1
General

Transition Metals for Organic Synthesis, Vol. 1, 2nd Edition.
Edited by M. Beller and C. Bolm

ISBN: 3-527-30613-7

1.1
Basic Aspects of Organic Synthesis with Transition Metals

Barry M. Trost

Chemistry is described as a central science – one in which phenomena are defined at a molecular level. Understanding functions ranging from material science to biology occurs increasingly at the molecular level. At the heart of such an exercise is synthesis. Designing structure for function requires the greatest flexibility in putting together the molecular edifice. A key in synthesis is efficiency, which may be defined as the ability to convert readily available building blocks into the target molecule in relatively few synthetic operations that require minimal quantities of raw materials and produce minimal waste.

Synthetic efficiency may be divided into two major sub-categories – selectivity [1] and atom economy [2]. Four types of selectivity categorize reactions. First, differentiation among bond types is termed chemoselectivity. Such selectivity can be rather simple, such as selective additions to a carbon–carbon double bond in the presence of a carbon–oxygen double bond or vice versa. Alternatively, such differentiation can be quite subtle, such as differentiating among several carbonyl groups in the same molecule. Second, orienting reactants with respect to each other is termed regioselectivity. Markovnikov vs. anti-Markovnikov additions to a carbon–carbon double bond are classical illustrations. The regioselectivity of the additions of the equivalent of allyl anions to carbonyl groups represents a continuing contemporary challenge [3].

The remaining selectivity issues revolve around stereochemistry. Controlling relative stereochemistry, termed diastereoselectivity, is generally simpler than controlling absolute stereochemistry, termed enantioselectivity. Because of this fact, a frequent approach to the latter problem is to convert it into one of controlling relative stereochemistry. In reactant design, such a strategy has given birth to the concept of chiral auxiliaries [4]. While such an approach is useful and practical, its requirement of a stoichiometric amount of the auxiliary clearly defines it as a less desirable one. Controlling absolute stereochemistry in which the chiral inducing agent is needed only catalytically is clearly the penultimate goal.

Selectivity helps assure that reactions proceed with minimal byproducts that must be separated and disposed of. However, it does not tell the whole story. An additional issue relates to the question of how much of what one puts into a pot ends up in a product. Too often, this issue, which may be called atom economy [2], is sacrificed to resolve problems of selectivity. Consider the Wittig olefination

Transition Metals for Organic Synthesis, Vol. 1, 2nd Edition.
Edited by M. Beller and C. Bolm

ISBN: 3-527-30613-7

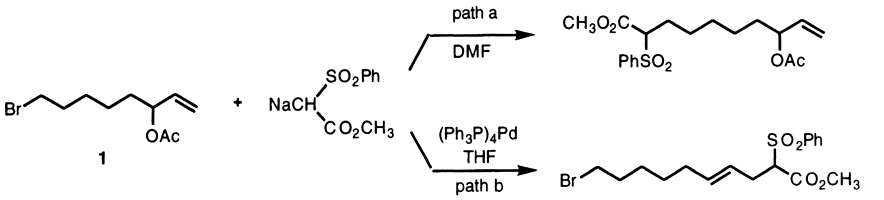
[5] which was introduced to solve the problem of regioselectivity of introduction of a double bond. For the synthesis of a methylenecycloalkane, a reagent whose mass is 357 transfers a unit of mass 14. The remainder of the reagent which constitutes >95% of its original mass becomes byproducts that must be disposed of. Nevertheless, the uniqueness of the process makes it important. It also indicates that an opportunity exists for invention of a more atom economical one.

The development of reactions and reagents that achieve both selectivity and atom economy must be a prime goal of synthetic chemistry. Furthermore, creating new types of bond forming reactions that also address the twin issues of selectivity and atom economy enhance opportunities for simplification of synthetic strategies. The ability of transition metal complexes to catalyze organic reactions constitutes one of the most powerful strategies to address these fundamental issues. Choice of the transition metal combined with the design of the ligand environment provide opportunities for electronic and steric tuning of reactivity to a high degree.

