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Designing a Receptor for Molecular Recognition in a Catalytic Synthetic Reaction: Allylic Alkylation

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Introduction

One of the potential benefits of allylic alkylations catalyzed by transition metals compared to noncatalyzed processes is the prospect of excercising control of absolute stereochemistry by a chiral scalemic (i.e., enantiomerically enriched or pure) transition-metal complex. Before addressing enantioselectivity, diastereoselectivity of such processes must be considered as outlined in Scheme 1. Good evidence exists that reactions proceeding through paths A,[2] B,[3] and D[4] have been observed. While documentation for reactions proceeding through path C is lacking, it likely does occur too. Path A is distinct from all the other paths in that neither the bond-breaking event, i.e., ionization, nor the bond-making event, i.e., alkylation, occurs within the coordination sphere of the metal. From the perspective of imposing absolute stereochemical control by chiral inducing elements ligated to the metal, influencing events occurring outside the coordination sphere of the metal (and thereby distal to the asymmetric inducing elements) becomes a considerable challenge. Such a process is distinct from all other transition-metal-catalyzed chiral events for which good enantioselectivity has been achieved exemplified by catalytic hydrogenation, epoxidation, dihydroxylation, and cyclopropanation.[5] The reactions of stabilized or soft nucleophiles catalyzed by Pd proceed through path A.[2]

Scheme 1. Diastereoselectivity of Metal-Catalyzed Allylic Alkylation

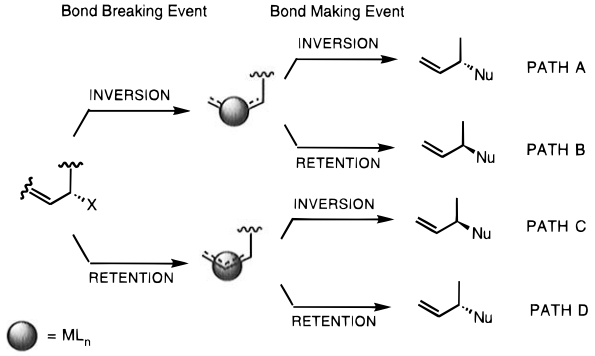

Figure 1 summarizes the different types of asymmetric inducing events for such Pd-catalyzed reactions. Each stage of the catalytic cycle offers the possibility of controlling absolute stereochemistry. For the ionization phase, either differentiating enantiotopic faces of the alkene double bond of the substrate (type A) or discriminating between enantiotopic leaving groups (type B) provides asymmetric induction. For the alkylation phase, recognition of two enantiotopic termini of a *meso*-π-allyl intermediate (type C) or differentiating between two enantiotopic transition states of a rapidly equilibrating enantiomeric pair (type D) allows imparting of enantioselec-

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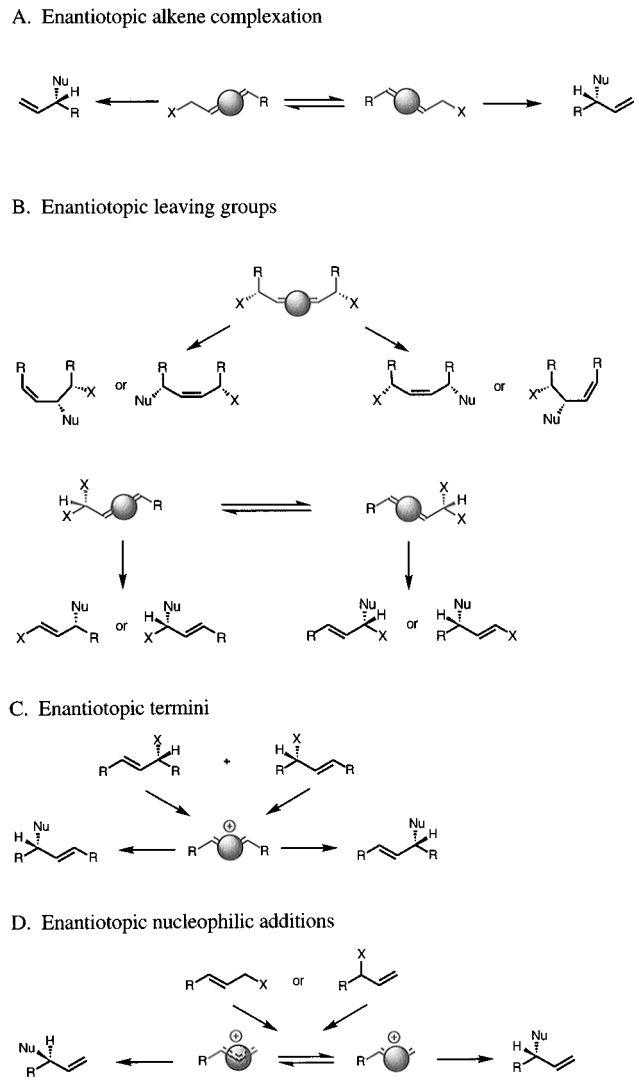
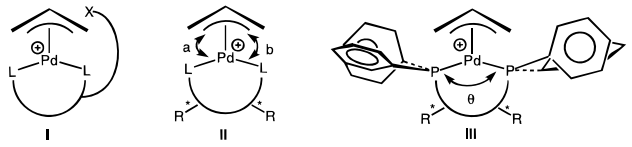


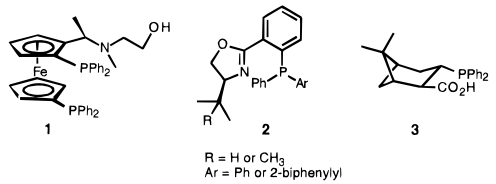
Figure 1. Types of asymmetric induction.

tivity. In all of these cases, the key question becomes how the transition metal and its attendant ligands transmit their stereochemical information to the bond-breaking or -making events occurring distally.

The challenge of the problem has stimulated a great deal of work that has been exploding in recent times. Three concepts have been advanced: (1) attaching a substituent to the ligand via a tether long enough to reach the other side of the π-allyl unit to interact with any incoming nucleophile as in **I**,[6,7] (2) effecting electronic dissymmetrization wherein different C−Pd bond lengths a and b in **II** lead to bias toward attack at one enantiotopic terminus over another,[8,9] and (3) immersing the substrate in chiral space as illustrated in **III** for the case of a chiral propeller created by the conformational bias for edge−face interactions of the phenyl groups of the diarylphosphino moieties induced by the primary stereogenic centers.[10,11]



For type **I**, the ferrocenyl ligands represented by **1** have given excellent results.[6] The oxazolines illustrated by **2**[8,9] and, more recently, the carboxylate **3**[12] may be examples of type **II** that have shown exciting enantioselectivities. However, ligands based upon type **III** have proven to be the most general in inducing asymmetry in allylic alkylations to date and form the subject of this Account.[13]



Ligand Design

The chiral space enveloping the allyl substrate depicted in **III** is envisioned to be related to the P−Pd−P bite angle. Increasing this angle will push the aryl groups creating the chiral space upward, thereby better embracing the π-allyl moiety. The geometric constraints of large chelating rings may increase this bite angle.[10] Combining this concept with the notion of simplicity for synthesis led to a schematic for a modular approach as depicted in **IV** in Figure 2. Borrowing from enzymes, in which primary chirality imposes a folding (a conformational chirality) to create the chiral space of the catalytic active site, the primary chirality of a chiral scaffold will induce conformational chirality of the diarylphosphino moieties and a linker to create the chiral space of the catalytically active site.

