8

Reactions Involving Transition Metals

Introduction

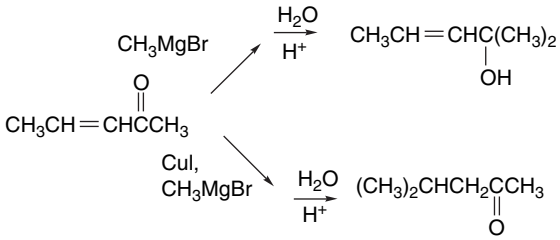
In this chapter we discuss important synthetic reactions that involve transition metal compounds and intermediates. Reactions involving copper and palladium, the transition metals that have the widest applications in synthesis, are discussed in the first two sections. In the third section, we consider several other transition metals, including nickel, rhodium, and cobalt. In contrast to lithium, magnesium, and zinc, where the organometallic reagents are used in stoichiometric quantities, many of the transition metal reactions are catalytic processes. The mechanisms are described in terms of *catalytic cycles* that show the role of the catalytic species in the reaction and its regeneration. Another distinguishing feature of transition metal reactions is that they frequently involve changes in oxidation state at the metal atom. In the final two sections we deal with transition metal–catalyzed alkene exchange (*metathesis*) reactions and organometallic compounds that feature π bonding of the organic component.

8.1. Organocopper Intermediates

8.1.1. Preparation and Structure of Organocopper Reagents

The synthetic application of organocopper compounds received a major impetus from the study of the catalytic effect of copper salts on reactions of Grignard reagents with α,β-unsaturated ketones.[1] Although Grignard reagents normally add to such compounds to give the 1,2-addition product, the presence of catalytic amounts of Cu(I) results in conjugate addition. Mechanistic study pointed to a very fast reaction by an organocopper intermediate.

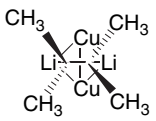
[1] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).



Subsequently, much of the development of organocopper chemistry focused on stoichiometric reagents prepared from organolithium compounds. Several types of organometallic compounds can result from reactions of organolithium reagents with copper(I) salts.[2] Metal-metal exchange reactions using a 1:1 ratio of lithium reagent and a copper(I) salt give alkylcopper compounds that tend to be polymeric and are less useful in synthesis than the 2:1 or 3:1 "ate" compounds.

$$\text{RLi} + \text{Cu(I)} \longrightarrow [\text{RCu}]_n + \text{Li}^+$$
$$2\ \text{RLi} + \text{Cu(I)} \longrightarrow [\text{R}_2\text{CuLi}] + \text{Li}^+$$
$$3\ \text{RLi} + \text{Cu(I)} \longrightarrow [\text{R}_3\text{CuLi}_2] + \text{Li}^+$$

The 2:1 species are known as *cuprates* and are the most common synthetic reagents. Disubstituted Cu(I) species have the $3d^{10}$ electronic configuration and would be expected to have linear geometry. The Cu is a center of high electron density and nucleophilicity, and in solution, lithium dimethylcuprate exists as a dimer $[\text{LiCu}(\text{CH}_3)_2]_2$.[3] The compound is often represented as four methyl groups attached to a tetrahedral cluster of lithium and copper atoms. However, in the presence of LiI, the compound seems to be a monomer of composition $(\text{CH}_3)_2\text{CuLi}$.[4]



Discrete diarylcuprate anions have been observed in crystals in which the lithium cation is complexed by crown ethers.[5] Both tetrahedral Ph_4Cu_4 and linear $[\text{Ph}_2\text{Cu}]^-$ units have been observed in complex cuprates containing $(\text{CH}_3)_2\text{S}$ as a ligand. $[(\text{Ph})_3\text{Cu}]^{2-}$ units have also been observed as parts of larger aggregates.[6] Larger clusters of composition $[(\text{Ph}_6\text{Cu}_4)\text{Li}]^-$ and $[\text{Ph}_6\text{Cu}_4\text{Mg}\cdot\text{OEt}_2]$ have been characterized by crystallography,[7] as shown in Figure 8.1.

Cuprates with two different copper ligands have been developed. These compounds have important advantages in cases in which one of the substituents

2. E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **42**, 2805 (1977); E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.*, **99**, 5312 (1977).
3. R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.*, **98**, 4098 (1976); B. H. Lipshutz, J. A. Kozlowski, and C. M. Breneman, *J. Am. Chem. Soc.*, **107**, 3197 (1985).
4. A. Gerold, J. T. B. H. Jastrezebski, C. M. P. Kronenburg, N. Krause, and G. Van Koten, *Angew. Chem. Int. Ed. Engl.*, **36**, 755 (1997).
5. H. Hope, M. M. Olmstead, P. P. Power, J. Sandell, and X. Xu, *J. Am. Chem. Soc.*, **107**, 4337 (1985).
6. M. M. Olmstead and P. P. Power, *J. Am. Chem. Soc.*, **112**, 8008 (1990).
7. S. I. Khan, P. G. Edwards, H. S. H. Yuan, and R. Bau, *J. Am. Chem. Soc.*, **107**, 1682 (1985).

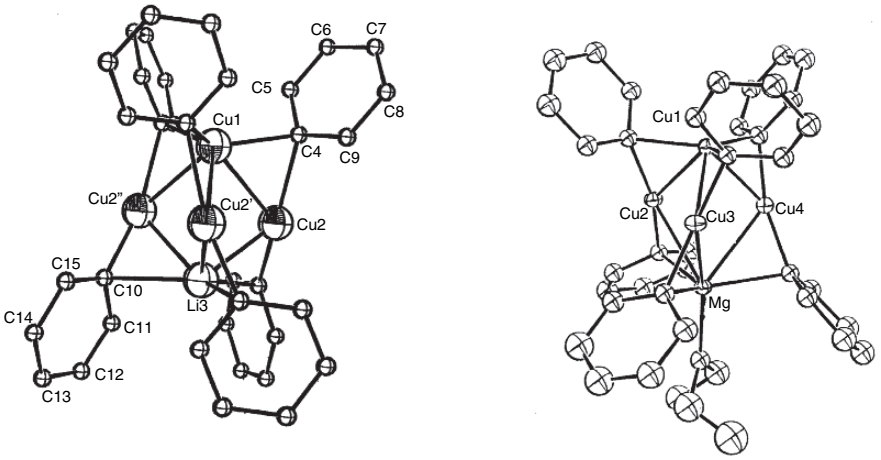


Fig. 8.1. Crystal structures of $[(Ph_6Cu_4)Li]^-$ (left) and $[Ph_6Cu_4Mg{\cdot}OEt_2])$ (right). Reproduced from *J. Am. Chem. Soc.*, **107**, 1682 (1985), by permission of the American Chemical Society.

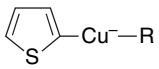
is derived from a valuable synthetic intermediate. The group R, representing alkyl, alkenyl, or aryl, is normally transferred in preference to the other copper ligand. Table 8.1 presents some of these mixed cuprate reagents and summarizes their reactivity. The group listed first is the nonreactive copper ligand and R is the organic group that is delivered as a nucleophile.

There has been a great deal of study concerning the effect of solvents and other reaction conditions on the stability and reactivity of organocuprate species.[8] These studies have found, for example, that $(CH_3)_2S$-CuBr, a readily prepared and purified complex of CuBr, is an especially reliable source of Cu(I) for cuprate preparation.[9] Copper(I) cyanide and iodide are also generally effective and, in some cases, preferable.[10]

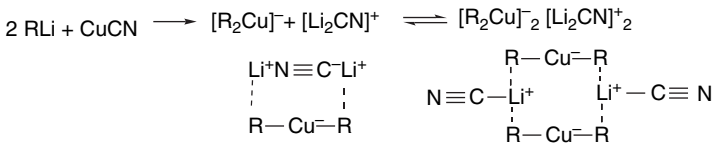
An important type of mixed cuprate is prepared from a 2:1 ratio of an alkyllithium and CuCN.[11] Called *higher-order cyanocuprates*, their composition is $R_2CuCNLi_2$ in THF solution, but it is thought that most of the molecules are probably present as dimers. The cyanide does not seem to be bound directly to the copper, but rather to the lithium cations.[12] The dimers most likely adopt an eight-membered ring motif.[13]

8. R. H. Schwartz and J. San Filippo, Jr., *J. Org. Chem.*, **44**, 2705 (1979).
9. H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975).
10. B. H. Lipshutz, R. S. Wilhelm, and D. M. Floyd, *J. Am. Chem. Soc.*, **103**, 7672 (1981); S. H. Bertz, C. P. Gibson, and G. Dabbagh, *Tetrahedron Lett.*, **28**, 4251 (1987); B. H. Lipshutz, S. Whitney, J. A. Kozlowski, and C. M. Breneman, *Tetrahedron Lett.*, **27**, 4273 (1986).
11. B. H. Lipshutz, R. S. Wilhelm, and J. Kozlowski, *Tetrahedron*, **40**, 5005 (1984); B. H. Lipshutz, *Synthesis*, 325 (1987).
12. T. M. Barnhart, H. Huang, and J. E. Penner-Hahn, *J. Org. Chem.*, **60**, 4310 (1995); J. P. Snyder and S. H. Bertz, *J. Org. Chem.*, **60**, 4312 (1995); T. L. Semmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Bohme, and G. Frenking, *J. Am. Chem. Soc.*, **117**, 12489 (1995); S. H. Bertz, G. B. Miao, and M. Eriksson, *J. Chem. Soc., Chem. Commun.*, 815 (1996).
13. E. Nakamura and S. Mori, *Angew. Chem. Int. Ed. Engl.*, **39**, 3750 (2000).