In drawing upon examples from my laboratories to illustrate the principles, I am giving a personal account of my conversion to the world of transition metals to solve problems of selectivity and atom economy. The many chapters that follow provide the readers with the vast scope of the effort throughout the world and the rewards to date. Allylic alkylation becomes a good starting point [6] since the initial question is why bother to use transition metal catalyzed reactions when such alkylations proceed in the absence of catalysts with suitably reactive leaving groups. The answer to the question is embodied in the concept of selectivity – the transition metal catalyst provides an avenue for controlling chemo-, regio-, diastereo-, and enantioselectivity not possible in its absence. It also allows use of more easily handled, generally more readily available, and less noxious substrates. Other examples will illustrate reactions that are not possible in the absence of a transition metal. As these reactions are discussed, it will become apparent that a key phenomenon that underlies much of the ability of transition metals to function as they do is initial coordination. This prerequisite combined with the issues of selectivity leads me to compare transition metal complexes to the active sites of enzymes and to dub them the 'chemists' enzymes'.

1.1.1 Chemoselectivity

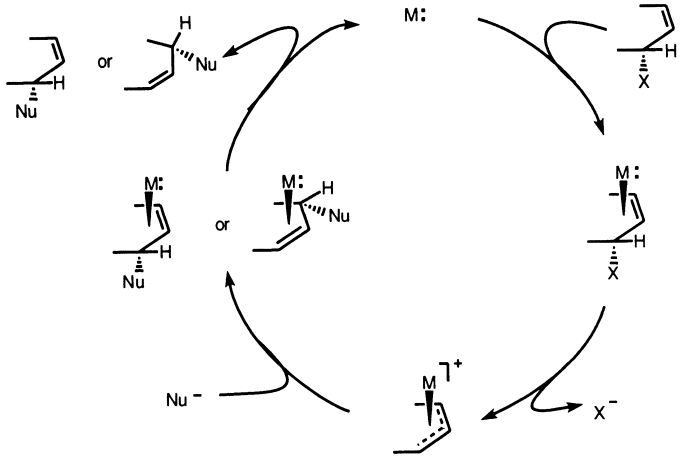
Consider the reactivity of the bromoester 1 towards nucleophiles (Eq. (1)) [7]. There is little question that simple treatment with a nucleophile in a solvent that promotes S_N2 reactions like DMF leads exclusively to substitution of bromide (Eq. (1), path a). On the other hand, employing a solvent like THF in which such direct substitutions are slower, addition of a Pd(0) complex completely changes the course of the reaction to substitution of the allylic ester (Eq. (1), path b).



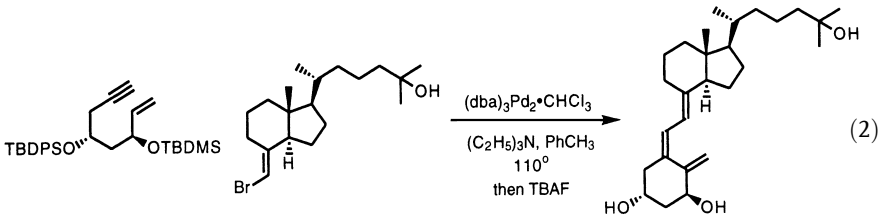
(1)

The phenomenon responsible for the reversal of chemo-selectivity is coordination, a prerequisite for the Pd(0) complex to effectively achieve ionization. The double bond proximal to the ester provides initial coordination to Pd(0), which sets the stage for the palladium to promote an intramolecular ionization of even relatively poor leaving groups like carboxylates to a π-allylpalladium intermediate as depicted in Scheme 1. In the absence of such precoordination, even relatively reactive leaving groups like bromide or iodide remain unreactive towards palladium under the above conditions.

Whereas main group organometallics preferentially add across polarized unsaturation, notably carbonyl groups; carbametallation when the metal is a transition metal normally involves addition across a relatively nonpolarized carbon–carbon unsaturation. This selectivity stems from the preferential coordination of the latter to the metal. Carbapalladation, a key step in the Heck arylation and vinylation [8], occurs across carbon–carbon double bonds selectively even in the presence of carbon–oxygen double bonds. The fact that unactivated carbon–carbon triple bonds are better ligands than unactivated carbon–carbon double bonds even allows discrimination between these two types of carbon–carbon unsaturation – a key issue in an approach to vitamin D and its analogues as illustrated in Eq. (2) [9].