In a first-generation approach, 2-(diphenylphosphino)benzoic acid (**4**) and a readily available chiral diol or diamine constitute the modules that can be easily joined by a simple acylation as depicted in eqs 1 and

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(5) For overviews, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994. Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(6) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. Hayashi, Y.; Sakai, H.; Kaneta, N.; Vemura, M. *J. Organomet. Chem.* **1995**, *503*, 143.

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(9) von Matt, P. J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, *15*, 2065.

(10) (a) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. (b) Also see: Hayashi, T.; Ohno, A., Lu, S.-J.; Matsumoto, Y.; Fukuyo, E.; Yanaga, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221.

(11) For a discussion of this and related concepts, see: Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.

(12) Knühl, G.; Sennhenn, P.; Helmchen, G. *Chem. Commun.* **1995**, 1845. However, see: Minami, T.; Okada, Y.; Otaguro, T.; Tawaraya, S. Furuichi, T.; Okauchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2469.

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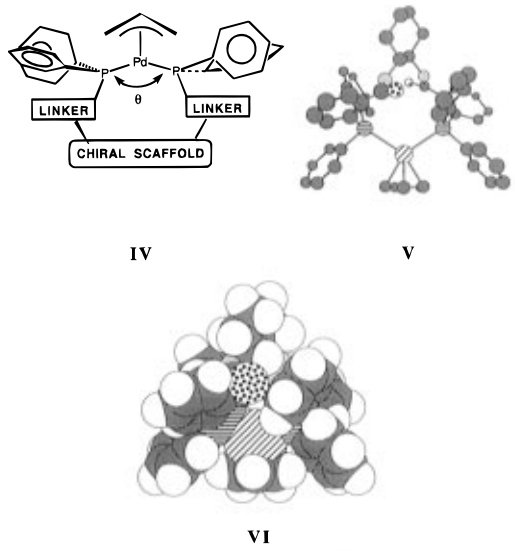
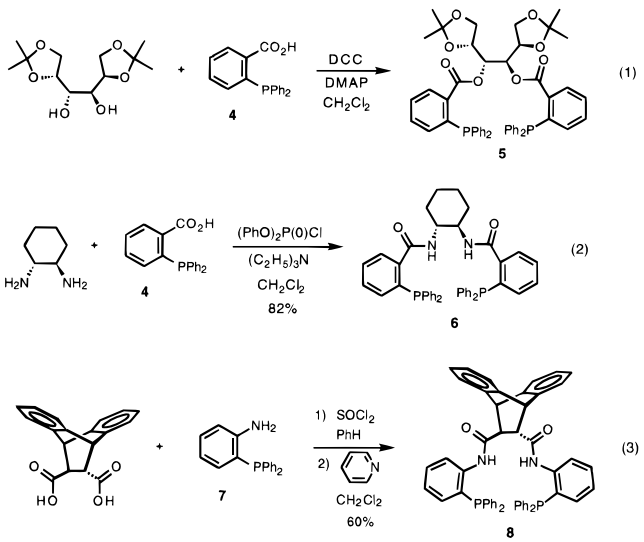


Figure 2. Model for ligand design.

2.[13] Molecular mechanics calculations of the cyclopentenyl π-allylpalladium complex derived from ligand **6** (Figure 2, **V** and **VI**) reveal a structure in good accord with the schematic of **IV**.[14] A second-generation platform built upon 2-(diphenylphosphino)aniline (**7**) provides ligands from readily available chiral dicarboxylic acids (eq 3).[15] An X-ray structure of the



parent π-allylpalladium complex derived from **8** (Figure 3) supports the model proposed. First, the π-allyl unit sits in a chiral pocket defined by the propeller arrangements of the aryl rings which clearly orient in edge−face relationships. Second, the P−Pd−P bite angle is 110.5°, considerably larger than the more normal approximately 90° bite angle of square planar Pd complexes.

Ligand Evaluation

Evaluating the effectiveness of the asymmetric ligands focused on the ionization rather than the alkylation phase because of the complications intro-

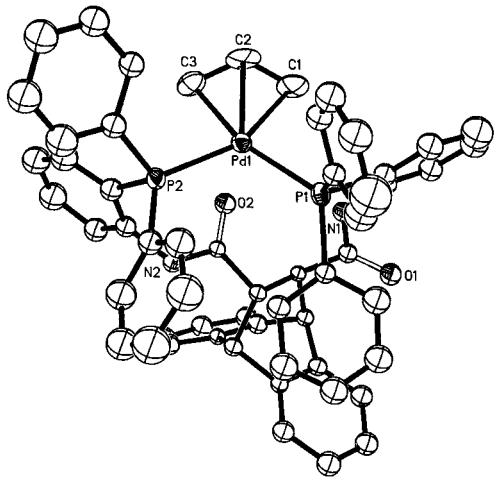


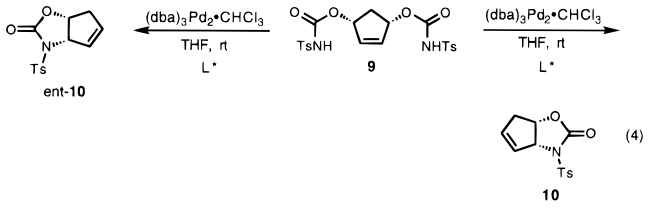
Figure 3. ORTEP depiction of the π-allylpalladium complex (perchlorate salt) with ligand **8**. (a) The perchlorate salt and hydrogens were omitted for clarity.

Table 1. Effect of Ligand on Oxazolidinone Formation

entry	ligand	yield	**10**:*ent*-**10**	ee[a] (%)
1	5	100%	18:82	64
2	6	97%	11:89	78
3	11	88%	94:6	88
4	8	99%	6:94	88
5	12	75%	82.5:17.5	65
6	13	88%	94:6	88
7	14	88%	95.5:4.5	91

[a] Enantiomeric excess.

duced by the uncertainty of the exact structure (e.g., the nature of the ion pair, state of aggregation, etc.) of the nucleophile, which is involved in the enantiodiscriminating step (i.e., that step in which the asymmetry is created) of the alkylation phase but not the ionization event. Interest in asymmetric syntheses of glycosidase inhibitors[16] led to the oxazolidinone synthesis outlined in eq 4 as the test reaction. Table 1



compares the ester **5** with the amide **6**, revealing that the amide ligand enhanced the enantiomeric excess (ee) significantly compared to the ester, a trend that proved general. Simple geometric considerations suggest that opening the dihedral angle between the two amides as in **11** would increase the P−Pd−P bite angle and thus the ee. Indeed, the ee jumps to 88% with ligand **11** (Table 1, entry 3).[13] Inverting the amide linkage of **11** as in ligand **8** but maintaining the identical sense of chirality of the scaffold produces a catalyst that gives product with the same ee but opposite chirality (Table 1, entry 4)![15] Thus, the linker functions as a translator for communicating between the chiral scaffold and the conformationally chiral space.