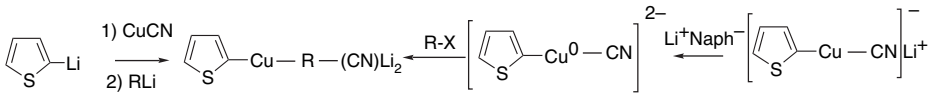
Table 8.1. Mixed-Ligand Organocopper Reagents

Mixed ligand reagent	Reactivity and properties	Reference
$[R'C{\equiv}C{-}Cu{-}R]Li$	Conjugate addition to α,β-unsaturated ketones and certain esters	a
$[ArS{-}Cu{-}R]Li$	Nucleophilic substitution and conjugate addition to unsaturated ketones; ketones from acyl chlorides	b,c
$[(CH_3)_3CO{-}Cu{-}R]Li$	Nucleophilic substitution and conjugate addition to α,β-unsaturated ketones	b
$[(c\text{-}C_6H_{11})_2N{-}Cu{-}R]Li$	Normal range of nucleophilic reactivity; improved thermal stability	d
$[Ph_2P{-}Cu{-}R]Li$	Normal range of nucleophilic reactivity; improved thermal stability	d
$[CH_3\overset{O}{\overset{\|}{S}}CH_2{-}Cu{-}R]Li$	Normal range of nucleophilic reactivity; improved thermal stability	e
$[N{\equiv}C{-}Cu{-}R]Li$	Efficient opening of epoxides	f
$[N{\equiv}C{-}CuR_2]Li_2$	Nucleophilic substitution, conjugate addition	g
	Nucleophilic substitution, conjugate addition and epoxide ring-opening	h
$[(CH_3)_3CCH_2{-}Cu{-}R]Li$	Conjugate addition	i
$[(CH_3)_3SiCH_2{-}Cu{-}R]Li$	High reactivity, thermal stability	j
$\{[(CH_3)_3Si]_2N{-}Cu{-}R]\}Li$	High reactivity, thermal stability	j
$BF_3{-}Cu{-}R$	Conjugate addition, including acrylate esters and acrylonitrile; S_N2' substitution of allylic halides	k

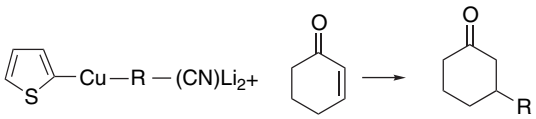
a. H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); E. J. Corey, D. Floyd, and B. H. Lipshutz, *J. Org. Chem.* **43**, 3418 (1978).
b. G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).
c. G. H. Posner and C. E. Whitten, *Org. Synth.*, **58**, 122 (1975).
d. S. H. Bertz, G. Dabbagh, and G. M. Villacorta, *J. Am. Chem. Soc.*, **104**, 5824 (1982).
e. C. R. Johnson and D. S. Dhanoa, *J. Org. Chem.*, **52**, 1885 (1987).
f. R. D. Acker, *Tetrahedron Lett.*, 3407 (1977); J. P. Marino and N. Hatanaka, *J. Org. Chem.*, **44**, 4667 (1979).
g. B. H. Lipshutz and S. Sengupta, *Org. React.*, **41**, 135 (1992).
h. H. Malmberg, M. Nilsson, and C. Ullenius, *Tetrahedron Lett.*, **23**, 3823 (1982); B. H. Lipshutz, M. Koernen, and D. A. Parker, *Tetrahedron Lett.*, **28**. 945 (1987).
i. C. Lutz, P. Jones, and P. Knochel, *Synthesis*, 312 (1999).
j. S. H. Bertz, M. Eriksson, G. Miao, and J. P. Snyder, *J. Am. Chem. Soc.*, **118**, 10906 (1996).
k. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977); Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978).



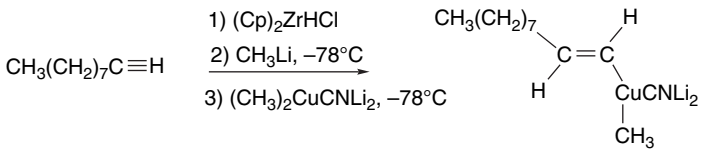
These reagents are qualitatively similar in reactivity to other cuprates but they are more stable than the dialkylcuprates. As cyanocuprate reagents usually transfer only one of the two organic groups, it is useful to incorporate a group that does not transfer, and the 2-thienyl group has been used for this purpose.[14] Usually, these reagents are prepared from an organolithium reagent, 2-thienyllithium, and CuCN. These reagents can also be prepared by reaction of an alkyl halide with 2-thienylcopper. The latter method is compatible with functionalized alkyl groups.[15]



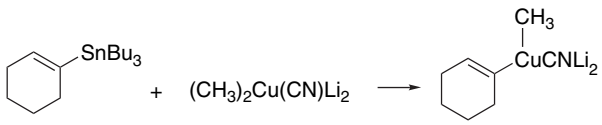
In a mixed alkyl-thienyl cyanocuprate, only the alkyl substituent is normally transferred as a nucleophile.



Another type of mixed cyanocuprate has both methyl and alkenyl groups attached to copper. Interestingly, these reagents selectively transfer the alkenyl group in conjugate addition reactions.[16] These reagents can be prepared from alkynes via hydrozirconation, followed by metal-metal exchange.[17]



Alkenylcyanocuprates can also be made by metal-metal exchange from alkenylstannanes.[18]



14. B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen, and K. E. McCarthy, *J. Organomet. Chem.*, **285**, 437 (1985); B. H. Lipshutz, M. Koerner, and D. A. Parker, *Tetrahedron Lett.*, **28**, 945 (1987).
15. R. D. Rieke, W. R. Klein, and T.-S. Wu, *J. Org. Chem.*, **58**, 2492 (1993).
16. B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *J. Org. Chem.*, **49**, 3938 (1984).
17. B. H. Lipshutz and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 7440 (1990).
18. J. R. Behling, K. A. Babiak, J. S. Ng, A. L. Campbell, R. Moretti, M. Koerner, and B. H. Lipshutz, *J. Am. Chem. Soc.*, **110**, 2641 (1988).

The 1:1 organocopper reagents can be prepared directly from the halide and highly reactive copper metal prepared by reducing Cu(I) salts with lithium naphthalenide.[19] This method of preparation is advantageous for organocuprates containing substituents that are incompatible with organolithium compounds. For example, nitrophenyl and cyanophenyl copper reagents can be prepared in this way, as can alkylcopper reagents having ester and cyano substituents.[20] Allylic chlorides and acetates can also be converted to cyanocuprates by reaction with lithium naphthalenide in the presence of CuCN and LiCl.[21]

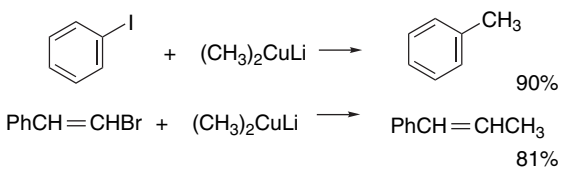
$$(CH_3)_2C{=}CHCH_2Cl \xrightarrow[\text{CuCN, LiCl}]{\text{Li naphthalenide}} [(CH_3)_2C{=}CHCH_2]_2CuCNLi_2$$

Organocopper reagents can also be prepared from Grignard reagents, which are generated and used in situ by adding a Cu(I) salt, typically the bromide, iodide, or cyanide.

8.1.2. Reactions Involving Organocopper Reagents and Intermediates

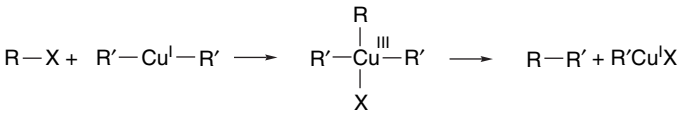
The most characteristic feature of the organocuprate reagents is that they are excellent *soft nucleophiles*, showing greater reactivity in S_N2, S_N2', and conjugate addition reactions than toward direct addition at carbonyl groups. The most important reactions of organocuprate reagents are nucleophilic displacements on halides and sulfonates, epoxide ring opening, conjugate additions to α,β-unsaturated carbonyl compounds, and additions to alkynes.[22] These reactions are discussed in more detail in the following sections.