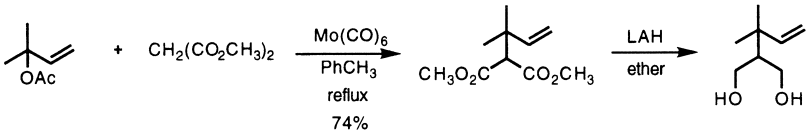
Scheme 1 A metal-catalyzed allylic alkylation.



(2)

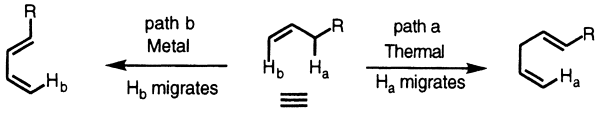
1.1.2 Regioselectivity

Transition metal complexes may control the orientation of chemical reactions. Allylic alkylations illustrate this phenomenon in an intermolecular case. Whereas, palladium-catalyzed reactions normally are dominated by steric effects leading to attack on an unsymmetrical π-allylpalladium intermediate at the less substituted carbon (Eq. (1)) [10], more electropositive metals like molybdenum [11] or tungsten [12] promote reaction at the more electron deficient allyl terminus, which will be the more substituted one. As shown in Eq. (3), the molybdenum-catalyzed reaction was employed to make a product which is a fragment of the saponaceolides [13].



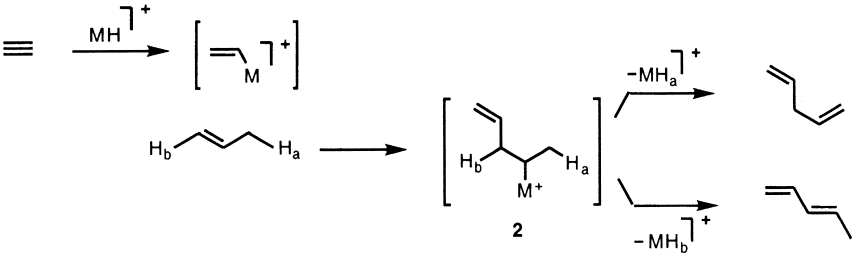
(3)

Directing reactions along regiochemical pathways not possible in a nonmetal-catalyzed reaction constitutes another aspect of transition metal chemistry. Consider the Alder ene reaction [14] as shown in Eq. (4), path a. By virtue of the mechanism of the concerted thermal reaction, the resultant product between an alkene and an alkyne is a 1,4-diene regioselectively. On the other hand, migration of a vinyl hydrogen H_b can lead to the synthetically particularly useful 1,3-diene, Eq. (4), path b, which participates in Diels–Alder and other cycloadditions. In this case, the role of a catalyst would be not only to increase the rate of the reaction and permit it to proceed at temperatures significantly below its thermal version, which may permit reactions to proceed which otherwise might fail, but also to redirect the regioselectivity when desired.

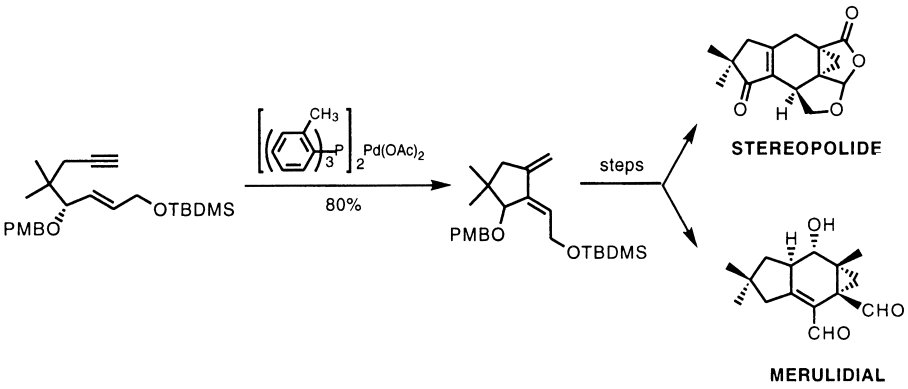


(4)