(14) Marschner, C. Unpublished work in these laboratories.
(15) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2386.
(16) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
(17) Breit, B. Unpublished work in these laboratories.

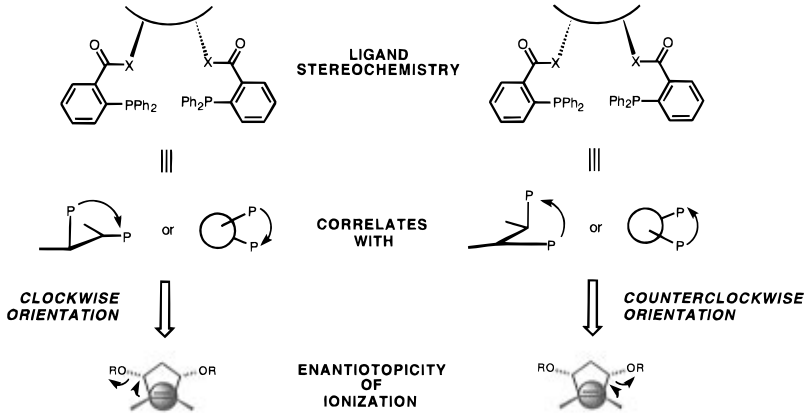
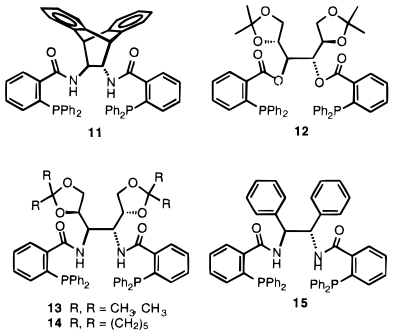


Figure 4. Correlation of ligand stereochemistry with reaction enantioselectivity.

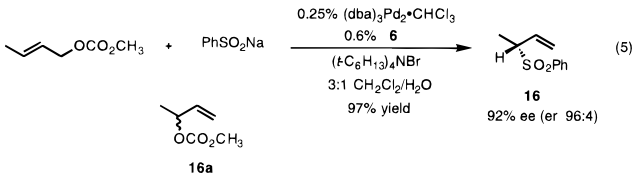


The stereochemistry of the stereogenic centers to which the linker is attached rather than the global chirality of the scaffold dominates the molecular recognition. Thus, the catalyst derived from the 2,3-di-*epi*-mannitol-based ligand **12**, where the stereochemistry of the scaffold is the same as that of **5** except for the anchoring points of the binding posts, gives identical levels of enantiomeric recognition but in the mirror image sense compared to **5** (Table 1, entry 5 vs entry 1).[17] As noted previously, switching from the diester to the diamide but maintaining the same scaffold significantly increases the ee (Table 1, entry 6 vs entry 5). Although the chirality of the remainder of the scaffold does not have a primary effect on the molecular recognition, it does have some, albeit small, effect. Thus, modification of the ketal from the acetone (i.e., **13**) to the cyclohexanone (i.e., **14**) based ketal causes a small but significant enhancement of ee (Table 1, entry 7 vs entry 6). Indeed, the highest ee observed for this reaction, 91% (enantiomeric ratio (er) 95.5:4.5), derives from the catalyst prepared using ligand **14**.

The dependence of the sense of chirality of the product on the stereochemistry of the point of attachment of the binding posts revealed a mnemonic which correlates the absolute stereochemistry of the product with that of the chiral ligand as depicted in Figure 4 for the normal ester and amide series (i.e., **5**, **6**, **11**–**14**).[13] The ligands can be described as having a clockwise or counterclockwise sense with respect to the relationship of the phosphine metal binding posts when viewed as an extended Newman projection. Placing the substrate in the plane of the paper and the catalyst above that plane leads to the prediction that a clockwise ligand induces a clockwise motion of the catalyst with respect to the substrate, thereby preferentially ionizing the *pro-R* leaving group and vice versa for the counterclockwise ligands.

Type A. Enantiotopic Alkene Complexation

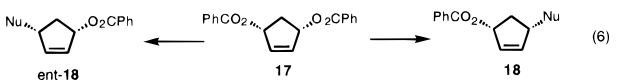
Type A selectivity (Figure 1) raises a second issue in addition to enantioselectivity—regioselectivity. While steric factors frequently lead to preferential alkylation at the primary carbon, electronic factors favor alkylation at the most electron deficient terminus, the secondary carbon. Fortunately, some nucleophiles exhibit a selectivity for the latter, sulfinate being among the best.[18] As shown in eq 5, with a catalyst



derived from ligand **6**, the internal regioisomer **16** is the major product (~6:1).[19] More significantly, the ee is excellent. Both the regio- and enantioselectivities exceed those reported with a number of other ligands. Control experiments with the chiral racemic regioisomeric substrate **16a** verify that the asymmetric induction derives from chiral discrimination of the enantiotopic faces of crotyl carbonate.

Type B. Enantiotopic Leaving Groups

As shown in the ligand evaluation section, *meso*-2-ene-1,4-diol diesters may be desymmetrized by chiral Pd catalysts. To a first approximation, the degree of asymmetric induction should be independent of the nucleophile. Experimentally, that proves to be the case for most nucleophiles (*vide infra*) as shown by eq 6 and Table 2. A striking difference between the

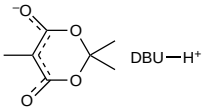
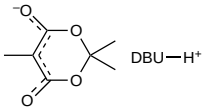


reactions in eqs 4 and 6 is the significantly higher ee values in the latter case using the same ligands. Since the leaving group is involved in the enantiodiscriminating step, changing from urethane as in eq 4 to benzoate as in eq 6 gives higher molecular recognition.

(18) Hiroi, K.; Kitayama, R.; Sato, S. *Chem. Pharm. Bull.* **1984**, *32*, 2628. Hiroi, K.; Makino, K. *Chem. Lett.* **1986**, 617. Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 643.

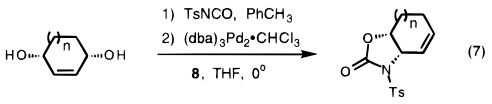
(19) Trost, B. M.; Krische, Radinov, R.; M. J.; Zanoni, G. *J. Am. Chem. Soc.*, in press.

Table 2. Asymmetric Induction in Desymmetrization of Dibenzoate 17

entry	nucleophile	ligand	yield (%)	ee (%) (er (**18**:*ent* **18**))
1	$NaCH(CO_2CH_3)_2$	6	80	93 (96.5:3.5)
2	$NaCH(CO_2CH_3)_2$	15	68	92 (4:96)
3[a]		6	95	91 (95.5:4.5)
4[b]		6	84	98 (99:1)
5	$PhCH_2NHCH_3$	15	71	95 (2.5:97.5)
6	$PhCH_2NHCH_3$	6	75	78 (89:11)
7	$TMSN_3$	15	77	>98 (<1:>99)

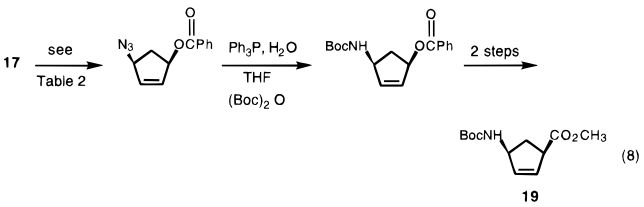
[a] 1.0 equiv of nucleophile. [b] 1.2 equiv of nucleophile.