8.1.2.1. S_N2 *and* S_N2' *Reactions with Halides and Sulfonates.* Corey and Posner discovered that lithium dimethylcuprate can replace iodine or bromine by methyl in a wide variety of compounds, including aryl, alkenyl, and alkyl derivatives. This halogen displacement reaction is more general and gives higher yields than displacements with Grignard or lithium reagents.[23]

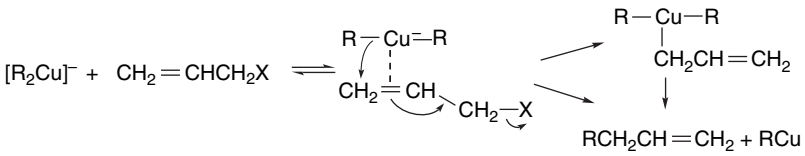


19. G. W. Ebert and R. D. Rieke, *J. Org. Chem.*, **49**, 5280 (1984); *J. Org. Chem.*, **53**, 4482 (1988); G. W. Ebert, J. W. Cheasty, S. S. Tehrani, and E. Aouad, *Organometallics*, **11**, 1560 (1992); G. W. Ebert, D. R. Pfennig, S. D. Suchan, and T. J. Donovan, Jr., *Tetrahedron Lett.*, **34**, 2279 (1993).
20. R. M. Wehmeyer and R. D. Rieke, *J. Org. Chem.*, **52**, 5056 (1987); T.-C. Wu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **52**, 5059 (1987); R. M. Wehmeyer and R. D. Rieke, *Tetrahedron Lett.*, **29**, 4513 (1988).
21. D. E. Stack, B. T. Dawson, and R. D. Rieke, *J. Am. Chem. Soc.*, **114**, 5110 (1992).
22. For reviews of the reactions of organocopper reagents, see G. H. Posner, *Org. React.*, **19**, 1 (1972); G. H. Posner, *Org. React.*, **22**, 253 (1975); G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York, 1980; N. Krause and A. Gerold, *Angew. Chem. Int. Ed. Engl.*, **36**, 187 (1997).
23. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967).

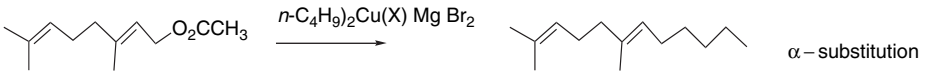
Secondary bromides and tosylates react with inversion of stereochemistry, as in the classical S_N2 substitution reaction.[24] Alkyl iodides, however, lead to racemized product. Aryl and alkenyl halides are reactive, even though the direct displacement mechanism is not feasible. For these halides, the overall mechanism probably consists of two steps: an *oxidative addition* to the metal, after which the oxidation state of the copper is +3, followed by combination of two of the groups from the copper. This process, which is very common for transition metal intermediates, is called *reductive elimination*. The $[R'_2Cu]^-$ species is linear and the oxidative addition takes place perpendicular to this moiety, generating a T-shaped structure. The reductive elimination occurs between adjacent R and R′ groups, accounting for the absence of R′ – R′ coupling product.



Allylic halides usually give both S_N2 and S_N2' products, although the mixed organocopper reagent RCu-BF_3 is reported to give mainly the S_N2' product.[25] Other leaving groups can also be used, including acetate and phosphate esters. Allylic acetates undergo displacement with an allylic shift (S_N2' mechanism).[26] The allylic substitution process may involve initial coordination with the double bond.[27]



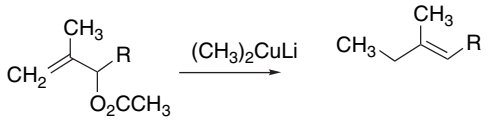
For substituted allylic systems, both α- and γ-substitution can occur. Reaction conditions can influence the α- versus γ-selectivity. For example, the reaction of geranyl acetate with several butylcopper reagents was explored. Essentially complete α- or γ-selectivity could be achieved by modification of conditions.[28] In ether both CuCN and CuI led to preferential γ-substitution, whereas α-substitution was favored for all anions in THF.



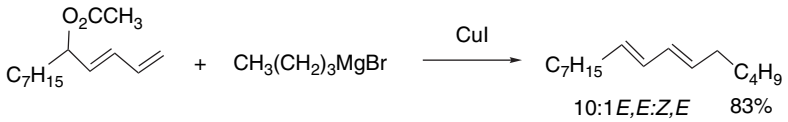
X	solvent	Ratio α:γ	solvent	Ratio α:γ
CN	ether	<1:99	THF	>99:1
Cl	ether	>99:1	THF	>99:1
Br	ether	>99:1	THF	>99:1
I	ether	6 :96	THF	96:4

24. C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973); B. H. Lipshutz and R. S. Wilhelm, *J. Am. Chem. Soc.*, **104**, 4696 (1982); E. Hebert, *Tetrahedron Lett.*, **23**, 415 (1982).
25. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977).
26. R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Am. Chem. Soc.*, **92**, 735 (1970); E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **92**, 737 (1970).
27. H. L. Goering and S. S. Kantner, *J. Org. Chem.*, **49**, 422 (1984).
28. E. S. M. Persson and J. E. Backvall, *Acta Chem. Scand.*, **49**, 899 (1995).

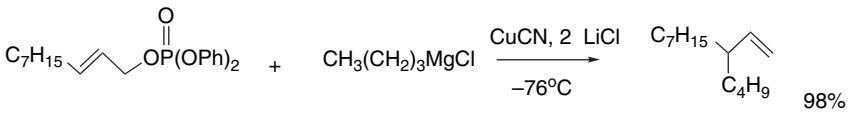
3-Acetoxy-2-methyl-1-alkenes react primarily at C(1), owing to steric factors.[29]



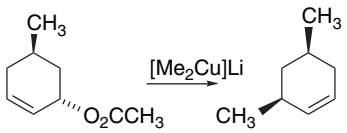
5-Acetoxy-1,3-alkadienes give mainly ϵ-alkylation with dialkylcopper-magnesium reagents.[30]



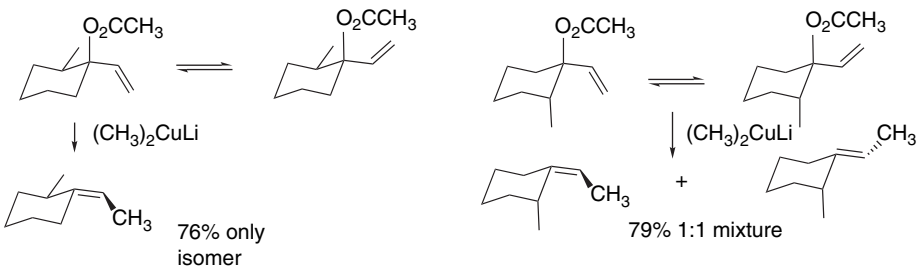
High γ-selectivity has been observed for allylic diphenyl phosphate esters.[29]



The reaction of cyclic allylic acetates shows a preference for *anti* stereochemistry.[31]

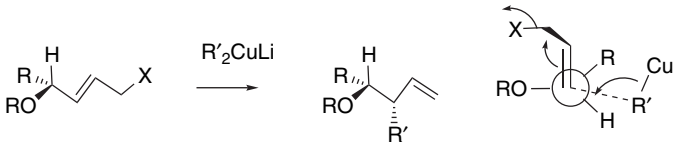


The preferred stereoelectronic arrangement is perpendicular alignment of the acetate with respect to the double bond. For example, the *cis* and *trans* isomers of 1-vinyl-2-methylcyclohexyl acetate show divergent stereochemical results. Only the exocyclic *E*-isomer is formed from the *cis* compound, whereas the *trans* compound gives a 1:1 mixture of the *E*- and *Z*-isomers. This is the result of a strongly preferred conformation for the *cis* isomer, as opposed to a mixture of conformations for the *trans* isomer.[32]

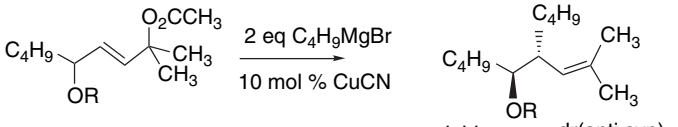


29. R. J. Anderson, C. A. Hendrick, and J. B. Siddall, *J. Am. Chem. Soc.*, **92**, 735 (1970).
30. N. Nakanishi, S. Matsubara, K. Utimoto, S. Kozima, and R. Yamaguchi, *J. Org. Chem.*, **56**, 3278 (1991).
31. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.*, **98**, 7854 (1976); H. L. Goering and C. C. Tseng, *J. Org. Chem.*, **48**, 3986 (1983).
32. P. Crabbe, J. M. Dollat, J. Gallina, J. L. Luche, E. Velarde, M. L. Maddox, and L. Tokes, *J. Chem. Soc., Perkin Trans. 1*, 730 (1978).