Using a carbametallation as shown in Eq. (5) as the key C–C bond forming reaction produces an intermediate **2** for which β-elimination of hydrogen can involve either H_a or H_b. The weaker allylic H_b bond might be anticipated to eliminate more facilely thereby producing the 1,3-diene. As shown in Eq. (6), this process can indeed be realized [15] and served as a key step in the synthesis of the isolactaranes sterepolide [16] and merulidial [17] in which the subsequent regio- and diastereoselective Diels–Alder reaction of 2-bromomethylmaleic anhydride introduces all of the remaining carbon atoms in both total syntheses.



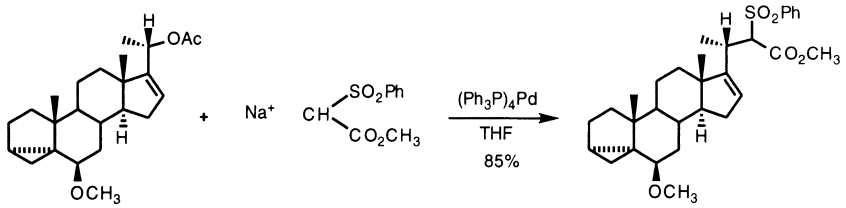
(5)

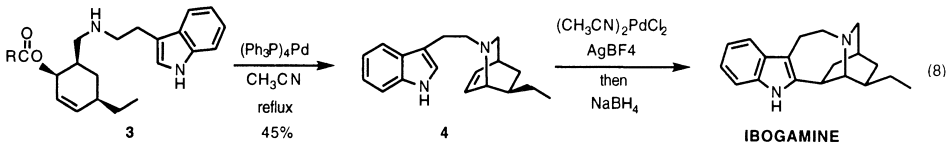


(6)

1.1.3
Diastereoselectivity

Changing the 'rules' of reactivity is an exciting prospect offered by transition metal-catalyzed reactions. Allylic alkylations nicely illustrate this phenomenon. The stereochemical rule for S_N2 reactions is substitution with inversion of configuration. Examination of Scheme 1 indicates that a metal-catalyzed reaction effects substitution with net retention of configuration regardless of the regioselectivity, i.e. the nucleophile approaches the same face of the allyl fragment from which the leaving group departed. This result stems from either a double inversion mechanism (as depicted) [18] or a double retention mechanism (not depicted) [19]. Equation (7) illustrates employment of this phenomenon for direct substitution in the elaboration of the steroid side chains of the ecdysones, insect molting hormones [20]. Another example of this principle is shown in Eq. (8). The diastereoselectivity of the Diels–Alder reaction arising from an *endo* transition state generates the all *cis* isomer such as 3. Cyclization to the quinuclidine system 4, common in alkaloids represented by ibogamine [21] and catharanthine [22], then requires an S_N2' substitution with retention of configuration which is equally accessible by the transition-metal catalyzed chemistry. The final cyclization to form ibogamine required a new type of reactivity that derived from the Heck arylation but initiated by an electrophilic aromatic substitution by a palladium(+2) salt and terminated by reductive cleavage of a σ-C–Pd bond. Thus, the availability of two palladium mediated reactions as illustrated in Eq. (8) created a four-step synthesis of ibogamine from the Diels–Alder partners.

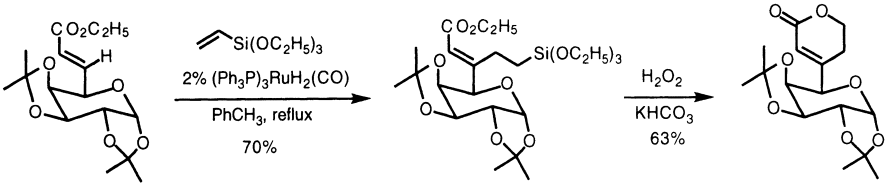




(8)

Controlling relative stereochemistry also applies to sp^2 carbon in terms of alkene geometry. The geometry of trisubstituted alkenes is difficult to control by most olefination protocols; whereas, 1,2-disubstituted alkenes are readily available by such methods in either the *E* or *Z* configuration [5]. If the disubstituted alkene can be specifically converted to a trisubstituted alkene by stereospecific replace-

ment of a vinyl C–H bond by a C–C bond, a new way to create trisubstituted alkenes of defined geometry will be available. Activation of C–H bonds by transition metals is one of their fundamental reactions. Using pre-coordination to direct regioselectivity, a new strategy for stereocontrolled construction of trisubstituted alkenes emerges as illustrated in Eq. (9) using a Ru catalyst [23, 24].