The five-membered ring substrate proves to be the most demanding; the ee values normally increase with the six- and seven-membered rings. For example, oxazolidinone formation in the five-membered ring (eq 4 and Table 1, entry 4) gave an ee of 88% (er 94:6) with ligand **8** but ee values of 97% (er 98.5:1.5) and 95% (er 97.5:2.5) for the six- and seven-membered rings (82% yield each), respectively (eq 7).[15]



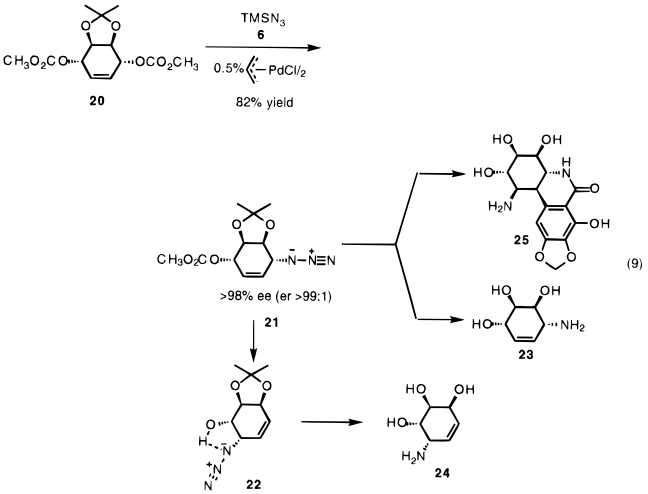
(7)

The azide nucleophile proves effective (Table 2, entry 7). Staudinger reduction followed by a two-step sequence to introduce the methoxycarbonyl group (*vide infra*) produces the amino ester **19**, a useful building block for carbanucleosides, the antiviral agent amidinomycin, the coronary vasodilator C-NECA, etc. in >98% ee (er >99:1) and 31% overall yield from **17** (eq 8).[20] An interesting feature of allylic azides is their



(8)

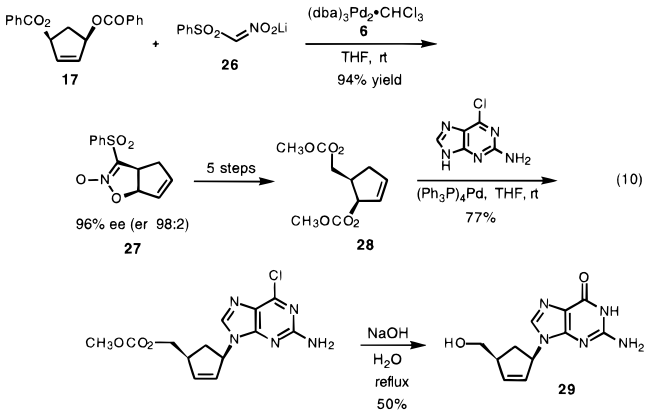
ability to undergo [3,3] sigmatropic rearrangements.[21] As illustrated in eq 9, either allylic regioisomer **21** or **22** is available in excellent ee and yield from dibenzoate **20**.[22] While thermal equilibration favors the allylic regioisomer of **21** to the extent of 3:1, the corresponding alcohol favors the regioisomer **22** by 9:1, presumably because of intramolecular hydrogen bonding. The enantiomerically pure **22** can be isolated in 82% yield. Reduction and deblocking converts **21** and **22** into conduramines A (**23**) and E (**24**), respectively.



(9)

More significantly, the former serves as a useful precursor to the important antitumor agent (+)-pancratistatin (**25**) which is available in 11% overall yield from dicarbonate **20**.[23]

Since the product of monoalkylation is still an allylic ester, Pd(0)-catalyzed substitution can be performed a second time. For example, a novel annulation of an isoxazoline 2-oxide (e.g., **27**) occurs when (phenylsulfonyl)nitromethane is employed as the pronucleophile (eq 10).[24] This heterocycle functions as a synthon for

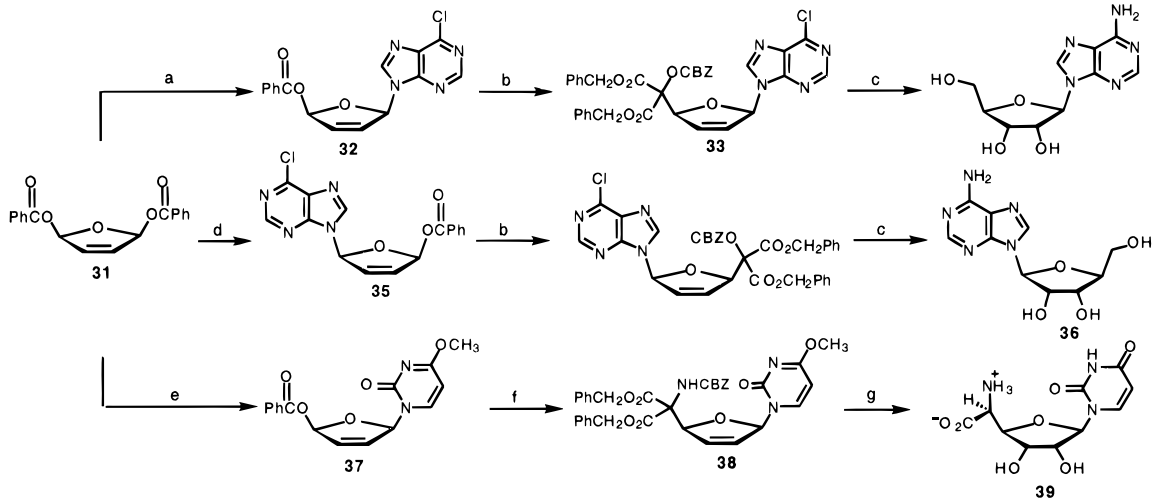


(10)

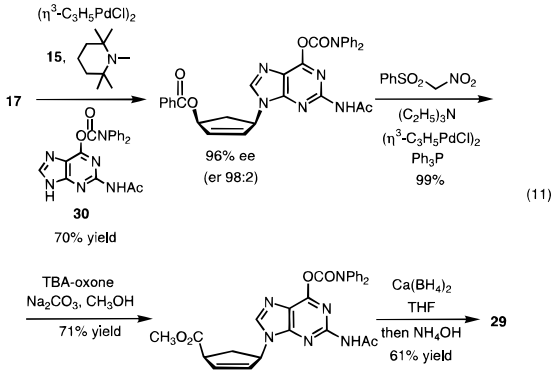
a cis-vicinal hydroxycarboxylic ester whose reduction and esterification produces dicarbonate **28**, a very useful carbanucleoside building block available enantiomerically pure in 60% overall yield from dibenzoate **17**. From a medicinal chemist's point of view, such a pivotal intermediate in which the allyl carbonate can be substituted with high regio- and diastereoselectivity by a broad range of nucleophiles is desirable. For example, the anti-AIDS agent (−)-carbovir (**29**) results from use of 2-amino-6-chloropurine as the nucleophile in this second Pd-catalyzed reaction. From a process chemist's point of view, fewer steps are always desirable. As shown in eq 11, reversing the order of addition of the two cyclopentenyl substitutents creates a four-step synthesis of (−)-carbovir.[25]

(20) Trost, B. M.; Stenkamp, D.; Pulley, S. R. *Chem. Eur. J.* **1995**, *1*, 568.
(21) Gagneaux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956.
(22) Trost, B. M.; Pulley, S. R. *Chem. Eur. J.* **1995**, *1*, 568.
(23) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
(24) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1995**, *114*, 8746.
(25) Trost, B. M.; Madsen, R. Guile, S. *Angew. Chem., Int. Ed. Engl.*, in press.