Excellent diastereoselectivity is observed for δ-oxy allylic acetates. The stereoselectivity is attributed to a Felkin-type TS with addition *anti* to the oxy substituent.

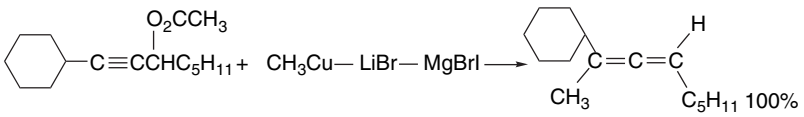


Similar results were obtained using *n*-BuMgBr-CuCN and tertiary allylic acetates, although under these conditions there is competition from S_N2' substitution with primary acetates.[33] The stereoselectivity is reversed with a hydroxy group, indicating a switch to a chelated TS.

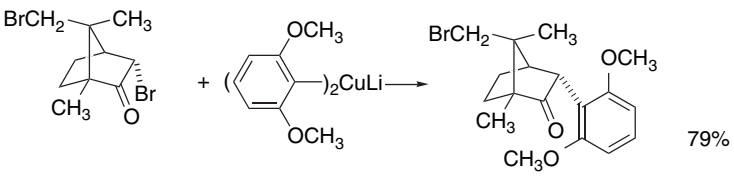


R	yield	dr(anti:syn)
$PhCH_2$	72	86:4
CH_3OCH_2	80	>98:2
TBDMS	89	90:10
H	84	7:93

Propargylic acetates, halides, and sulfonates usually react with a double-bond shift to give allenes.[34] Some direct substitution product can be formed as well. A high ratio of allenic product is usually found with CH_3Cu-LiBr-MgBrI, which is prepared by addition of methylmagnesium bromide to a 1:1 LiBr-CuI mixture.[35]



Halogens α to carbonyl groups can be successfully coupled using organocopper reagents. For example, 3,9-dibromocamphor is selectively arylated α to the carbonyl.

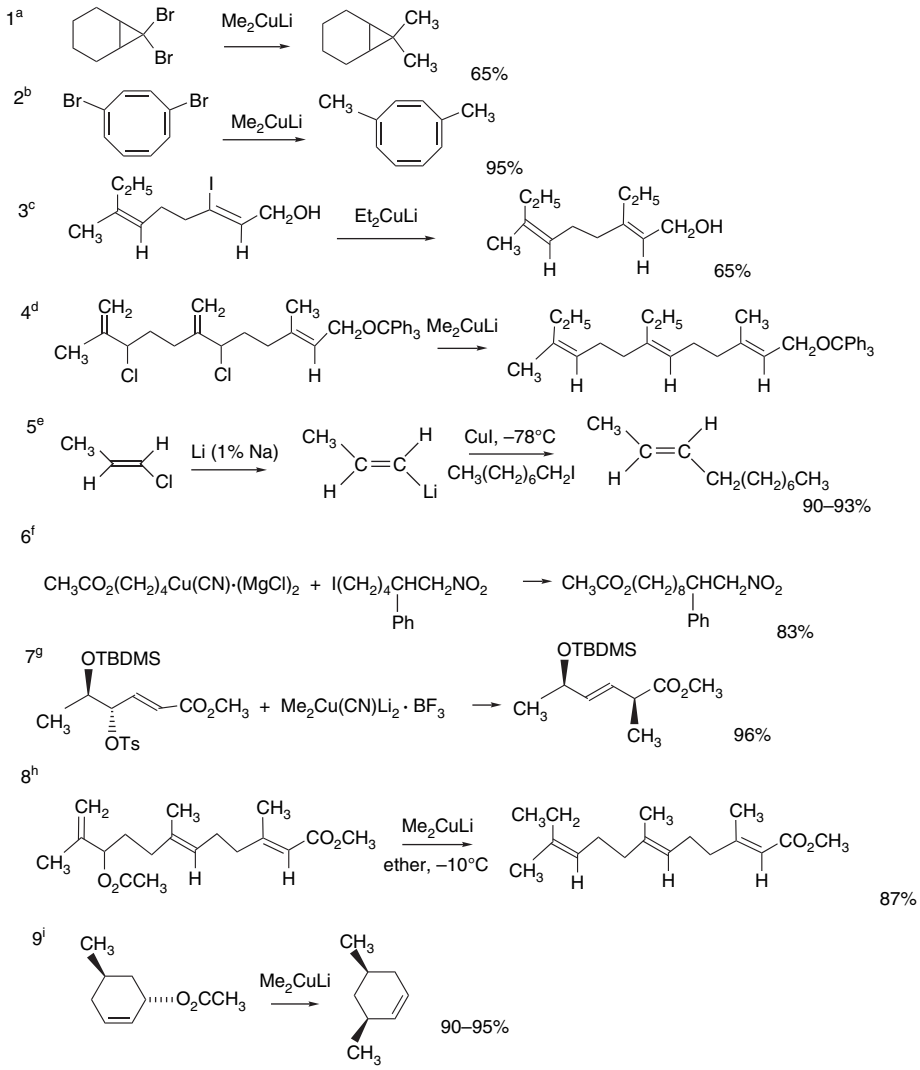


Ref. 36

Scheme 8.1 gives several examples of the use of coupling reactions of organocuprate reagents with halides and acetates. Entries 1 to 3 are examples of the

33. J. L. Belelie and J. M. Chong, *J. Org. Chem.*, **67**, 3000 (2002).
34. P. Rona and P. Crabbe, *J. Am. Chem. Soc.*, **90**, 4733 (1968); R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.*, **43**, 555 (1978); D. J. Pasto, S.-K. Chou, E. Fritzen, R. H. Shults, A. Waterhouse, and G. F. Hennion, *J. Org. Chem.*, **43**, 1389 (1978).
35. T. L. Macdonald, D. R. Reagan, and R. S. Brinkmeyer, *J. Org. Chem.*, **45**, 4740 (1980).
36. V. Vaillancourt and F. F. Albizatti, *J. Org. Chem.*, **51**, 3627 (1992).

Scheme 8.1. Nucleophilic Substitution Reactions of Organocopper Reagents

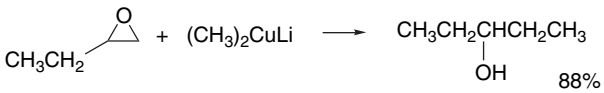


a. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967).
b. W. E. Konz, W. Hechtl, and R. Huisgen, *J. Am. Chem. Soc.*, **92**, 4104 (1970).
c. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).
d. E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **92**, 737 (1970).
e. G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, *Org. Synth.*, **55**, 103 (1976).
f. C. E. Tucker and P. Knochel, *J. Org. Chem.*, **58**, 4781 (1993).
g. T. Ibuka, T. Nakao, S. Nishii, and Y. Yamamoto, *J. Am. Chem. Soc.*, **108**, 7420 (1986).
h. R. L. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurfluh, *J. Am. Chem. Soc.*, **94**, 5379 (1972).
i. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.*, **98**, 7854 (1976).

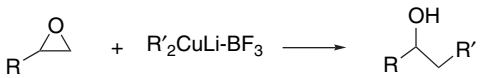
use of dialkylcuprates. In each case the halide is not susceptible to S_N2 substitution, but the oxidative addition mechanism is feasible. Entry 4 is an example of S_N2' substitution. This reaction, carried out simultaneously at two allylic chloride moieties, was used in the synthesis of the "juvenile hormone" of the moth *Cecropia*. Entry

5 illustrates the alkylation of a vinyl halide with retention of configuration at each stage of the reaction. Entry 6 is an example of a functionalized mixed magnesium-cyanocuprate reagent, which was prepared from an organozinc reagent by treatment with $(CH_3)_2CuCNMg_2Cl_2$. Entry 7 is an S_N2' displacement on a tosylate that occurs stereospecifically. Entries 8 and 9 are S_N2' displacements of allylic acetates.

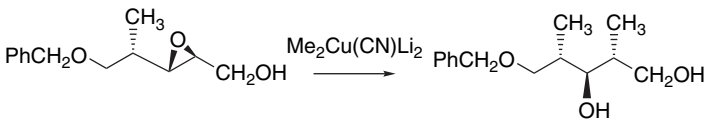
8.1.2.2. Opening of Epoxides. Organocopper reagents are excellent nucleophiles for opening epoxide rings. Saturated epoxides are opened in good yield by lithium dimethylcuprate.[37] The methyl group is introduced at the less hindered carbon of the epoxide ring.



Even mixed reagents with Lewis acids attack at the less-substituted position, indicating dominance of the nucleophilic bond making over the electrophilic component of ring opening.[38]

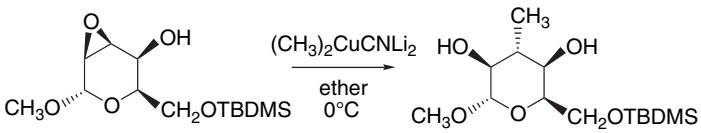


The predictable regio- and stereochemistry make these reactions valuable in establishing stereochemistry in both acyclic and cyclic systems.



