ASYMMETRIC ALLYLIC SUBSTITUTION: MECHANISM AND RECENT ADVANCES USING PALLADIUM AND MOLYBDENUM

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INTRODUCTION

Transition metal catalyzed asymmetric synthesis using chiral ligands, has become an active area of research in the field of organic chemistry. The need to synthesize enantiomerically pure bioactive compounds has driven the evolution of known reactions into non-racemic manifolds, as well as the search for novel asymmetric transformations. The creation of chiral C_{sp^3}-C_{sp^3} and C_{sp^3}-$Z_{heteroatom}$ bonds provides a synthetic challenge that has been attacked by numerous methods. In 1973, Trost and Fullerton reported a new palladium-mediated synthetic reaction termed allylic alkylation.[1] Within a few months, this group reported a stoichiometric asymmetric variant employing chelating chiral bisphosphine ligands.[2] Four years later, their catalytic version of this reaction set off a storm of work that continues to this day.[3]

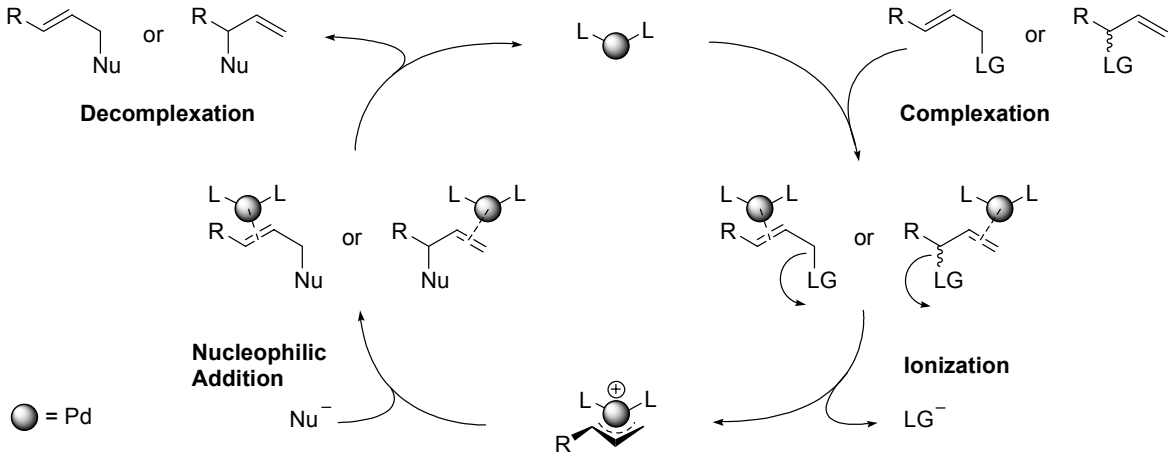
There have been over 300 publications, including several reviews, on asymmetric allylic substitution.[4,5,6,7] This reaction stands apart from other transition metal-catalyzed processes because asymmetry is induced outside the coordination sphere of the metal. By contrast, in most asymmetric reactions, induction occurs by differentiation of enantiotopic faces of a π-system by the metal catalyst. While asymmetric allylic substitution can use this form of induction, there exist four additional mechanisms by which chirality can be transferred. The metal most commonly used has been Pd; however, Mo, W, Ir, Rh, Pt, and Ni have also been employed.[5] Of these, Mo has proven to be most useful and it complements Pd in regioselectivity.[6] This report will cover mechanistic insights into Pd and Mo-catalyzed asymmetric allylic substitution and then highlight recent advances in the methodology.