Scheme 2. A New Paradigm for Nucleoside Synthesis[a]

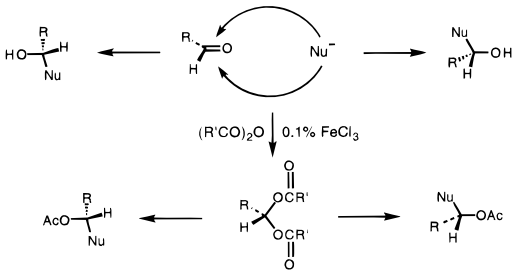


[a] Conditions: (a) 6-Chloropurine, $(C_2H_5)_3N$, 2 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 6% **15**, 74% yield. (b) $CBZOCH(CO_2CH_2Ph)_2$, 1.7 mol% $(dba)_3Pd_2{\cdot}CHCl_3$, 12% Ph_3P, Cs_2CO_3, THF, CH_3CN, rt, 96−97%. (c) Six steps; see the text. (d) As in (a) except 6% *ent*-**15**, 85% yield. (e) 4-Methoxy-2-pyrimidinone, $(C_2H_5)_3N{\cdot}HCl$, $(C_2H_5)_3N$, THF, 0 °C, 85%. (f) $CBZNHCH(CO_2CH_2Ph)_2$, as in (b), 95% yield. (g) Three steps; see the text.



(11)

Scheme 3. Equivalent of Asymmetric Carbonyl Addition



The ready availability of the dibenzoate **31** by the direct oxidation of furan with lead tetrabenzoate in 76% yield suggests a new paradigm for the synthesis of nucleosides (see Scheme 2).[26] 6-Chloropurine effectively participates in desymmetrization with **31** to give **32** in 74% yield and 93% ee (er 96.5:3.5). One recrystallization gives enantiopure **32**. A de novo synthesis of either enantiomer of adenosine from noncarbohydrate achiral starting materials is available just by properly choosing the chiral ligand. Thus, performing the initial alkylation as described produces adenosine via **32** and **33** and, with *ent*-**15** as ligand, *ent*-adenosine **36** via **35**, obtained enantiomerically pure in 85% yield.

A pyrimidine base may also be employed. Using 4-methoxypyrimidin-2-one as nucleophile, an 85% yield of **37** of >98% ee (er >99:1) is formed. Variation of the side chains can be readily accommodated by this methodology. For a synthesis of the nucleoside core of many polyoxins and nikkomycins,[27,28] aminomalonate is employed in the second Pd(0)-catalyzed alkylation to give **38**.[26] Dihydroxylation, catalytic hydrogenolysis accompanied by decarboxylation, and hydrolysis complete this six-step synthesis. The use of other classes of ligands for the desymmetrization of *meso*-2-ene-1,4-diesters has barely been reported.[29]

Scheme 3 addresses another type of enantioselectivity that can be translated to a desymmetrization. Asymmetric addition to a carbonyl group recognizes the two π faces as being enantiotopic. An alternative concept considers the carbonyl group as consisting of two enantiotopic C−O bonds. Experimentally, this concept can be realized by the Lewis acid-catalyzed addition of acid anhydrides whereby *gem*-dicarboxylates form, typically in nearly quantitative yields.[30] In this scenario, asymmetric substitution of the enantiotopic leaving groups constitutes the equivalent of an asymmetric carbonyl addition.

Using the previously established mnemonic, the following predictions may be proffered. Assuming preferential ionization to the *syn*,*syn* complex, ionization from alkene complex **VII** requires a counterclockwise ligand like **6** to give **VIII**, whereas complex **IX** requires a clockwise ligand like *ent*-**6** to give **X** (see Figure 5). These predictions are fully verified by the

(26) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037.
(27) For a review, see: Isono, K. *J. Antibiot.* **1988**, *41*, 1711.
(28) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812. Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. Saksena, A. K.; Lovey, R. G.; McPhail, A. T. *J. Org. Chem.* **1986**, *51*, 5024. Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772. Dondoni, A.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1994**, *35*, 9439.
(29) Yoshizaki, H.; Satoh, H.; Sata, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016.
(30) For an example, see: Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765.

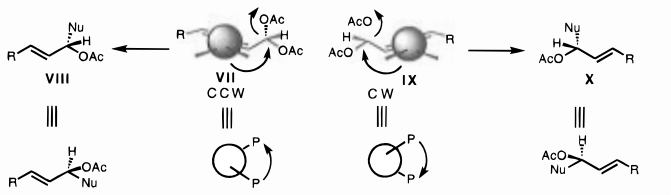


Figure 5. Predictions of enantiodiscrimination of *gem*-dicarboxylates.

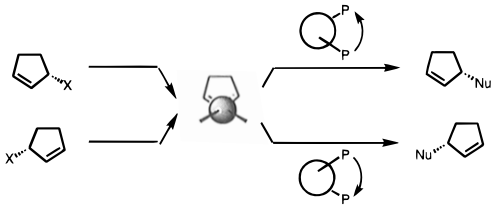
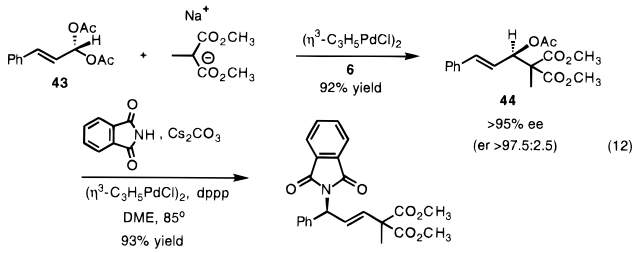


Figure 6. Predictions of enantiodiscrimination via meso intermediates.

alkylation of the *gem*-diacetate **43** derived from cinnamaldehyde (eq 12) whereby the catalyst using

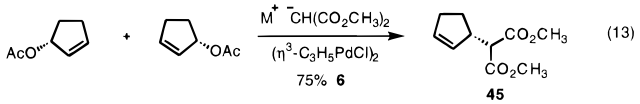


(12)

ligand **6** produces enantiomerically pure **44** in 92% yield.[31] Thus, the equivalent of the asymmetric addition of stabilized nucleophiles to carbonyl groups becomes feasible. The presence of an allylic acetate in the product permits a second alkylation whereby the chirality is transferred as shown in eq 12.[32]

Type C. Enantiotopic Termini

Asymmetric alkylations of chiral allyl esters that generate meso intermediates correspond to a deracemization event. In order to avoid the conformational ambiguities of acyclic systems, attention has focused on cyclic substrates which, with other ligands, proved to give rather marginal results.[33] Figure 6 outlines the predictions.[34] Initial results proved disappointing for the reaction of racemic 3-acetoxycyclopentene with dimethyl malonate (eq 13 and Table 3, entry 7). While



(13)

(31) Trost, B. M.; Lee, C.-B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247.