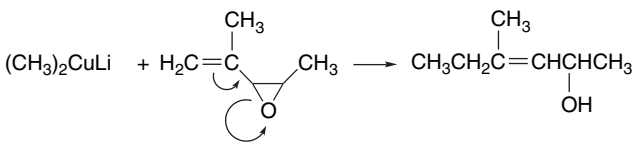
Ref. 39

With cyclohexene epoxides, the ring opening is *trans*-diaxial.



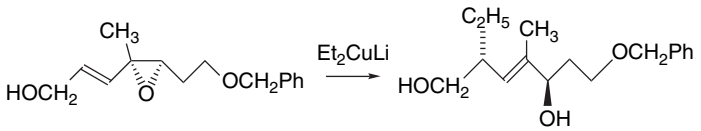
Ref. 40

Epoxides with alkenyl substituents undergo alkylation at the double bond with a double-bond shift accompanying ring opening, leading to formation of allylic alcohols.



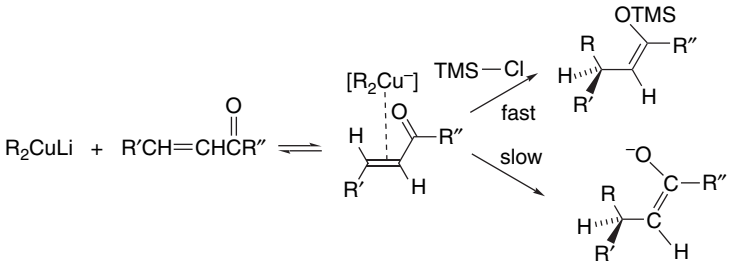
Ref. 41

37. C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973).
38. A. Alexis, D. Jachiet, and J. F. Normant, *Tetrahedron*, **42**, 5607 (1986).
39. A. B. Smith, III, B. A. Salvatore, K. G. Hull, and J. J.-W. Duan, *Tetrahedron Lett.*, **32**, 4859 (1991).
40. R. G. Linde, M. Egbertson, R. S. Coleman, A. B. Jones, and S. J. Danishefsky, *J. Org. Chem.*, **55**, 2771 (1990).
41. R. J. Anderson, *J. Am. Chem. Soc.*, **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *J. Am. Chem. Soc.*, **92**, 4979 (1970); J. A. Marshall, *Chem. Rev.*, **89**, 1503 (1989).

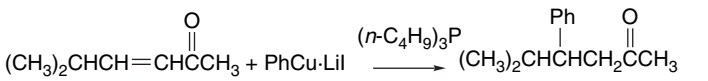


Ref. 42

8.1.2.3. Conjugate Addition Reactions. All of the types of mixed cuprate reagents described in Scheme 8.1 react by conjugate addition with enones. A number of improvements in methodology for carrying out the conjugate addition reactions have been introduced. The addition is accelerated by trimethylsilyl chloride alone or in combination with HMPA.[43] Under these conditions the initial product is a silyl enol ether. The mechanism of the catalysis remains uncertain, but it appears that the silylating reagent intercepts an intermediate and promotes carbon-carbon bond formation, as well as trapping the product by O-silylation.[44]



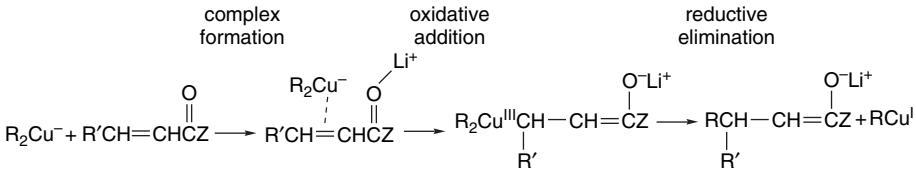
This technique also greatly improves yields of conjugate addition of cuprates to α, β-unsaturated esters and amides.[45] Trimethylsilyl cyanide also accelerates conjugate addition.[46] Another useful reagent is prepared from a 1:1:1 ratio of organolithium reagent, CuCN, and BF_3-$O(C_2H_5)_2$.[47] The BF_3 appears to interact with the cyanocuprate reagent, giving a more reactive species.[48] The efficiency of the conjugate addition reaction is also improved by the inclusion of trialkylphosphines.[49] Even organocopper reagents prepared from a 1:1 ratio of organolithium compounds are reactive in the presence of phosphines.[50]



84%

42. J. A. Marshall, T. D. Crute, III, and J. D. Hsi, *J. Org. Chem.*, **57**, 115 (1992).
43. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6019 (1985); E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986); S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **45**, 449 (1989); C. R. Johnson and T. J. Marren, *Tetrahedron Lett.*, **28**, 27 (1987); S. H. Bertz and G. Dabbagh, *Tetrahedron*, **45**, 425 (1989); S. H. Bertz and R. A. Smith, *Tetrahedron*, **46**, 4091 (1990); K. Yamamoto, H. Ogura, J. Jukuta, H. Inoue, K. Hamada, Y. Sugiyama, and S. Yamada, *J. Org. Chem.*, **63**, 4449 (1998); M. Kanai, Y. Nakagawa, and K. Tomioka, *Tetrahedron*, **55**, 3831 (1999).
44. M. Eriksson, A. Johansson, M. Nilsson, and T. Olsson, *J. Am. Chem. Soc.*, **118**, 10904 (1996).
45. A. Alexakis, J. Berlan, and Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986).
46. B. H. Lipshutz and B. James, *Tetrahedron Lett.*, **34**, 6689 (1993).
47. T. Ibuka, N. Akimoto, M. Tanaka, S. Nishii, and Y. Yamamoto, *J. Org. Chem.*, **54**, 4055 (1989).
48. B. H. Lipshutz, E. L. Ellsworth, and T. J. Siahaan, *J. Am. Chem. Soc.*, **111**, 1351 (1989); B. H. Lipshutz, E. L. Ellsworth, and S. H. Dimock, *J. Am. Chem. Soc.*, **112**, 5869 (1990).
49. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, 1247 (1980).
50. T. Kawabata, P. A. Grieco, H.-L. Sham, H. Kim, J. Y. Jaw, and S. Tu, *J. Org. Chem.*, **52**, 3346 (1987).

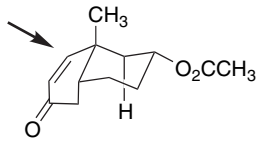
The mechanism of conjugate addition reactions probably involves an initial complex between the cuprate and enone.[51] The key intermediate for formation of the new carbon-carbon bond is an adduct formed between the enone and the organocopper reagent. The adduct is formulated as a Cu(III) species, which then undergoes reductive elimination. The lithium ion also plays a key role, presumably by Lewis acid coordination at the carbonyl oxygen.[52] Solvent molecules also affect the reactivity of the complex.[53] The mechanism can be outlined as occurring in three steps.



Isotope effects indicate that the collapse of the adduct by reductive elimination is the rate-determining step.[54] Theoretical treatments of the mechanism suggest similar intermediates. (See Section 8.1.2.7 for further discussion of the computational results.)[55]

There is a correlation between the reduction potential of the carbonyl compounds and the ease of reaction with cuprate reagents.[56] The more easily it is reduced, the more reactive the compound toward cuprate reagents. Compounds such as α, β-unsaturated esters and nitriles, which are not as easily reduced as the corresponding ketones, do not react as readily with dialkylcuprates, even though they are good acceptors in classical Michael reactions with carbanions. α, β-Unsaturated esters are marginal in terms of reactivity toward standard dialkylcuprate reagents, and β-substitution retards reactivity. The RCu-BF_3 reagent combination is more reactive toward conjugated esters and nitriles,[57] and additions to hindered α, β-unsaturated ketones are accelerated by BF_3.[58]

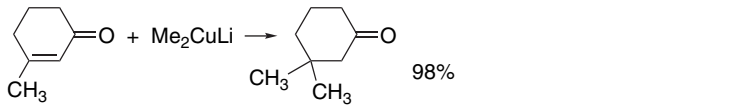
There have been many applications of conjugate additions in synthesis. Some representative reactions are shown in Scheme 8.2. Entries 1 and 2 are examples of addition of lithium dimethylcuprate to cyclic enones. The stereoselectivity exhibited in Entry 2 is the result of both steric and stereoelectronic effects that favor the approach *syn* to the methyl substituent. In particular, the axial hydrogen at C(6) hinders the α approach.