(9)

1.1.4 Enantioselectivity

Controlling absolute stereochemistry certainly must be classified as one of the major challenges of contemporary organic synthesis. Doing so wherein the asymmetric inducing entity is used only catalytically is the most effective approach [25]. The pioneering studies of Knowles [26], Kagan [27], and others [25] on asymmetric catalytic hydrogenation proved the principle that transition metal complexes can indeed achieve excellent enantioselectivity. How far can this concept be pushed? In all cases of successful enantioselectivity, the bond forming event introducing stereochemistry occurs within the coordination sphere of the metal. Can reactions in which the enantiodiscrimination occurs outside the coordination sphere of the metal also proceed with synthetically useful ee's? Using the chemists' enzymes concept, can chiral space analogous to an active site of an enzyme be created to influence the absolute stereochemistry? Fig. 1 illustrates the concept in the case of a complex for asymmetric allylic alkylation [28, 29]. This catalyst system efficiently induces asymmetry via a number of different mechanisms. Equation (10) illustrates an example of inducing stereochemistry in an ionization event leading to the synthesis of nucleosides [30]. Since the starting dibenzoate derives from furan in one step, a six step synthesis of the complex of the polyoxinnikkomycin complex results. Equation (11) illustrates inducing enantioselectivity in the nucleophilic addition step wherein an enantioconvergence occurs since both enantiomers of the racemic butadiene monoepoxide produce the same enantiomeric product [31]. This simple synthesis of vinylglycinol in a protected form from cheap, commercially available starting materials makes it an excellent building block. For example, vigabatrin, an anti-epileptic in the *S* form, is available in either enantiomeric form in only four steps [32].

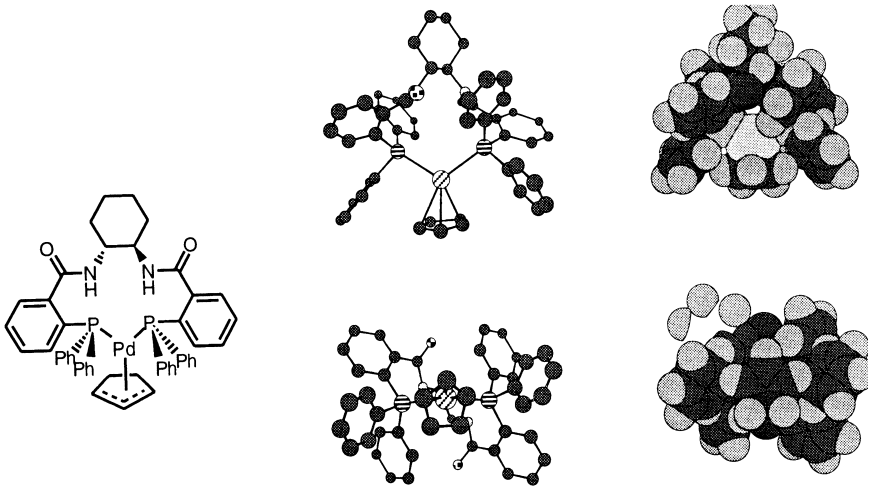
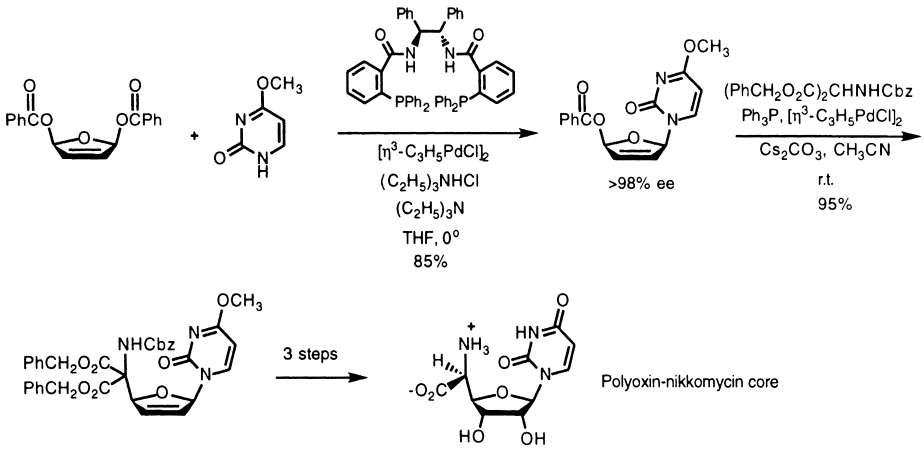
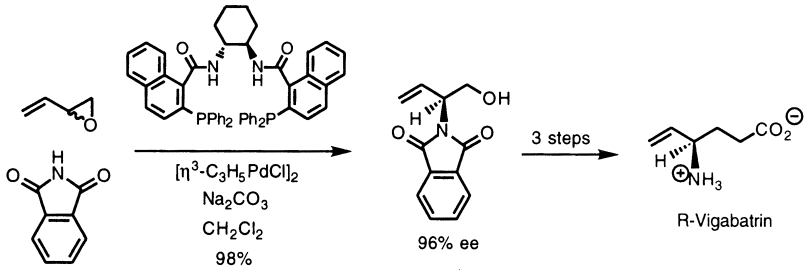


