, 1435, 1313 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.8 (d, $J = 8.2$ Hz, 2H), 7.7 (d, $J = 9.1$ Hz, 2H), 7.6 (d, $J = 8.9$, 2H), 7.2−7.4 (m, 22H), 7.0 (m, 4H), 6.6 (d, $J = 5.5$ Hz, 2H), 3.8 (m, 2H), 2.3 (m, 2H), 1.7 (m, 2H), 1.2−1.3 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (d, $J = 4.2$ Hz), 142.0 (d, $J = 34.2$ Hz), 136.8 (d, $J = 11.3$ Hz), 136.8 (d, $J = 11.3$ Hz), 133.5 (d, $J = 19.6$ Hz), 133.4 (d, $J = 19.3$ Hz), 133.3, 131.3 (d, $J = 18.1$ Hz), 129.9 (d, $J = 7.9$ Hz), 129.4, 129.2, 128.7, 128.7, 128.6, 128.5, 128.4 (d, $J = 6.7$ Hz), 127.7, 127.2, 126.9, 125.6, 54.7, 31.5, 24.4. Anal. Calcd for $C_{52}H_{44}N_2O_2P_2$: C, 78.97; H, 5.61; N, 3.54; P, 7.83. Found: C, 78.76; H, 5.86; N, 3.38; P, 7.67.

2-(*S*)-*N*-Phthalimido-3-buten-1-ol (12). A mixture of 14.6 mg (0.004 mmol) of π-allylpalladium chloride dimer (**11**) 94.6 mg (0.012 mmol) of (*R*,*R*)-**17**, 53.0 mg (0.05 mmol) of sodium carbonate and 1.47 g (10 mmol) of phthalimide was purged with nitrogen for 1 h. After addition of 80 mL of dichloromethane, the resulting mixture was stirred 10 min at room temperature at which point butadiene monoepoxide (810 μL, 10 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h and concentrated in vacuo, and the residue was purified by flash-chromatography on silica gel (gradient diethyl ether:hexanes 4:6 to 6:4) to give 2.1 g (98%) of **12** as a crystalline white solid, mp 62 °C, in 96% ee as determined by chiral HPLC. The enantiomeric excess was raised to ≥99% by two recrystallizations from diisopropyl ether, $[\alpha]^{28}_D = -72.2$ (*c* 2.02, CH_2Cl_2), $R_f = 0.65$ (diethyl ether). IR (film) 3450, 1767, 1704, 1644, 1614, 1469, 1386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.8 (m, 2H), 7.7 (m, 2H), 6.1 (ddd, $J = 17.3$, 10.2, 6.9 Hz, 1H), 5.3 (m, 2H), 4.9 (m, 1H), 4.1−4.2 (m, 1H), 3.9−4.0 (m, 1H), 2.9 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 133.9, 132.0, 131.4, 123.0, 118.6, 61.7, 55.5. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.60; H, 5.33; N, 6.65.

2-(*S*)-*N*-Phthalimido-3-butenyl Triflate (21b). To a solution of **12** (109 mg, 0.502 mmol) and triethylamine (92 μL, 0.547 mmol) in 4 mL of dichloromethane at 0 °C was added trifluoromethanesulfonic anhydride (76 μL, 0.547 mmol) in 1 mL of methylene chloride dropwise. The resulting mixture was stirred at 0 °C, under nitrogen for 1 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography on silica gel (hexanes:ethyl acetate 8:2) to give 169 mg (97%) of **21b** as a clear syrup which solidified upon cooling, $[\alpha]^{26}_D = -86$ (*c* 2.62, CH_2Cl_2). IR (neat) 1753, 1693, 1655, 1468, 1387, 1333, 1290, 1205, 1132, 1104, 1087 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88−7.84 (m, 2H), 7.78 (m, 2H), 5.45 (d, $J = 17.1$ Hz, 1H), 5.20−5.10 (m, 2H), 4.80−4.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.56, 134.55, 134.29, 131.56, 129.13, 123.74, 123,50, 122.12, 120.65, 116.40, 73.25, 52.44. HRMS: Calcd for $C_{13}H_{10}NO_5F_3S$: 349.0232. Found: 349.0221.