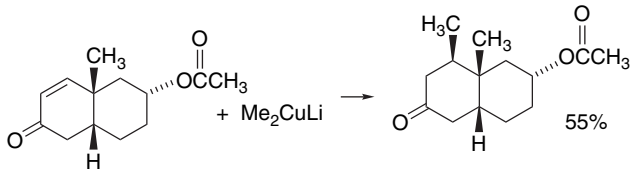
51. S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **103**, 141 (1981); E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985); E. J. Corey and F. J. Hannon, *Tetrahedron Lett.*, **31**, 1393 (1990).
52. H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976); H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770, 2778 (1975); H. O. House and K. A. J. Snoble, *J. Org. Chem.*, **41**, 3076 (1976); S. H. Bertz, G. Dabbagh, J. M. Cook, and V. Honkan, *J. Org. Chem.*, **49**, 1739 (1984).
53. C. J. Kingsbury and R. A. J. Smith, *J. Org. Chem.*, **62**, 4629, 7637 (1997).
54. D. E. Frantz, D. A. Singleton, and J. P. Snyder, *J. Am. Chem. Soc.*, **119**, 3383 (1997).
55. E. Nakamura, S. Mori, and K. Morukuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997); S. Mori and E. Nakamura, *Chem. Eur. J.*, **5**, 1534 (1999).
56. H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); B. H. Lipshutz, R. S. Wilhelm, S. T. Nugent, R. D. Little, and M. M. Baizer, *J. Org. Chem.*, **48**, 3306 (1983).
57. Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978); Y. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **25**, 947 (1986).
58. A. B. Smith, III, and P. J. Jerris, *J. Am. Chem. Soc.*, **103**, 194 (1981).

Scheme 8.2. Conjugate Addition Reactions of Organocopper Reagents

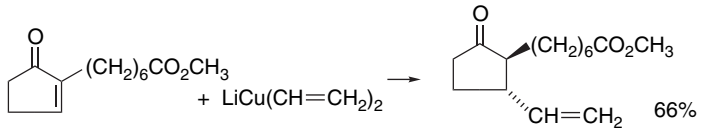
1[a]



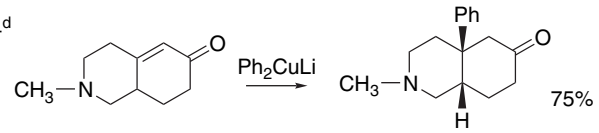
2[b]



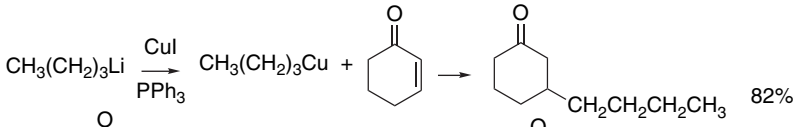
3[c]



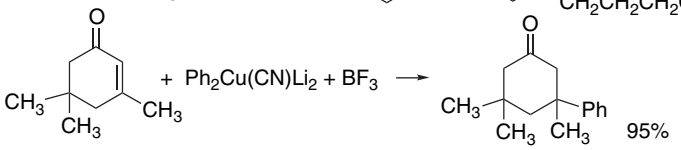
4[d]



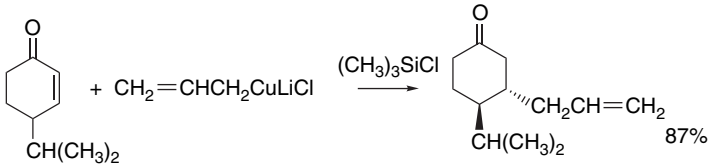
5[e]



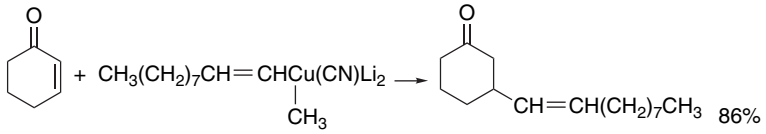
6[f]



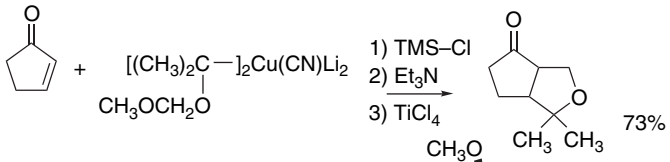
7[g]



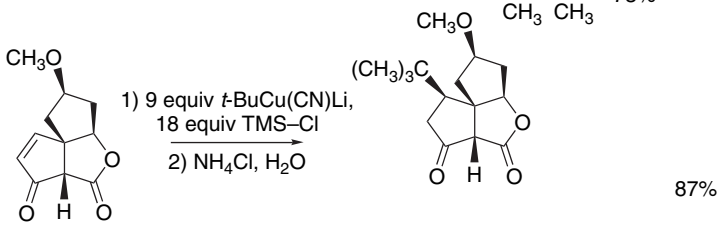
8[h]



9[i]



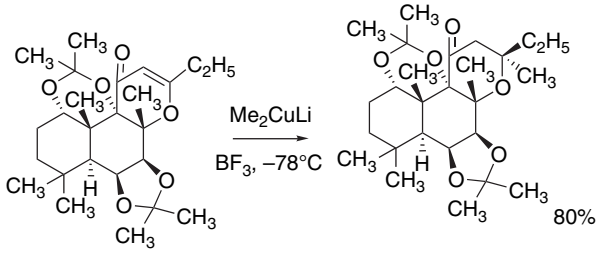
10[j]



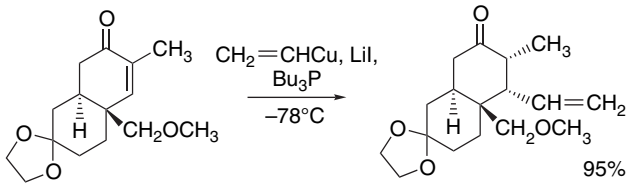
(*Continued*)

Scheme 8.2. (*Continued*)

11[k]

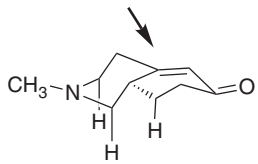


12[l]



a. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
b. J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971).
c. F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.*, **94**, 7823 (1972).
d. N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.*, **39**, 1118 (1974).
e. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980).
f. B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, and S. L. Nguyen, *Tetrahedron Lett.* **25**, 5959 (1984).
g. B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, and R. A. J. Smith, *J. Am. Chem. Soc.*, **112**, 4404 (1990).
h. B. H. Lipshutz and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 7440 (1990).
i. R. J. Linderman and A. Godfrey, *J. Am. Chem. Soc.*, **110**, 6249 (1988).
j. E. J. Corey and K. Kamiyama, *Tetrahedron Lett.*, **31**, 3995 (1990).
k. B. Delpech and R. Lett, *Tetrahedron Lett.*, **28**, 4061 (1987).
l. T. Kawabata, P. Grieco, H. L. Sham, H. Kim, J. Y. Jaw, and S. Tu, *J. Org. Chem.*, **52**, 3346 (1987).

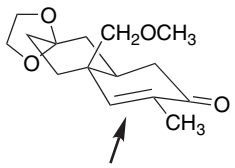
In Entry 3, the *trans* stereochemistry arises at the stage of the protonation of the enolate. Entry 4 gives rise to a *cis* ring juncture, as does the corresponding carbocyclic compound.[59] Models suggest that this is the result of a steric differentiation arising from the axial hydrogens on the α-face of the molecule.



Entries 5 to 9 illustrate some of the modified reagents and catalytic procedures. Entry 5 uses a phosphine-stabilized reagent, whereas Entry 6 includes BF_3. Entry 7 involves use of TMS-Cl. Entries 8 and 9 involve cyanocuprates. In Entry 9, the furan ring is closed by a Mukaiyama-aldol reaction subsequent to the conjugate addition (Section 2.1.4).

59. S. M. McElvain and D. C. Remy, *J. Am. Chem. Soc.*, **82**, 3960 (1960).

Entries 10 to 12 illustrate the use of organocopper conjugate addition in the synthesis of relatively complex molecules. The installation of a *t*-butyl group adjacent to a quaternary carbon in Entry 10 requires somewhat forcing conditions, but proceeds in good yield. In Entry 11, the addition is to a vinylogous ester, illustrating the ability of the BF_3-modified reagents to react with less electrophilic systems. Steric shielding by the axial methoxymethyl substituent accounts for the stereoselectivity observed in Entry 12.