Fig. 1 A chiral pocket for asymmetric induction.



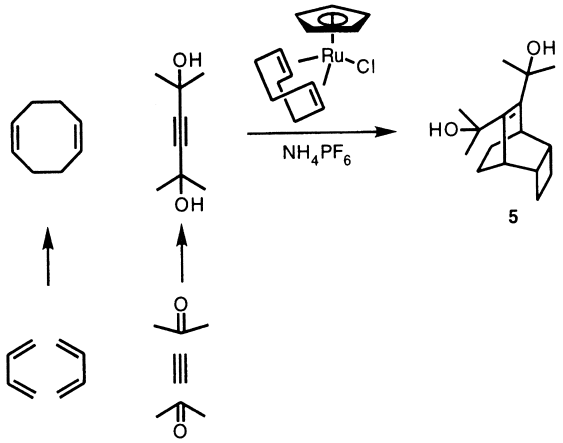
(10)



(11)

1.1.5
Atom Economy

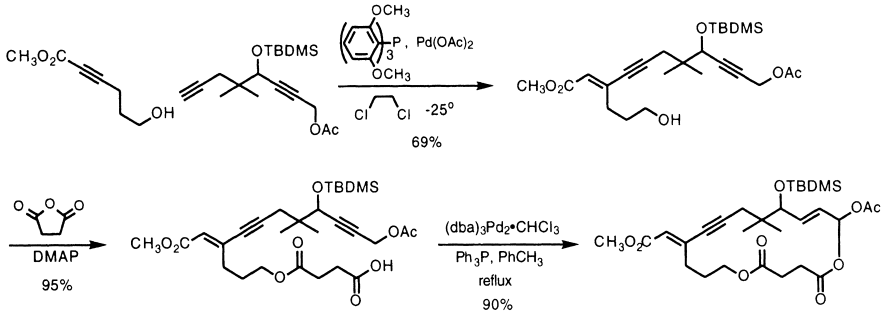
While most attention has focused on solving problems of selectivity, that is not sufficient for synthetic efficiency. Consideration of maximal use of raw materials and minimal generation of waste calls for solutions to be atom economical – i.e. as many as possible of the atoms of the reactants should end up in the product with the ideal being the product as simply the sum of the reactants, i.e. the reaction involves only additions with anything else being required catalytically. The serendipitous discovery that a ruthenium complex catalyzed a novel cycloaddition of 1,5-cyclooctadiene provides easy entry to the energy rich tricycle **5** nearly quantitatively [33]. The starting materials are also made by addition reactions – cyclooctadiene by the dimerization of butadiene catalyzed by a nickel complex [34] and the diol from acetylene and 2 equivalents of acetone [35]. Thus, a fairly complicated bridged bicycle arises by a series of three additions from butadiene, acetylene, and acetone.