PALLADIUM CATALYSIS

Catalytic Cycle with Palladium

The widely accepted mechanism by which Pd oversees the asymmetric allylic substitution reaction is depicted in Scheme 1.[5] Much spectroscopic[8] and crystallographic[9] data exist to support this catalytic cycle. Although the transient nature of most of the intermediates precludes their spectroscopic observation, mechanistic studies have probed the fleeting intermediates of interest to a degree that satisfies most scientific scrutiny. The cycle begins by formation of an η^2 π-allyl-Pd^0 complex. Oxidative addition of Pd^0 to form the π-allyl species then occurs with inversion at the leaving group center, providing the key η^3 π-allyl-Pd^{2+} complex. This intermediate has been observed spectroscopically and crystallographically. A suitable nucleophile then approaches displacing the

Scheme 1. Catalytic Cycle with Palladium (Shown for Achiral and Chiral Racemic Substrates)

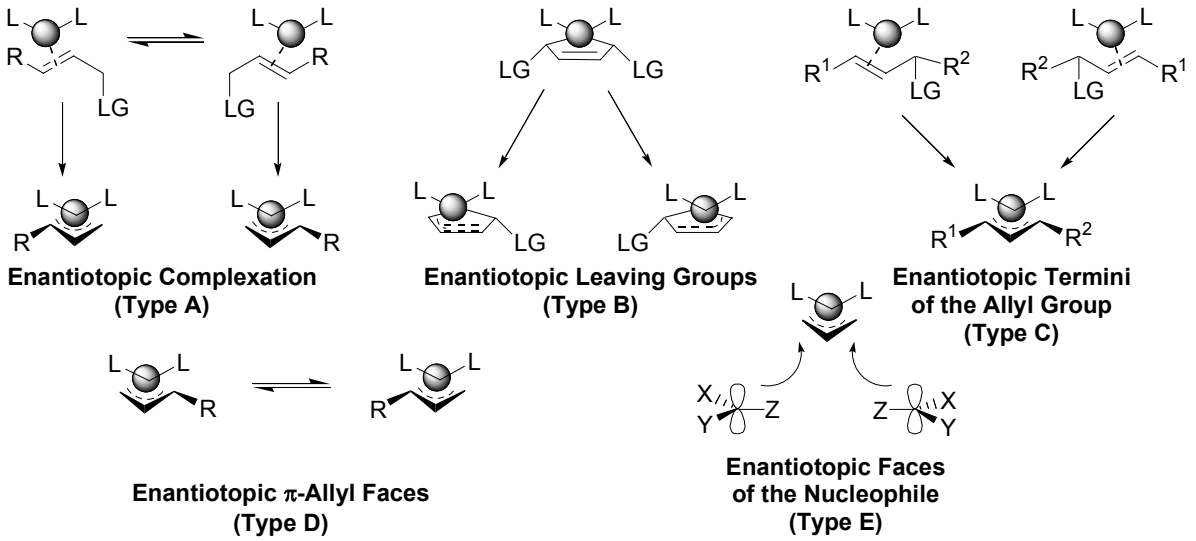


palladium with inversion at either the proximal or distal terminus of the allyl moiety generating a second η^2 π-allyl-Pd^0 complex. Upon decomplexation, the Pd catalyst is regenerated and the product is released. This mechanism holds only for nucleophiles with a $pK_a < 25$. Nucleophiles with a $pK_a > 25$ undergo a more conventional pathway involving direct coordination of the nucleophile to the metal center that will not be discussed in this report.[5]

Mechanisms of Asymmetric Induction with Palladium

Shown in Scheme 2 are the five plausible mechanisms by which enantioselectivity can be achieved in the palladium-catalyzed asymmetric allylic substitution.[7] In enantiotopic complexation, the Pd differentiates the enantiotopic faces of the π-system in an η^2 fashion (Type A). Interconversion of the resulting complexes can erode the stereoselectivity. In the case of a meso η^2 allyl complex having enantiotopic leaving groups, the Pd may oxidatively add to either end of the allyl system. Thus, enantioselection can be obtained by the desymmetrization of the meso intermediate (Type B). Another opportunity for enantiodiscrimination involves the differentiation of the enantiotopic termini of the allyl group (Type C). Interestingly, when a chiral racemic substrate is used, the process constitutes a