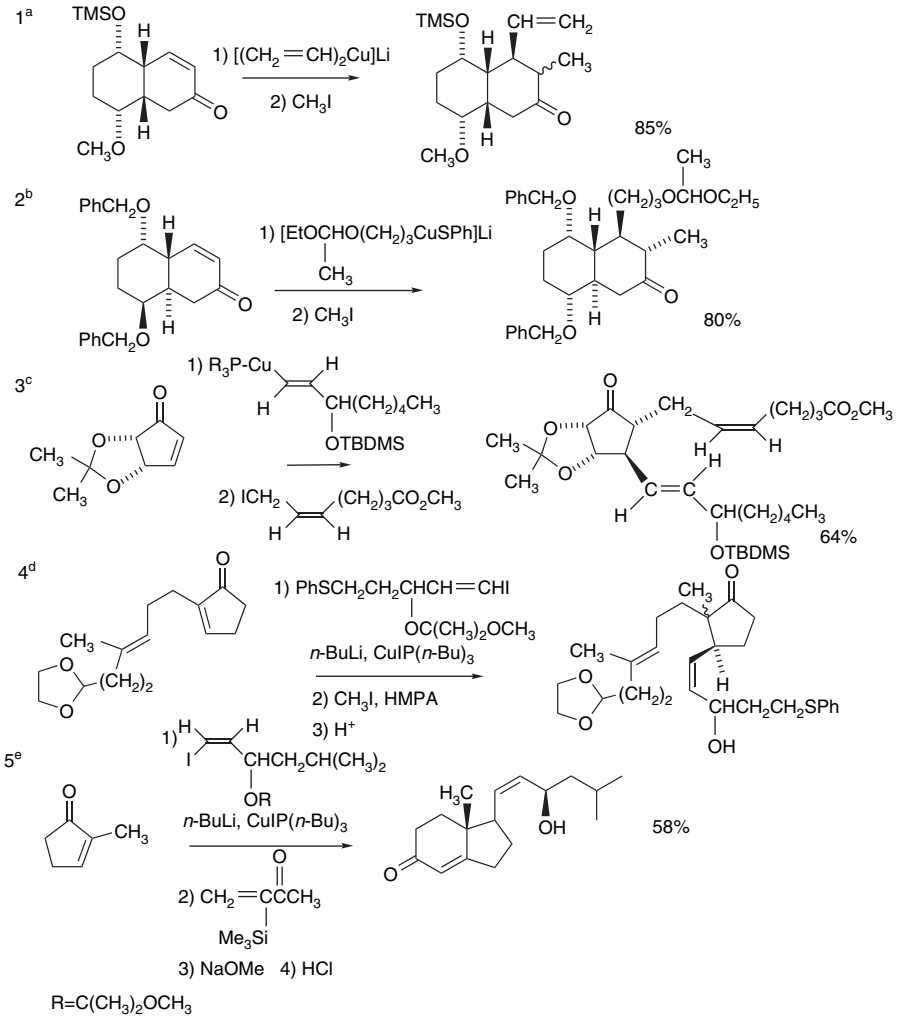


Prior to protonolysis, the products of conjugate addition are enolates and, therefore, potential nucleophiles. A useful extension of the conjugate addition method is to combine it with an alkylation step that adds a substituent at the α-position.[60] Several examples of this *tandem conjugate addition-alkylation* method are given in Scheme 8.3. In Entry 1 the characteristic β-attack on the *cis* decalone ring is observed (see Scheme 8.2, Entry 2). The alkylation gives a β : α ratio of 60:40. In Entry 2, the methylation occurs *anti* to the 4-substituent, presumably because of steric factors. These reactions are part of the synthesis of the cholesterol-lowering drug compactin. Entry 3 illustrates a pattern that has been extensively developed for the synthesis of prostaglandins. In this case, the dioxolane ring controls the stereoselectivity of the conjugate addition step and steric factors lead to *anti* alkylation and formation the *trans* product. Entry 4 is a part of a steroid synthesis. This reaction shows a 4:1 preference for methylation from the β-face (*syn* to the substituent). In Entry 5, the conjugate addition is followed by a Robinson annulation. The product provides a C,D-ring segment of the steroid skeleton.

8.1.2.4. Copper-Catalyzed Reactions. The cuprate reagents that were discussed in the preceding sections are normally prepared by reaction of an organolithium reagent with a copper(I) salt, using a 2:1 ratio of lithium reagent to copper(I). There are also valuable synthetic procedures that involve organocopper intermediates that are generated in the reaction system by use of only a catalytic amount of a copper salt.[61] Coupling of Grignard reagents and primary halides and tosylates can be catalyzed by Li_2CuCl_4.[62] This method was used, for example, to synthesize long-chain carboxylic acids in more than 90% yield.[63]

60. For a review of such reactions, see R. J. K. Taylor, *Synthesis*, 364 (1985).
61. For a review, see E. Erdik, *Tetrahedron*, **40**, 641 (1984).
62. M. Tamura and J. Kochi, *Synthesis*, 303 (1971); T. A. Baer and R. L. Carney, *Tetrahedron Lett.*, 4697 (1976).
63. S. B. Mirviss, *J. Org. Chem.*, **54**, 1948 (1989); see also M. R. Kling, C. J. Eaton, and A. Poulos, *J. Chem. Soc., Perkin Trans. 1*, 1183 (1993).

Scheme 8.3. Tandem Conjugate Addition-Alkylation Using Organocopper Reagents



a. N. N. Girotra, R. A. Reamer, and N. L. Wendler, *Tetrahedron Lett.*, **25**, 5371 (1984).
b. N.-Y. Wang, C.-T. Hsu, and C. J. Sih, *J. Am. Chem. Soc.*, **103**, 6538 (1981).
c. C. R. Johnson and T. D. Penning, *J. Am. Chem. Soc.*, **110**, 4726 (1988).
d. T. Takahashi, K. Shimizu, T. Doi, and J. Tsuji, *J. Am. Chem. Soc.*, **110**, 2674 (1988).
e. T. Takahashi, H. Okumoto, J. Tsuji, and N. Harada, *J. Org. Chem.*, **49**, 948 (1984).

$$CH_2{=}CH(CH_2)_9MgCl + Br(CH_2)_{11}CO_2MgBr \xrightarrow[2)\ H^+]{1)\ Li_2CuCl_4} CH_2{=}CH(CH_2)_{20}CO_2H$$

Another excellent catalyst for coupling is a mixture of CuBr-$S(CH_3)_2$, LiBr, and LiSPh. This catalyst can effect coupling of a wide variety of Grignard reagents with tosylates and mesylates and is superior to Li_2CuCl_4 in coupling with secondary sulfonates.[64]

64. D. H. Burns, J. D. Miller, H.-K. Chan, and M. O. Delaney, *J. Am. Chem. Soc.*, **119**, 2125 (1997).

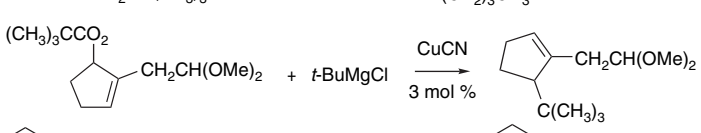
Scheme 8.4. Copper-Catalyzed Reactions of Grignard Reagents

A. Alkylations

1[a] $n\text{-}C_8H_{17}Br + CH_2{=}CHC(MgCl){=}CH_2 \xrightarrow[2\ \text{mol}\ \%]{Li_2CuCl_4} CH_2{=}CHC((CH_2)_7CH_3){=}CH_2$ 80%

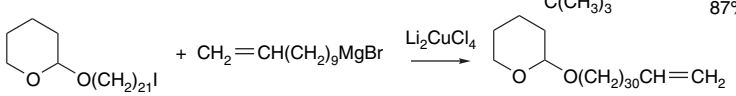
2[b] $PhCH{=}CHCH(O_2CC(CH_3)_3)CH_3 + n\text{-}C_4H_9MgBr \xrightarrow[1\ \text{mol}\ \%]{CuCN} PhCHCH(CH_2)_3CH_3{=}CHCH_3$ 95%

3[c]



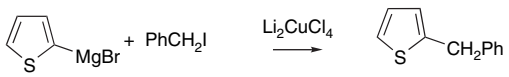
87%

4[d]



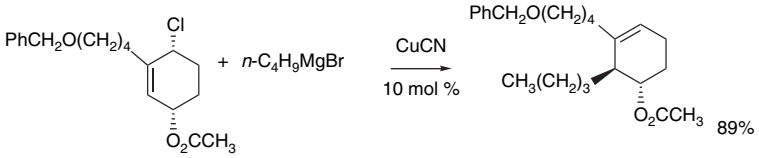
70%

5[e]



6[f] $CH_3(CH_2)_9CH{=}CH(CH_2)_3I + (CH_3)_2CHMgBr \xrightarrow[10\ \text{mol}\ \%]{Li_2CuCl_4} CH_3(CH_2)_9CH{=}CH(CH_2)_3CH(CH_3)_2$

7[g]



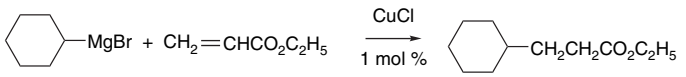
89%

8[h] $n\text{-}C_4H_9MgCl + \triangle O \xrightarrow[10\ \text{mol}\ \%]{CuBr} CH_3(CH_2)_5OH$ 88%

B. Conjugate additions

9[i] $(CH_3)_2C{=}C(CO_2CH_3)_2 + CH_3MgBr \xrightarrow[2\ \text{mol}\ \%]{CuCl} \xrightarrow{H_2O} (CH_3)_3CCH(CO_2CH_3)_2$ 84–94%

10[j]