2-[2-(*R*)-*N*-Phthalimido-but-3-enyl]-malonate (23). To a solution of **21b** (400 mg, 1.14 mmol) in 5 mL of THF were added 5 mL of a solution of dimethyl sodiomalonate which, in turn, was prepared by slowly adding dimethyl malonate (520 μL, 4.58 mmol) into a suspension of sodium hydride (60%, 184.0 mg, 4.60 mmol) in 10 mL of THF. The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was then evaporated in vacuo and purified by flash chromatography (gradient hexanes/ethyl acetate 9/1 to 7/3) to give 242 mg (64%) of **23** as a syrup, $[\alpha]^{26}_D = -27$ (*c* 1.2, CH_2Cl_2). IR (neat): 1770, 1468, 1437, 1385, 1357, 1335 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.72 (m, 2H), 6.19 (ddd, $J = 17.3$, 10.2, 7.6 Hz, 1H), 5.27 (d, $J = 10.2$ Hz, 1H), 4.78 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 3.35 (dd, $J = 8.2$, 6.9 Hz, 1H), 2.72 (ddd, $J = 14.3$, 9.4, 6.9 Hz, 1H), 2.56 (ddd, $J = 14.3$, 8.2, 6.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.13, 167.93, 134.47, 134.20, 131.87, 123.42, 118.70, 52.72, 52.64, 51.81, 48.92, 31.86. HRMS: Calcd for $C_{17}H_{17}NO_6$: 331.1056. Found: 331.1067.

***(R)*-Vigabatrin (24).** A solution of **23** (170 mg, 0.513 mmol) in 5 mL of a 6 N aqueous solution of hydrochloric acid was stirred at 100 °C for 14 h. The reaction mixture was then cooled to 0 °C, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (2-propanol/ethyl acetate/water 3/3/1) to give 81.8 mg (yield 96%) of a yellowish compound, the hydrochloride salt. ^1H NMR (300 MHz, D_2O): δ 5.80 (m, 1H), 5.46 (d, $J = 9.7$ Hz, 1H), 5.44 (d, $J = 17.5$ Hz, 1H), 3.83 (m, 1H), 2.47 (m,

2H), 2.10 (m, 1H), 1.94 (m, 1H). ^{13}C NMR (75 MHz, D_2O): δ 178.2, 133.3, 122.7, 54.3, 30.7, 27.9. The compound was introduced in water on a Dowex-50W-X8-200 (H^+) ion-exchange column (3 mL), washed with water (25 mL), and then eluted with a 0.6 N aqueous solution of ammonium hydroxide. Vigabatrin was thus obtained as a white solid, mp 165 °C [lit.[12c,d] mp 164−165 °C], whose ^{1}H and ^{13}C NMR spectra were identical to the ones previously reported, $[\alpha]^{26}_D = -12.12$ (*c* 2.35, H_2O) [lit.[12c,d] $[\alpha]^{25}_D = -12.0$ (*c* 2.5, H_2O)].

2-(*S*)-*N*-Phthalimido-3-buten-1-yl Benzyl Ether (25). Sodium hydride (60%, 220 mg, 5.50 mmol) was added potionwise to a mixture of **12** (930 mg, 4.28 mmol) and benzyl bromide (610 μL, 5.10 mmol) in 10 mL of DMF cooled to 0 °C. After stirring at 0 °C for 2 h, the reaction was diluted with methylene chloride and washed with water. The aqueous phase was extracted with methylene chloride. The combined organic layers, once dried over magnesium sulfate and filtered through cotton, were evaporated in vacuo. The residue was purified by flash chromatography (gradient hexanes/ethyl acetate 9.5:0.5 to 9:1) to give 1.081 g (82% yield) of **25** as a clear syrup, $[\alpha]^{28}_D = -9$ (*c* 2.31, CH_2Cl_2). IR (neat): 1773, 1710, 1613, 1496, 1468, 1455, 1385, 1358, 1336. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (m, 2H), 7.71 (m, 2H), 7.28−7.20 (m, 5H), 6.15 (ddd, J = 17.8, 10.4, 7.4 Hz, 1H), 5.30 (d, J = 17.8 Hz, 1H), 5.25 (d, J = 10.4 Hz, 1H), 5.07 (m, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.11 (t, J = 9.9 Hz, 1H), 3.74 (dd, J = 9.9, 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.25, 137.94, 134.00, 132.31, 132.02, 128.39, 127.67, 123.31, 119.08, 72.79, 68.87, 53.12. HRMS: Calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1200.