Scheme 2. Five Mechanisms of Enantioselection with Palladium



dynamic kinetic asymmetric transformation (DYKAT). A typical DYKAT involves the conversion of a chiral racemic material into an enantiomerically enriched product. Thus, the theoretical yield becomes 100%; as opposed to 50% in a traditional kinetic resolution.[10] A form of enantioselection similar to enantiotopic complexation involves the differentiation of enantiotopic faces of the π-allyl (Type D). In this case, the two diastereomeric complexes interconvert faster than they are consumed by a nucleophile. The enantiodiscrimination results from the differential rates of attack on the complexes. This type can involve either achiral or chiral racemic starting material. When chiral racemic substrates are used, this manifold also constitutes a DYKAT. Of the four previously mentioned forms of enantioselection, all involve induction at the π-allyl. A serious synthetic challenge would be discrimination of the enantiotopic faces of the incoming nucleophile (Type E). Considering the remote nature of the allyl moiety with respect to the chiral space about the ligands, it is intriguing that induction can, in fact, occur at the nucleophile. This type of enantiodiscrimination has been used in a number of examples, some of which will be discussed in this report. The mechanism by which enantioselection is achieved depends upon the substrate, catalyst, and nucleophile used.[7]

Ligand Design for Palladium

There are currently more than 100 ligands designed for use with Pd in the asymmetric allylic substitution reaction.[5] These ligands are engineered to induce asymmetry through various manifolds. While all essentially utilize steric bulk to create chiral space, the specific strategies used to forge the desired environment vary. The most common approaches include the formation of a chiral pocket, ligands with different electronics, and interaction of a tethered group on the ligand with the substrate or nucleophile.[6] By far, the most successful ligand designs are those that create a chiral pocket for the substrate. Thus, this report will focus on the design shown in Figure 1. This ligand type has been used with many modifications. For example, the backbone, tethers, and phosphine substituents have all been varied in order to fine tune catalyst activity toward a specific substrate.[6] For the sake of brevity, a detailed discussion of the mechanism of asymmetric induction with this ligand type will be omitted from this report. The mechanistic details of how these ligands induce asymmetry have been reviewed.[5,6,7]

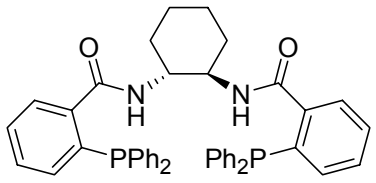


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Figure 1. Chiral Pocket Type Ligand

RECENT HIGHLIGHTS WITH PALLADIUM

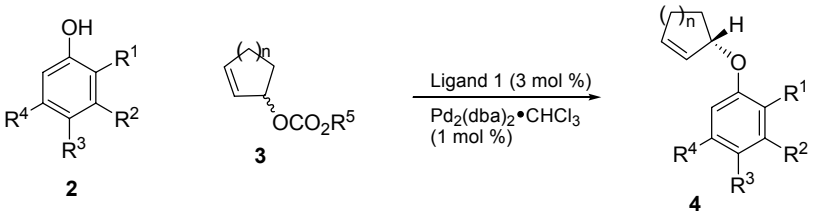
Use of Phenol Nucleophiles

Many nucleophiles have been used in this reaction, including carbon nucleophiles. Heteroatom nucleophiles exhibit significantly different behavior than enolate-derived systems.[11] Phenols,

specifically, are important because there are a large number of natural products containing aryl ether functionalities. The methodology can also be used to set the chirality of an allylic hydroxyl moiety. This use of phenol-type nucleophiles in asymmetric allylic substitution has become one of the most proficuous aspects of the overall methodology.

Good to excellent enantiomeric ratios have been obtained with a wide variety of substituted phenol nucleophiles (Table 1). With cyclic allyl components, enantioselection was better with 6- and 7-membered ring systems than with 5-membered rings. Good enantioselectivity was observed with 5-membered rings when reaction temperature was optimized (Entries 1-3). The good yields and excellent enantiomeric ratios obtained for entry 9 are particularly noteworthy, since many methylenedioxy substituted phenyl rings are present in natural products. The products of type **4** were also used as substrates to undergo lanthanide-catalyzed aromatic Clasien rearrangements, the products of which are equivalent to those from an asymmetric ortho-alkylation of a phenol.[12]