(32) Lee, C.-B. Unpublished work in these laboratories.

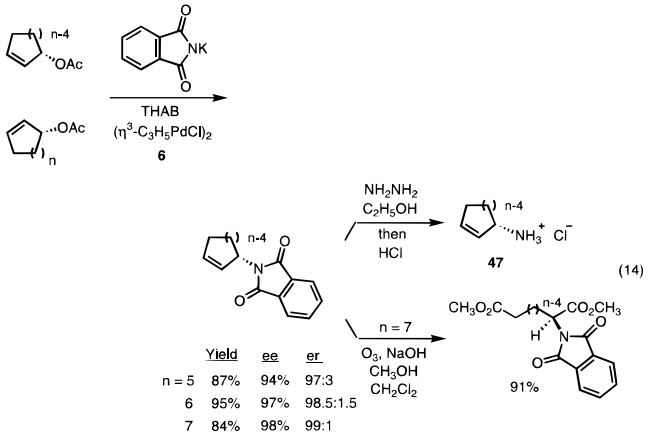
(33) For example, see: (a) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399. (b) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683. (c) Fiaud, J.; Legros, J. *Tetrahedron Lett.* **1991**, *32*, 5089. (d) Okada, Y.; Minami, T. Yamamoto, T.; Ichikawa, J. *Chem. Lett.* **1992**, 547. (e) Yamazaki, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 2287. (f) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 8595. (h) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1995**, *50*, 4493.

(34) The *sine qua non* of this mechanistic motif is that such π-allylpalladium complexes are meso, an assumption that proves not to be quite correct. See: Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.

the sense of chirality was as predicted, the ee was only 38% with the sodium salt.[35] Because the nucleophile is undoubtedly an ion pair, being a salt in a rather nonpolar medium, variation of the cation by using tetraalkylammonium salts to influence the nature of the ion pair was explored. Interestingly, the tetramethylammonium salt behaved very similarly to the sodium salt but the ee increased systematically as the size of the alkyl group increased until it plateaued at the tetraoctyl salt (Table 3, entries 1−4). Since the solvent should influence the nature of the ion pair, the solvent was switched to the even less polar methylene chloride where the ee jumped precipitiously so that the product was virtually enantiomerically pure.

To ascertain whether any special effects could be attributed to the tetralkylammonium cation, the series of alkali-metal salts was also examined.[36] Surprisingly, there was a remarkable parallelism between the two series (cf. entries 1−4 with entries 7−10). Thus, cesium and tetrahexylammonium cations behave analogously. The excellent ee values observed have made them the cations of choice for synthetic applications. The one anomaly is lithium. The ee increased but generated the mirror image product! In a sense, it follows the trend. As the cation becomes smaller, the amount of *ent*-**45** increases. In the case of lithium, it increased to the extent that *ent*-**45** is now the dominant product. Thus, although the anion is what becomes attached to the π-allyl moiety, the molecular recognition depends more upon the escort, i.e., the cation.

The enantioselectivity is remarkably independent of the anion portion of the nucleophile. As shown in eq 14, phthalimide gives excellent ee values indepen-



(14)

dent of ring size.[35] The resulting phthalimides could be hydrolyzed to the corresponding allylic amines **47** or oxidatively cleaved to amino acid derivatives such as (*S*)-2-aminopimelic acid, dipeptides from which have shown antibiotic activity.

A sulfinate anion as nucleophile reacts at sulfur to provide an effective route for the asymmetric synthesis of allylic sulfones.[37] For example, the enantiomerically pure allylic sulfone **48** from racemic 3-acetoxycyclohexene is easily converted to an enantiomerically pure γ-siloxy α,β-unsaturated sulfone, **49** (eq 15).

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

(36) Bunt, R. C. Unpublished work in these laboratories.

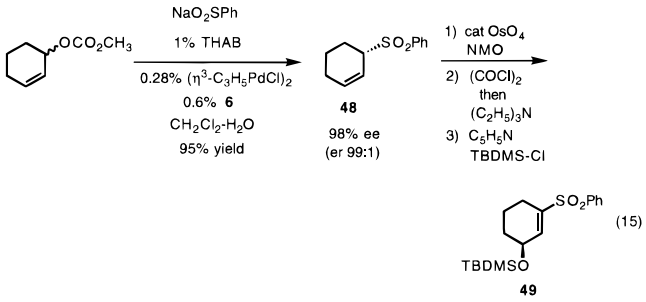
(37) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

Table 3. Dependence of Enantioselectivity on Malonate Counterion[a] of Ammonium Cations

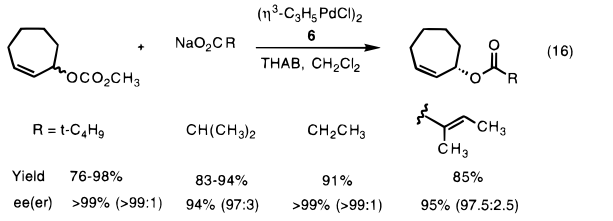
entry	M^+	yield (%)	ee (%) (er)	entry	M^+	yield (%)	ee (%) (er)
1	$(CH_3)_4N$	88	41 (60.5:29.5)	6[d]	Li	75	−63 (18.5:81.5)
2	$(n\text{-}C_4H_9)_4N$	74	57 (78.5:21.5)	7	Na	77	38 (60.5:29.5)
3	$(n\text{-}C_6H_{13})_4N$	92	68 (84:16)	8	K	90	51 (78.5:21:5)
4[b,c]	$(n\text{-}C_6H_{13})_4N$	81	98 (99:1)	9	Cs	76	76 (88:12)
5	$(n\text{-}C_8H_{17})_4N$	74	66 (83:17)	10[b]	Cs	98	>99 (>99:01)

[a] All reactions performed in THF at 0 °C unless otherwise noted. [b] In methylene chloride. [c] $(n\text{-}C_6H_{13})_4NBr$ = THAB. [d] A minus sign before the ee signifies the enantiomer opposite that obtained in all other cases with the identical ligand.

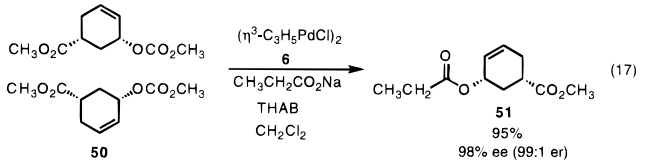
These structurally versatile intermediates now become readily available enantiomerically pure.