(12)

Activation of C–H bonds provides prime opportunity to rationally invent new addition reactions. Equation (9) illustrates one such example. Activation of the C–H

bond of terminal alkynes allows its addition across 'activated' alkynes [36]. Hydrogen shuffling by certain palladium complexes allows isomerization of alkynes into π-allylpalladium intermediates that also leads to additions [37]. Combining these ideas led to a structurally complex macrodiolide in which the final three steps were only addition reactions as illustrated in Eq. (13) [37].



(13)

1.1.6 Conclusion

Opportunities to invent new reactions catalyzed by transition metals to solve problems of selectivity and to do so with as much atom economy as possible appear infinite. The range of transition metals and their sensitive response to their ligand environment assure the truth of that statement. In the ideal, we can achieve both objectives, which is clearly what we must strive for. On the other hand, problems must be solved to meet the needs of society today. Thus compromises must also be made. Clearly, the practice of organic chemistry today with respect to accessing sophisticated structures for various practical end uses arose from the availability of new paradigms for molecular transformations derived from organometallic chemistry. As our understanding of the underlying reactivity principles increases, our ability to rationally invent new synthetic reactions that move us toward the ideal will undoubtedly increase. At this point, it is already clear that catalysts have gone far beyond their traditional function as simple rate enhancers to become the ultimate arbiter of which path a reaction will take [38].

1.1.7 References

1 B. M. Trost, *Science* **1983**, *279*, 245.

2 B. M. Trost, *Science* **1991**, *254*, 1471; B. M. Trost, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

3 For a few interesting recent developments, see: B. S. Guo, W. Doubleday, T. Cohen, *J. Am. Chem. Soc.* **1987**, *109*, 4710; A. Yanagisawa, S. Habane, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6131.

4 For an early example of the concept of a chiral auxiliary, see: A. I. Meyers, G. Knaus, K. Kamata, M. E. Ford, *J. Am. Chem. Soc.* **1976**, *98*, 567. Chiral oxazolidinones have proven to be exceptionally useful, see: D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737. Pseudoephedrine appears to be a very practical chiral auxiliary for enolate alkylations, see: A. G Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656. For an overview, see: J. Seyden-Penn, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**.

5 For a review, see: S. E. Kelly in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon Press, Oxford, **1991**, Vol. 1, pp. 729–817.

6 For a revew, see: S. A. Godleski in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, M. F. Semelhack), Pergamon Press, Oxford, **1991**, Vol. 4, pp. 585–662.

7 B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1980**, *102*, 4730; B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1987**, *109*, 1469; B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, *117*, 5156.

8 R. F. Heck in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon Press, Oxford, **1991**, Vol. 4, pp. 833–864; A. de Meijere, F. E. Meyer, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

9 B. M. Trost, J. Dumas, M. Villa, *J. Am. Chem. Soc.* **1992**, *114*, 9836.

10 B. M. Trost, M.-H. Hung, *J. Am. Chem. Soc.* **1984**, *106*, 6837; B. Akermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg, *Organomet.* **1984**, *3*, 679; B. M. Trost, C. J. Urch, M.-H. Hung, *Tetrahedron Lett.* **1986**, *27*, 4949; for reviews, see: Ref. [6] and B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385; J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer-Verlag, Berlin, **1980**.

11 B. M. Trost, M. Lautens, *Tetrahedron* **1987**, *43*, 4817; B. M. Trost, C. A. Merlic, *J. Am. Chem. Soc.* **1990**, *112*, 9590.

12 B. M. Trost, M.-H. Hung, *J. Am. Chem. Soc.* **1983**, *105*, 7757; B. M. Trost, G. B. Tometzki, M.-H. Hung, *J. Am. Chem. Soc.* 1987, *109*, 2176; G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. For a recent report of similar regioselectivity with an Ir catalyst, see: R. Takeuchi, M. Kashio, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263.