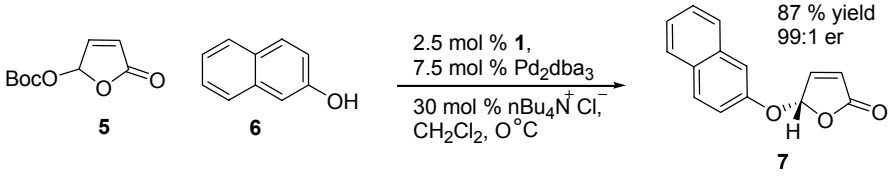
Table 1. Asymmetric allylic substitution with phenol nucleophiles



entry	R^1	R^2	R^3	R^4	R^5	n	temp. (°C)	yield (%)	er
1	H	H	OMe	H	t-Bu	1	25	96	80:20
2	H	H	OMe	H	t-Bu	1	-40	85	93:8
3	H	H	OMe	H	t-Bu	1	-78	82	89:11
4	H	H	OMe	H	Me	2	25	88	99:1
5	H	H	OMe	H	Me	3	25	89	96:4
6	H	H	F	H	Me	2	25	88	97:3
7	OMe	H	H	H	Me	2	25	89	97:3
8	OMe	H	H	CHO	Me	2	25	90	88:12
9	H	OCH_2O		H	Me	2	25	90	98:2

An example of Type D enantioselection with phenol nucleophiles is the reaction with a chiral racemic γ–acyloxybutenolide **5** (Equation 1).[13] This reaction presumably operated as a DYKAT, because racemic **5** yielded **7** in >50% yield, with excellent enantiomeric ratio. The specific reaction shown was optimized for the DYKAT manifold. Upon coordination of both enantiomers of **5**, oxidative addition occurs to generate diastereomeric π-allyl Pd complexes **9** and **11** (Figure 2),[13] that can interconvert via sigma complex, **10**. This isomerization, which occurs by well known mechanisms discussed at length in reviews of asymmetric allylic substitution,[5,6] provides for the DYKAT process. A number of further considerations can improve the enantioselectivity of this reaction. Addition of chloride facilitates the interconversion of **9** and **11**.[14] When chloride is omitted from the reaction, the enantiomeric ratio decreases by a factor of three.[13] Nucleophilicity is also important in DYKAT reactions. Thus,

Equation 1.



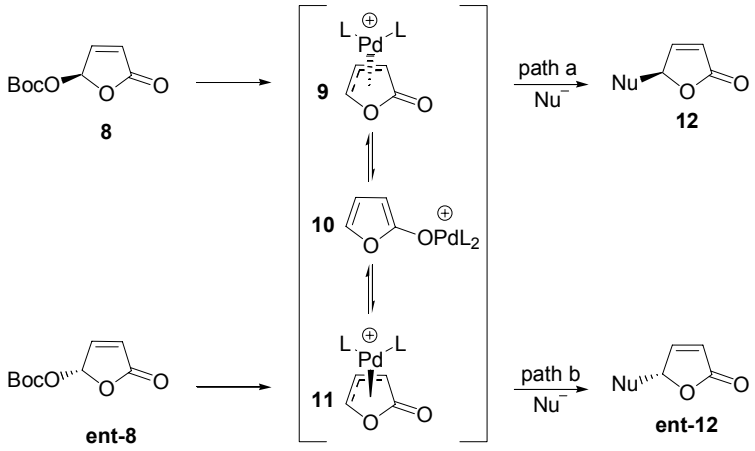
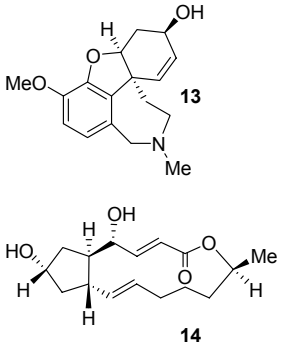
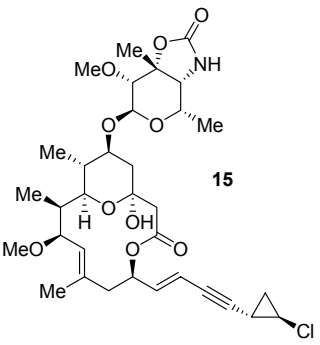