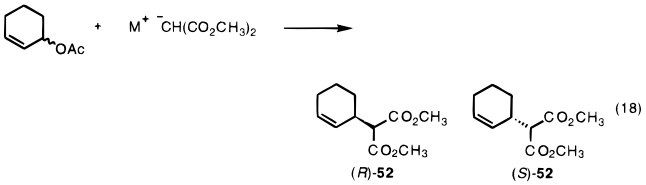
Particularly intriguing is the use of an oxygen nucleophile (eq 16).[38] Because the esters are formed by alkyl−oxygen bond formation, a wide range of R



groups prove satisfactory from the sterically hindered pivalate to the conjugated esters. In this way, allyl ester **51**, an important intermediate to a number of natural products such as the antitumor agent phyllanthocin[39] and the insect sex excitant periplanone,[40] is available from racemic **50** (eq 17).

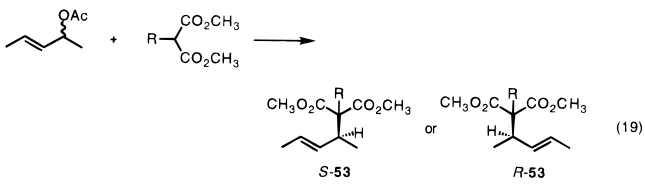


To date, the diamide ligands have proven to be the most general with respect to cyclic systems. For example, comparison of the (phosphinoaryl)oxazolines like **2**, which give superb enantiomeric recognition in many cases, with our ligands for the reaction of eq 18

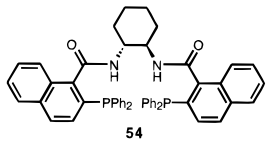


indicate the best ee to be 54% (er(*R*:*S*) 77:23) when R = H and Ar = 2-biphenyl.[34g] With **6**, the enantiomeric product (*S*)-**52** of 96% ee (er(*R*:*S*) 2:98) is obtained.[36] Very recently, a new class of ligands represented by **3** showed great promise in these cyclic cases. A catalyst bearing **32** as ligand produced (*S*)-**52** in 98% ee (er(*R*:*S*) 1:99).[12]

Switching to an acyclic allylic substrate becomes complicated by the flexibility of the π-allyl system to interconvert substituents between syn and anti orientations. For this reason, we introduced the 1,3-diphenylallyl system which should favor the syn,syn isomer.[10a] Subsequently, it has become the standard test system in the field.[41] Many of the chiral ligands achieve excellent selectivities with the 1,3-diphenylallyl systems. The selectivity appears to be sterically derived since the 1,3-diisopropyl system shows similar behavior, but the 1,3-dimethylallyl system shows less satisfactory results. For example, the Pd complex bearing the (phosphinoaryl)oxazolines **2** as ligands gives (*S*)-**53** (R = H) of 71% ee (er(*S*:*R*) 85.5:14.5, eq 19).[41b] Switching to **8** produces (*S*)-**53** (R = H) in a



slightly higher ee of 74% (er(*S*:*R*) 87:13, 90% yield).[15] In this latter case, changing the nucleophile to dimethyl methylmalonate gives (*S*)-**53** (R = CH_3) of 87% ee (er(*S*:*R*) 93.5:6.5, 93% yield). Variation of the linker in **54**, which further restricts the chiral space (vide



infra), increases the chiral recognition for the reaction with dimethyl malonate to 86% (er(*S*:*R*) 7:93, 80% yield), the highest recorded to date.[42a] In contrast to these exciting observations, the use of acyclic substrates bearing sterically bulky substituents as in the 1,3-diphenyl case proves less satisfactory with ligands

(38) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320.
(39) Trost, B. M.; Kondo, Y. *Tetrahedron Lett.* **1991**, *32*, 1613.
(40) Kuwahara, S.; Mori, K. *Tetrahedron Lett.* **1990**, *46*, 8075.

(41) Cf. refs 6−9 and 33b,f,h. For a few additional examples showing >95% ee with dimethyl malonate, see: (a) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron Lett.* **1990**, *31*, 5049. (b) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Eng.* **1993**, *32*, 566. (c) Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 6689. (d) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1417. (e) Kang, J.; Cho, W. O.; Cho, H. G. *Tetrahedron: Asymmetry* **1994**, *5*, 1347. (f) Wimmer, P.; Widhalm, M. *Tetrahedron: Asymmetry* **1995**, *6*, 65. (g) Anderson, P. G.; Harden, A.; Tanner, D.; Norby, P. O. *Chem. Eur. J.* **1995**, 12.

(42) (a) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99. (b) Note added in proof: Ligand **6** effects the alkylation of eq 19 to give (*R*)-**53** (R = H) of 92% ee in 98% yield; see: Trost, B. M.; Kruegger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.*, in press.

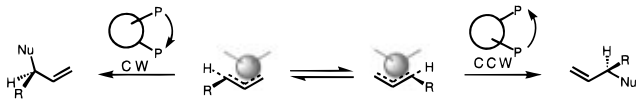
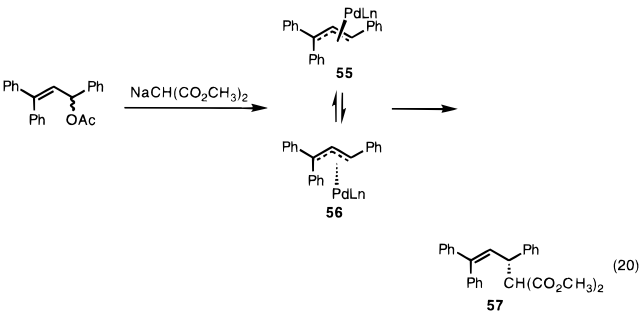


Figure 7. Predictions of enantiodiscrimination for nucleophilic addition of type D.

like **6** in which the rate as well as the enantioselectivity has been compromised. Thus, our class of ligands shows great promise for sterically nondemanding acyclic systems as well.[42b]

Type D. Enantiotopic Nucleophilic Additions

One of the early examples of high asymmetric induction occurred in the triphenylallyl case as shown in eq 20.[43] Since ionization of the racemate generates equal amounts of the initial complexes **55** and **56**,



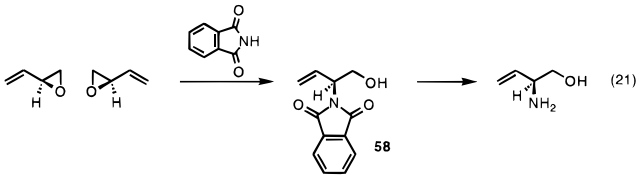
(20)

which are diastereomeric in the presence of chiral ligands, a mechanism for their equilibration and differentiation in the alkylation step must exist. The ease by which π-allylpalladium complexes interconvert syn and anti substituents via $\eta^3-\eta^1-\eta^3$ processes also effects migration of palladium from one diastereotopic face to the other. Such a process involving the η^1 complex at the disubstituted terminus provides the facile pathway for interconversion of **55** and **56**.[44] This process must be fast relative to the nucleophilic addition which constitutes the enantiodiscriminating step. The discrimination can evolve either from the relative stabilities of the two diastereomeric complexes wherein the attacking nucleophile plays a minimal role or from the ease of approach of the nucleophile wherein it plays the major role (a Curtin−Hammett situation). Early studies with (*S*,*S*)-chiraphos suggested the former scenario, at least in that case.[43] Recently, a significantly enhanced ee was obtained with the oxazoline ligands **2** wherein **57** of 99% ee (er >99:1) can be obtained in 92% yield.[44]

Using our diamide ligands, Figure 7 outlines the expected predictions for the general case. According to the mnemonic, a CW ligand induces a clockwise motion in the ionization when viewed with Pd above the plane of the π-allyl unit. In this event, we are considering the microscopic reverse which should lead to the microscopic reverse motion, i.e., a counterclockwise motion for nucleophilic addition.