13 J. R. Corte, unpublished results.

14 B. B. Snider, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon Press, Oxford, **1991**, Vol. 5, pp. 1–28.

15 B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. MacPherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255; B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.* **1994**, *116*, 4268.

16 B. M. Trost, J. Y. L Chung, *J. Am. Chem. Soc.* **1985**, *107*, 4586. Also see: B. M. Trost, P. A. Hipskind, J. Y. L. Chung, C. Chan, *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1502.

17 B. M. Trost, P. A. Hipskind, *Tetrahedron Lett.* **1992**, *33*, 4541.

18 B. M. Trost, L. Weber, *J. Am. Chem. Soc.* **1975**, *97*, 1611; B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1980**, *702*, 4730; T. Hayashi, A. Yamamoto, T. Hagihara, *J. Org. Chem.* **1986**, *51*, 723.

19 J. W. Fuller, D. Linebarrier, *Organomet.* **1988**, *7*, 1670; D. Drvorak, I. Stary, P. Kocovsky, *J. Am. Chem. Soc.* **1995**, *117*, 6130.

20 B. M. Trost, Y. Matsumura, *J. Org. Chem.* **1977**, *42*, 2036.

21 B. M. Trost, S. A. Godleski, J.-P. Gent, *J. Am. Chem. Soc.* **1978**, *100,* 3930.

22 B. M. Trost, S. A. Godleski, J. L. Belletire, *J. Org. Chem.* **1979**, *44,* 2052.

23 B. M. Trost, K. Imi, I. W. Davies, *J. Am. Chem. Soc.* **1995**, *117,* 5371.

24 For updated regioselective aromatic substitution, see: F. Kakuichi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatini, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68,* 62. For elaboration of trisubstituted acylcycloalkenes, see: F. Kakuichi, Y. Tanaka, T. Sato, N. Chatani, S. Murai, *Chem. Lett.* **1995**, 679.

25 R. Noyori, *Asymmetric Catalysis in Organic Synthesis,* John Wiley, New York, **1994**; I. Ojima, *Catalytic Asymmetric Synthesis,* VCH, New York, **1993**.

26 W. S. Knowles, M. J. Sabacky, *J. Chem. Soc., Chem. Commun.* **1968**, 1445; B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99,* 5946.

27 T.-P. Dang, H. B. Kagan, *J. Chem. Soc., Chem. Commun.* **1971**, 481; W. Dumont, J.-C. Poulin, T.-P. Dang, H. B. Kagan, *J. Am. Chem. Soc.* **1973**, *95,* 8295.

28 B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114,* 9327; B. M. Trost, D. L. Van Vranken, *Angew. Chem., Int. Ed. Engl.* **1992**, *31,* 228.

29 For reviews, see: B. M. Trost, *Ace. Chem. Res.* **1996**, *29,* 355; B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96,* 395.

30 B. M. Trost, Z. Shi, *J. Am. Chem. Soc.* **1996**, *118,* 3039.

31 B. M. Trost, R. C. Bunt, *Angew. Chem., Int. Ed. Engl.* **1996**, *35,* 99.

32 B. M. Trost, R. C. Lemoine, *Tetrahedron Lett.* **1996**, *37,* 9161.

33 B. M. Trost, K. Imi, A. F. Indolese, *J. Am. Chem. Soc.* **1993**, *115,* 8831.

34 P. W. Jolly, G. Wilke, *The Organic Chemistry of Nickel,* Academic Press, New York, **1975**, Vol. II.

35 W. Ziegenbein, *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Marcel Dekker, New York, **1969**, pp. 169–256.

36 B. M. Trost, M. Sorum, C. Chan, A. E. Harms, G. Rühter, *J. Am. Chem. Soc.* **1997**, *119,* 698; B. M. Trost, M. C. Mclntosh, *J. Am. Chem. Soc.* **1995**, *117,* 7255.

37 B. M. Trost, W. Brieden, K. H. Baringhaus, *Angew. Chem., Int. Ed. Engl.* **1992**, *31,* 1335.

38 M. E. Davis, S. L. Scrib, *Selectivity in Catalysis,* American Chemical Society, Washington, DC, **1993**.