Figure 2. Type D Enantioselection with Phenols

when 15 mol% Cs_2CO_3 is added to the reaction in Equation 1, the enantiomeric ratio is compromised, presumably because the phenoxide ion attacks the diastereomeric complexes at a rate that is more rapid than interconversion. This type of DYKAT mode asymmetric allylic substitution was used in a recent formal total synthesis of (-)-aflatoxin B.[13]

The methodology developed for the use of phenol nucleophiles has proven useful in many total syntheses. A few notable examples include (-)-galanthamine[15] **(13),** (+)-brefeldin[16] **(14)**, and callipeltoside A[17] **(15)**. These syntheses utilized the asymmetric allylic substitution in different ways. In the synthesis of **13**, for example, the aryl ether functionality formed is a part of the natural product. With **14**, the DYKAT manifold was used in a case very similar to that of Equation 1. The reaction set the first stereocenter in the synthesis, but the aryl ether was later discarded as elaboration continued. For **15**, the nucleophile used was *p*-methoxyphenol. The reaction set the configuration of an alcohol moiety, and the aryl ether functionality was again removed to make way for further manipulations. Other examples have also been reported.[18,19,20]

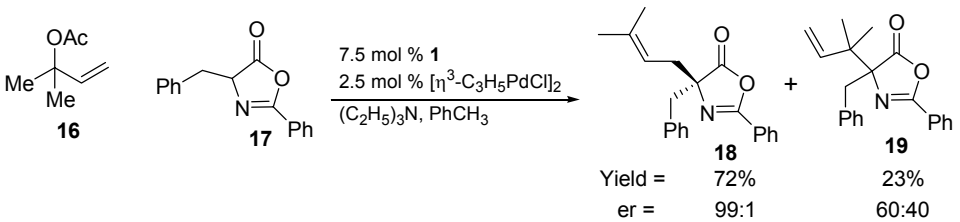




Issues of Regioselectivity with Palladium

When allyl substrates that incorporate non-symmetrical substitution patterns at the termini have been used, regioselectivity has been an issue. Palladium tends to favor delivery of the nucleophile to the least sterically hindered terminus of the allyl group (Equation 2).[21] In many cases, such as natural products synthesis, attack at the more sterically congested regioisomer is desired. With phenol nucleophiles that are not very hindered, the branched regioisomer can be obtained, in the best cases, at 91:9 regioselectivity.[18] However, the use of stabilized carbon nucleo-philes such as azlactone **17**, has been less successful (Equation 2).

Equation 2.



MOLYBDENUM CATALYSIS

Mechanism with Molybdenum

Tungsten[22] and molybdenum[23] have been used to address the issue of regioselectivity in the asymmetric allylic substitution reaction. The major difference between Pd and Mo is the geometry about the coordination sphere of the metal. The $4d^4$ Mo^{2+} prefers an octahedral arrangement, where as the $4d^8$ Pd^{2+} favors a square planar array. The details of the catalytic cycle of Mo-catalyzed asymmetric allylic substitution have not yet been experimentally determined, and mechanistic insights are currently being probed through ligand design.[24] It was initially proposed that chiral ligands such as bis-picolinamide **23** might bind to Mo in three different ways (Figure 3).[25] The common 90˚ chelate **20** would place the ligand furthest away from the π-allyl and incoming nucleophile. If all four nitrogens coordinate, as in **21**, a complex with helical chirality is created; however, this mode also causes a very hindered environment about the metal. A bridging mode, **22**, should provide the deepest chiral pocket. The binding shown in **21** and **22** would theoretically provide a more chiral space around the substrate by increasing the proximity of the substrate to the asymmetric ligand. Phosphines proved detrimental to asymmetric induction with Mo,[26] so, the bis(phosphinobenzamide) ligands **1** had to be avoided. A new chiral pocket type ligand, **23**, was designed and worked very well.[25]