2(*S*)-Amino-1−3-buten-1-yl Benzyl Ether Hydrochloride (26). A mixture of **25** (307 mg, 1 mmol) and ethylenediamine (270 μL, 4 mmol) in 15 mL of ethanol was stirred at reflux for 12 h. The mixture was then cooled to 0 °C, filtered through cotton, and evaporated in vacuo. The resulting residue was taken up in 5 mL of a 6 N aqueous hydrochloric acid solution, and the obtained mixture was evaporated in vacuo. Flash chromatography (gradient ethyl acetate/methanol 9/1 to 8/2) gave 200 mg of **26** (94% yield) as a white solid which could be recrystallized in ethyl acetate, (mp = 146 °C). Note: Using 2 equiv of ethylenediamine instead of 4 equiv gave a 91% yield of **26** on a 1.5 mmol scale, $[\alpha]^{28}_D = +19$ (*c* 0.98, CH_3OH). IR (KBr): 3449, 1654, 1589, 1508, 1500, 1458, 1369, 1118 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ 7.39−7.26 (m, 5H), 5.88 (m, 1H), 5.41 (d, J = 17.4 Hz, 1H), 5.37 (d, J = 11.2 Hz, 1H), 4.59 (s, 2H), 3.87 (m, 1H), 3.64 (dd, J = 10.1, 3.9 Hz, 1H), 3.49 (dd, J = 10.1, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.41, 130.43, 128.55, 137.93, 121.74, 73.43, 69.51, 53.70. Anal. Calcd for $C_{11}H_{16}NOCl$: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.69; H, 7.58; N, 6.53.

(2*S*,2′*S*)-(Oxalamido)-bis(5-buten-1-yl) Benzyl Ether (27). To a solution of **26** (180 mg, 0.842 mmol) in 1 mL of pyridine was added, at 0 °C, a solution of oxalyl chloride (37 μL, 0.424 mmol) in 1 mL of methylene chloride. The resulting mixture was stirred at 0 °C, under nitrogen, for 0.5 h. After addition of 1 mL of methanol, the reaction mixture was evaporated in vacuo and purified by flash chromatography on silica gel (gradient hexanes/ethyl acetate 8/2 to 7/3) to give 166 mg of **27** (97% yield) as a white solid which could be recrystallized in diisopropyl ether, mp = 80−81 °C, $[\alpha]^{28}_D = -52$ (*c* 0.95, CH_2Cl_2). IR (KBr): 3281, 1657, 1586, 1521, 1453, 1423, 1364 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 9.5 Hz, 1H), 7.37−7.28 (m, 5H), 5.87 (ddd, J = 17.4, 10.4, 5.7 Hz, 1H), 5.27 (bd, J = 17.4 Hz, 1H), 5.22 (bd, J = 10.4 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 3.57 (s, 1H), 3.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.35, 137.73, 134.57, 128.55, 127.88, 127.75, 117.07, 73.27, 71.22, 51.83. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.38; H, 6.83; N, 6.75.