With simple systems, the issue of regioselectivity also arises since the propensity is for monosubstituted complexes as depicted in Figure 7 to react at the primary carbon. Vinyl epoxides may resolve the regioselectivity problem by coordinating in some way with a pronucleophile.[45] The importance of vinylglycinol as a building block led to the examination of butadiene monoepoxide, an inexpensive starting material derived from direct oxidation of 1,3-butadiene and phthalimide as reactants. Initial results with a complex derived from ligand **6** were encouraging.[42]

A 10:1 regioselectivity favoring the 1,2-isomer **58** of 76% ee (er 88:12, 87% yield) was observed (eq 21).



(21)

Restricting the rotation around the carboxamide moiety as in **54** increased the regioselectivity to 75:1 (99% yield) and the enantioselectivity to 97% (er 98.5:1.5). The observed absolute configuration corresponds to that predicted by the mnemonic. Since removal of the phthalimide by hydrazinolysis occurs virtually quantitatively, this two-step route constitutes a very inexpensive, practical route to this basic building block.

Conclusion

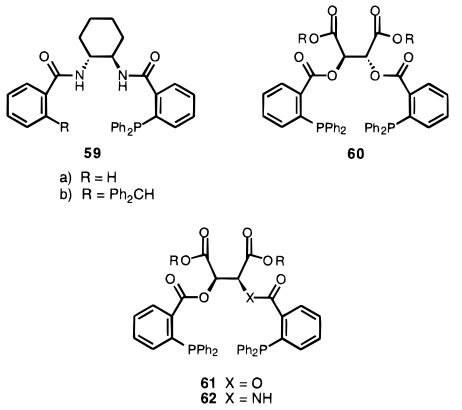
The metal-catalyzed allylic alkylation represents a unique challenge and opportunity for asymmetric induction. It differs in many respects from those catalytic processes which have succumbed to asymmetric induction. First, most reactions involve only one type of bond formation, C−H or C−O or C−N etc. However, in allylic alkylations, C−H, C−C, C−N, C−O, C−S, C−P, etc. bonds have all been formed, and the asymmetric version then impacts all of these bond types. Second, the enantiodiscriminating event of most reactions normally invokes one type of molecular recognition, such as the enantiotopic faces of a carbon−carbon or carbon−oxygen double bond. In allylic alkylations, at least four different mechanistic motifs are feasible. Third, most reactions involve the bond-forming (or -cleaving) event involved in the enantiodiscriminating step occurring within the coordination sphere of the metal and therefore proximal to the chiral inducing elements. In most cases of metal-catalyzed allylic alkylations, these bond changes occur outside the coordination sphere and therefore distal to the chiral ligands. Finally, the fluxional nature of the π-allylmetal intermediates makes control of their subsequent reactions particularly complicated.

Many of the above points highlight the magnitude of the challenge, but some also highlight the opportunities. While such reactions had been little explored between our initial report in 1973[46] and 1992, a literal explosion has occurred in the last three years, with nearly 50 different ligand systems being reported and the list growing rapidly. The catalyst system recorded herein appears to be quite practical, with as little as 0.025 mol % π-allylpalladium chloride dimer and 0.075 mol % ligand being satisfactory.

Is the concept valid? Direct structural evidence is still lacking in most cases. The most direct evidence

(43) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.
(44) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461; *Tetrahedron: Asymmetry* **1995**, *6*, 2535.
(45) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931. Trost, B. M.; Ito, N.; Greenspan, P. D. *Tetrahedron Lett.* **1993**, *34*, 1421.
(46) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200.

comes in the amide invertomer series (Figure 3) in which the X-ray structure of a π-allylpalladium complex supports the model.[15] In the normal series, circumstantial evidence also supports the model.[47] ^{31}P NMR studies of the olefin complex between a Pd(0) catalyst bearing **6** as ligand and dibenzylideneacetone (dba) reveal the presence of the 13-membered chelate ring. The importance of such chelation with the two phosphines in the enantiodiscriminating step is further supported by the poor ee's obtained in reactions catalyzed by complexes bearing the structurally close ligands **59a**,**b** which can involve chelate structures in which an amide is one of the chelating groups.



Further evidence derives from consideration of the tartrate-derived ligands **60**−**62**. The ee of any reaction involving the achiral (meso) ligand must, by definition, be zero in contrast to the chiral ligand **60** which should be finite. The close structural similarity of esters and secondary amides should translate into behavioral similarity as we do observe in the case of ligands **12** and **13**. The prediction that emerges is that the amide ester **62** should be considered as a pseudomeso ligand and exhibit behavior close to that of **61**. At a minimum, to the extent that the scaffold directly influences the molecular recognition, the pseudomeso ligand **62** should induce lower ee values than the chiral ligand **60**. Experimentally, the opposite is found, the ee nearly doubling in the case of **62**. Thus, the direct interactions with the chiral scaffold appear unlikely. How can a pseudomeso object give higher ee values than a chiral object? If the chiral space defined by the diaryl propellers determines the molecular recognition, this chiral space is the same regardless of the nature of the scaffold or whether it is chiral or achiral. The meso ligand **61** does not give racemic product because the active site is achiral. It is chiral as in all the other ligands. However, both enantiomers of the chiral space are equally present, and the transition state energies of reaction involving both are identical. Thus, racemic product ensues. However, for the amide ester **62**, these two features no longer apply. In fact, molecular mechanics calculations suggest that the two enantiomeric propellers (which become diastereomeric in the presence of a chiral scaffold) are different by nearly 5 kcal/mol, more than enough to account for the chiral recognition. Such a model predicts that there will be substrates incapable of fitting into the catalytically active site. Thus, the model rationalizes the inability of substrates like those related to the 1,3-diphenylallyl system to participate because of their inability to squeeze into the pocket containing the palladium. It must be emphasized that the model must be considered nothing more than a working hypothesis at this stage. However, it is becoming sufficiently successful that we are beginning to believe the model may be more than that.

The journey through the minefield of asymmetric Pd-catalyzed allylic alkylations in my laboratories began with Thomas J. Dietsche, Paul E. Strege, and Dennis J. Murphy in the first phase. The ligands reported herein emanated from the work of David L. Van Vranken followed by Carsten Bingel, Richard C. Bunt, Christoph Marschner, Bernhard Breit, Michael G. Organ, Shon R. Pulley, Jorge Zambrano, Zhongping Shi, Chul-Bom Lee, Dirk Stenkamp, Jochen M. Weiss, Stefan Peukert, and Ian Lennon, who have charted safe passage through the minefield. They made the story possible. Continuing financial support from the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, has provided the nourishment. We are also indebted to Johnson Matthey Alfa Aesar for generous loans of palladium salts.

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(47) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817.