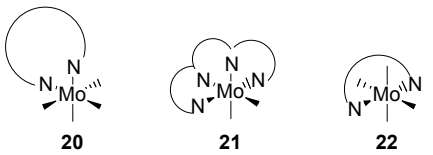
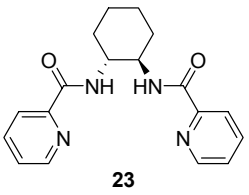
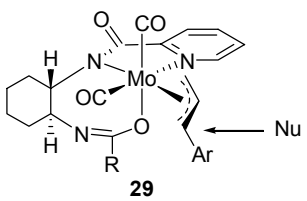
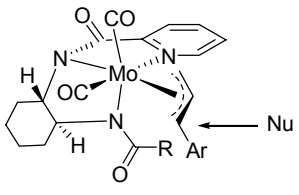


Figure 3. Initially Proposed Binding Modes

To understand how **23** might bind to Mo, many variants of this ligand were synthesized and employed in the reaction shown in Equation 4. With ligand **23** and allyl carbonate **24** (Ar = Ph), the reaction with sodiomalonate **26** proceeds in 93% yield, with a 46:1 (**27:28**) regioselectivity, and an enantiomeric ratio of 99:1 for **27**.[25] A study of which Lewis basic sites were necessary was carried out. Thus, when one of the picolinamide rings of **23** was replaced with phenyl, an increase in regioselectivity was observed, but when both were replaced, the catalyst showed little regioselectivity. Many steric and electronic variants were also examined.[24] Although only one picolinamide ring was needed, more than one point of coordination seemed to be involved, and the secondary amide nitrogens were thought to function as donors. Thus, ligands in which the nitrogens were blocked by methyl groups and in which the nitrogens were replaced by oxygens were synthesized, and these ligands showed a 200 fold decrease in rate and virtually no asymmetric induction.[24] A combination of NMR and computational studies[27] eventually narrowed the large number of possible binding modes to **29** or **30**,[24] the main difference being





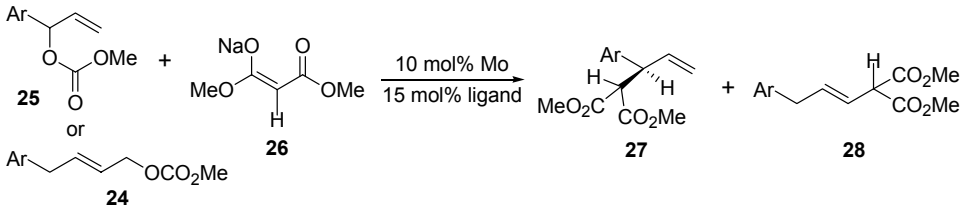


the axial coordination of either an imidate (**29**) or an amide (**30**). A preliminary report suggests that **29** is the active catalyst based upon NMR and X-ray diffraction analysis.[28]

RECENT HIGHLIGHTS WITH MOLYBDENUM

The first work with Mo in the asymmetric allylic substitution was done in the early 1980's,[23] and work resurged in 1998.[25] With ligand **23** and substrate **25** (Ar = naphthyl), excellent regioselectivity, yield, and enantioselectivity could be obtained with carbon nucleophiles (Equation 4). The reaction proceeded in 82% yield with 99:1 regioselectivity favoring **27**, where enantiomeric ratio was 93:7.[25] In addition, the reaction was adapted for use with polyenes and enynes.[29]

Equation 4.