(2*S*,2′*S*)-(Ethylenediimino)-bis(3-buten-1-yl) Benzyl Ether (28). To a solution of **27** (60 mg, 0.147 mmol) in 750 μL of toluene was added, at 0 °C, a solution of Red-Al (65% in toluene, 230 μL, 0.734 mmol). The resulting mixture was stirred at 45 °C for 20 h. The reaction mixture, diluted with ethyl acetate, was washed by a 1 M aqueous solution of sodium hydroxide. The aqueous phase was extracted with ethyl acetate, and the combined organic layers, after being washed with water, were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate/methanol 9/1) to give 43.9 mg of **28** (78% yield) as an oil, $[\alpha]^{28}_D = +12$ (*c* 2.61, CH_2Cl_2). IR (neat): 3319, 1668, 1644, 1496, 1454, 1416, 1362 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (d, J = 9.5 Hz, 1H), 7.37−7.28 (m, 5H), 5.87 (ddd, J = 17.4, 10.4, 5.7 Hz, 1H), 5.27 (bd, J = 17.4 Hz, 1H), 5.22 (bd, J = 10.4 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 3.57 (s, 1H), 3.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.18, 128.43, 127.69, 117.35, 73.38, 73.17, 61.22, 46.89. HRMS: Calcd for $C_{24}H_{32}N_2O_4$ ($-C_7H_7$): 289.1917. Found: 289.1927.

Ethambutol (10). To a suspension of 3% palladium on carbon (20 mg) in 1.5 mL of methanol, was added, under hydrogen (1 atm), a solution of **28** (40 mg, 0.105 mmol). After the mixture stirred at room temperature, under hydrogen (1 atm) for 12 h, 100 μL of a 1.2 M methanolic solution of hydrochloric acid was then added, and the resulting mixture was stirred at room temperature under hydrogen (1 atm) for 48 h. The reaction mixture was then filtered through Celite and evaporated in vacuo. The residue was introduced on a Dowex-50W-X8-200 (H^+) ion-exchange column, washed with water (25 mL), and eluted with a 0.6 M aqueous solution of ammonium hydroxide (50 mL). The combined pure fractions were evaporated in vacuo to give 18.0 mg (74% yield) of ethambutol as a white crystalline residue, mp = 84−85 °C [lit.[13a] 87.5−88.5 °C], $[\alpha]^{25}_D = +18.5$ (*c* 3.31, H_2O) [lit.[13a] $[\alpha]^{25}_D = +18.7$ (*c* 2, H_2O)] and whose spectral properties agree with those previously reported.[13]

2-(*S*)-*N*-Phthalimido-2-methyl-3-buten-1-ol (33). A dry mixture of phthalimide (32.4 mg, 0.22 mmol), cesium carbonate (3.6 mg, 0.01 mmol), [π-allyl)PdCl]$_2$ (1.8 mg, 0.005 mmol), and ligand **17** (11.9 mg, 0.015 mmol) was degassed with nitrogen for 10 min, and then 2 mL of anhydrous THF and 2-methyl-2-vinyl oxirane (16.8 mg, 0.2 mmol, 20μL) were added via syringe, respectively. The reaction mixture was stirred at 55 °C for 7 h and then washed with 0.5 N aqueous sodium hydroxide. The aqueous layer was then extracted with methelene chloride. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification was achieved via silica gel column chromatography with hexanes/ethyl acetate (7/3) affording 33.3 mg (72%) of a clear colorless oil, R_f = 0.35 (hexanes/ethyl acetate 7/3), $[\alpha]^{25}_D = +5.98$ (*d* = 1.38, CH_2Cl_2). Enantiomeric purity was determined by chiral HPLC using a Chiralcel OD column eluting with heptane/isopropyl alcohol (95/5) at 1 mL/min (detection at 254 nm) with retention times of 14.5 and 18.2 min. IR (film): 3465, 1770, 1707, 1370, 1313 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80−7.78 (m, 2H), 7.73−7.69 (m, 2H), 5.97 (dd, J = 17.3, 10.7 Hz, 1H), 5.21 (d, J = 10.7 Hz, 1H), 5.13 (d, J = 17.3 Hz, 1H), 4.13 (dd, J = 12.1, 6.0 Hz, 1H), 3.61−3.73 (m, 2H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 139.2, 134.2, 131.7, 123.1, 114.8, 68.3, 64.9, 20.8. HRMS: Calcd for $C_{13}H_{11}NO_2$ ($M^+ - H_2O$): 213.0709. Found: 213.0785.

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Supporting Information Available: Experimental procedures for **14**, **16**, **18**, **20**, **22**, **35** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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