One of the most important developments in the Mo-catalyzed asymmetric allylic substitution reaction is the use of azlactones as nucleophiles.[30] The products of the reaction can be converted directly into protected α-amino acids. The reaction of azlactones proceeds via type E enantioselection, discrimination of the enantiotopic faces of a nucleophile.[21] When Pd is used, the reaction works well for the construction of the less hindered regioisomer, whereas, the use of Mo affords the opposite regioisomer. Thus, very sterically bulky non-natural α-amino acids can be synthesized.[30]

The use of the DYKAT manifold has also been demonstrated with Mo.[31] This adds significantly to the synthetic utility of the asymmetric allylic substitution, because DYKAT reactions can now be performed with selected regiochemistry simply by choosing the appropriate metal and ligand. Another issue of importance is the pre-catalyst. Molybdenum sources such as $(EtCN)_3Mo(CO)_3$ and $(C_7H_8)Mo(CO)_3$ are expensive, and are air and moisture sensitive. Recently, it has been found that $Mo(CO)_6$ can be used as the pre-catalyst.[32] This catalyst is the only one of the three that is commercially available, and it is air stable. This advance saves synthetic efforts since the other two catalysts are made from $Mo(CO)_6$.

CONCLUSIONS

The catalytic cycles and mechanisms of asymmetric induction for Pd and Mo are becoming better understood. Compared to Pd, the use of Mo is still in its infancy. The complementary nature of these two metals in asymmetric allylic substitution greatly increases the synthetic utility of this reaction, and important work in this area continues to unfold. For example, the use of microwave heating affords

36 fold increases in rate with no decrease in asymmetric induction for both metals.[33] Asymmetric allylic substitution will no doubt continue to provide mechanistic and synthetic challenges for years to come.

REFERENCES

(1) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.
(2) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200.
(3) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.
(4) Scifinder search for "asymmetric allylic alkylation" limited to synthetically oriented journals written in English, 9/14/02, by KDB.
(5) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Oijima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 8E.
(6) Trost, B. M.; VanVranken D. L., *Chem. Rev.* **1996**, *96*, 395.
(7) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.
(8) Moberg, C.; Bremberg, U. ; Hallman, K. ; Svensson, M. ; Norrby, P. ; Hallberg, A. ; Larhed, M. ; Csoregh, I. *Pure & Appl. Chem.***1999**, *71*, 1477.
(9) Sauthier, N.; Fornies, J. ; Toupet, L. ; Reau, R. *Organometallics* **2000**, *19*, 553.
(10) Ward, R. S. *Tetrahedron Asymmetry* **1995**, *6*, 1475.
(11) Trost, B. M. *Pure & Appl. Chem.* **1996**, *68*, 779.
(12) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.
(13) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.
(14) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(15) Trost, B. M.; Tang, W., *Angew. Chem. Int. Ed.* **2002**, *41*, 2795.
(16) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9328.
(17) Trost, B. M.; Gunzer, J. L. ; Dirat, O. ; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.
(18) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.
(19) Trost, B. M.; Lee, C. *J. Am. Chem. Soc.* **2001**, *123*, 12191.
(20) Trost, B. M.; Bunt, R. C. ; Lemoine, R. C. ; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.
(21) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.
(22) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1983**, *105*, 7757.
(23) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543,
(24) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Yasuda, N.; Reider, P. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1929.
(25) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.
(26) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(27) Curtis, M. D.; Eisenstein, O. *Organometallics* **1984**, *3*, 887.
(28) Hughes, D. L. ; Krska, S. W. ; Reamer, R. A. ; Mathre, D. J. ; Reider, P. J. Mechanistic Studies of the Molybdenum-catalyzed Asymmetric Allylic Alkylation via NMR Spectroscopy, X-ray Crystallography, and Kinetics, *Abstracts of Papers, 223rd ACS NationalMeeting* , Orlando, FL **2002**; ACS: Washinton DC, 2002.
(29) Trost, B. M.; Hildbrand, S. ; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416.
(30) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256.
(31) Hughes, D. L.; Palucki, M. ; Yasuda, N. ; Reamer, R. A. ; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 2762.
(32) Palucki, M.; Um, J. M.; Conlon, D. A.; Yasuda, N.; Hughes, D. L. ; Mao, B. ; Wang, J.; Reider, P. J. *Adv. Synth. Catal.* **2001**, *343*, 46.
(33) Kaiser, N. K.; Bremberg, U.; Larhed, M. ; Moberg, C. ; Hallberg, A. *Angew. Chem, Int. Ed.* **2000**, *39*, 3596.