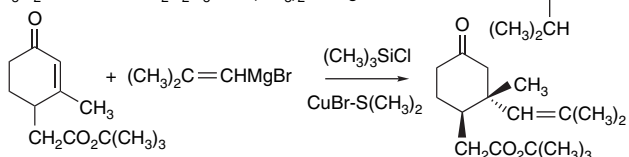


68%

11[k] $CH_3CH{=}CHCO_2CH(CH_3)CH_2CH_3 + CH_3(CH_2)_3MgBr \xrightarrow[1.4\ \text{mol}\ \%]{CuCl} CH_3(CH_2)_3CH(CH_3)CH_2CO_2CH(CH_3)CH_2CH_3$ 51%

12[l] $C_2H_5O_2CCH{=}CHCO_2C_2H_5 + (CH_3)_2CHMgBr \xrightarrow{CuCl} H_5C_2O_2CCH((CH_3)_2CH)CH_2CO_2C_2H_5$ 81%

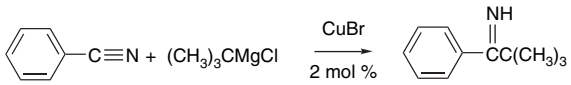
13[m]



78%

14[n] $CH_3O_2C(CH_2)_4COCl + CH_3(CH_2)_3MgBr \xrightarrow{CuI,\ 5\ \text{mol}\ \%} CH_3O_2C(CH_2)_4\overset{O}{\overset{\|}{C}}(CH_2)_3CH_3$ 85%

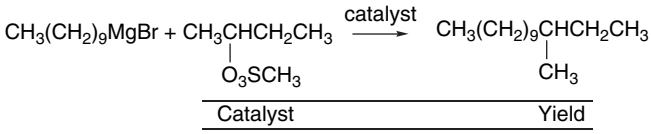
15[o]



95%

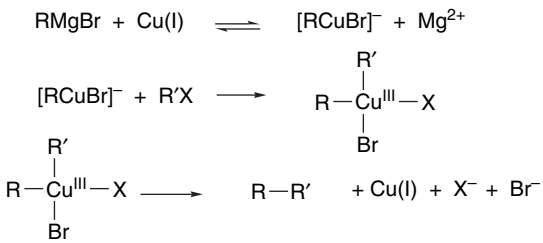
(*Continued*)

a. S. Nunomoto, Y. Kawakami, and Y. Yamashita, *J. Org. Chem.*, **48**, 1912 (1983).
b. C. C. Tseng, S. D. Paisley, and H. L. Goering, *J. Org. Chem.*, **51**, 2884 (1986).
c. E. J. Corey and A. V. Gavai, *Tetrahedron Lett.*, **29**, 3201 (1988).
d. U. F. Heiser and B. Dobner, *J. Chem. Soc, Perkin Trans. 1*, 809 (1997).
e. Y.-T. Ku, R. R. Patel, and D. P. Sawick, *Tetrahedron Lett.*, **37**, 1949 (1996).
f. E. Keinan, S. C. Sinha, A. Sinha-Bagchi, Z.-M. Wang, X.-L. Zhang, and K. B. Sharpless, *Tetrahedron Lett.*, **33**, 6411 (1992).
g. D. Tanner, M. Sellen, and J. Backvall, *J. Org. Chem.*, **54**, 3374 (1989).
h. G. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1503 (1979).
i. E. L. Eliel, R. O. Hutchins, and M. Knoeber, *Org. Synth.*, **50**, 38 (1971).
j. S.-H. Liu, *J. Org. Chem.*, **42**, 3209 (1977).
k. T. Kindt-Larsen, V. Bitsch, I. G. K. Andersen, A. Jart, and J. Munch-Petersen, *Acta Chem. Scand.*, **17**, 1426 (1963).
l. V. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.*, **16**, 947 (1962).
m. Y. Horiguchi, E. Nakamura, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 6257 (1989).
n. T. Fujisawa and T. Sato, *Org. Synth.*, **66**, 116 (1988).
o. F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, **52**, 3901 (1987).



Catalyst	Yield
Li_2CuCl_4	17%
CuBr/HMPA	30%
CuBr–$S(CH_3)_2$, LiBr, LiSPH	62%

These reactions presumably involve fast metal-metal exchange (see Section 7.1.2.4) generating a more nucleophilic organocopper intermediate. The reductive elimination regenerates an active Cu(I) species.



Other examples of catalytic substitutions can be found in Section A of Scheme 8.4.

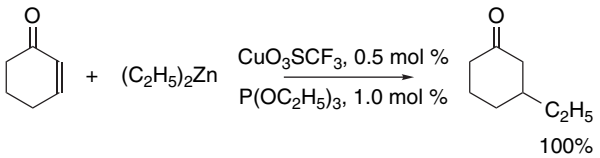
Conjugate addition to α, β-unsaturated esters can often be effected by copper-catalyzed reaction with a Grignard reagent. Other reactions, such as epoxide ring opening, can also be carried out under catalytic conditions. Some examples of catalyzed additions and alkylations are given in Scheme 8.4. These reactions are similar to those carried out with the stoichiometric reagents and presumably involve catalytic cycles that regenerate the active organocopper species. A remarkable aspect of these reactions is that the organocopper cycle must be fast compared to normal organomagnesium reactions, since in many cases there is a potential for competing reactions. The alkylations include several substitutions on allylic systems (Entries 2, 3, and 7). Entry 8 shows that the catalytic process is also applicable to epoxide ring opening. The latter example is a case in which an allylic chloride is displaced in preference to an acetate. The conditions have been observed in related systems to be highly regio- (S_N2') and stereo- (*anti*) specific.[65] The conjugate additions in Entries 9 to 12 show

[65] J.-E. Backvall, *Bull. Soc. Chim. Fr.*, 665 (1987).

that esters and enones (Entry 13) are reactive to the catalytic processes involving Grignard reagents. Entries 14 and 15 illustrate ketone syntheses from acyl chlorides and nitriles, respectively.

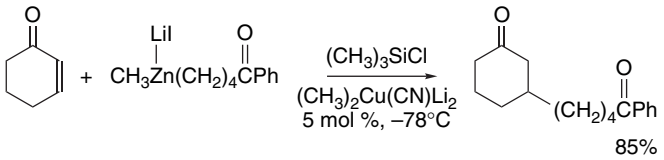
8.1.2.5. Mixed Organocopper-Zinc Reagents. The preparation of organozinc reagents is discussed in Section 7.3.1. Many of these reagents can be converted to mixed copper-zinc organometallics that have useful synthetic applications.[66] A virtue of these reagents is that they can contain a number of functional groups that are not compatible with the organolithium route to cuprate reagents. The mixed copper-zinc reagents are not very basic and can be prepared and allowed to react in the presence of weakly acidic functional groups that would protonate more basic organometallic reagents; for example, reagents containing secondary amide or indole groups can be prepared.[67] They are good nucleophiles and are especially useful in conjugate addition. Mixed zinc reagents can also be prepared by addition of CuCN to organozinc iodides.[68] They are analogous to the cyanocuprates prepared from alkyllithium and CuCN, but with Zn^{2+} in place of Li^{+}, and react with enones, nitroalkenes, and allylic halides.[69]

In addition to the use of stoichiometric amounts of cuprate or cyanocuprate reagents for conjugate addition, there are also procedures that require only a catalytic amount of copper and use organozinc reagents as the stoichiometric reagent.[70] Simple organozinc reagents, such as diethylzinc, undergo conjugate addition with 0.5 mol % CuO_3SCF_3 in the presence of a phoshine or phosphite.



Ref. 71

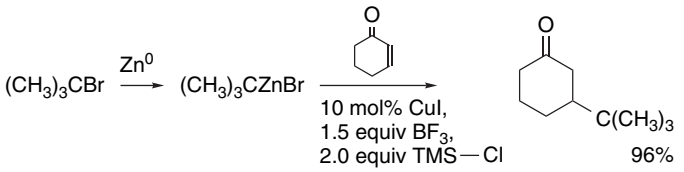
In the presence of LiI, TMS-Cl, and a catalytic amount of $(CH_3)_2CuCNLi_2$, conjugate addition of functionalized organozinc reagents occurs in good yield.



Ref. 72

Either CuI or CuCN (10 mol %) in conjunction with BF_3 and TMS-Cl catalyze addition of alkylzinc bromides to enones.

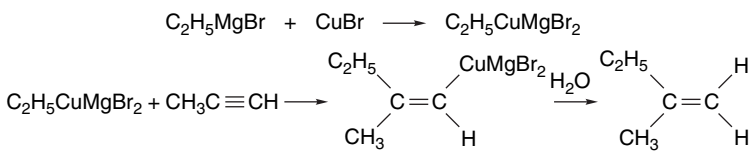
66. P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993); P. Knochel, *Synlett*, 393 (1995).
67. H. P. Knoess, M. T. Furlong, M. J. Rozema, and P. Knochel, *J. Org. Chem.*, **56**, 5974 (1991).
68. P. Knochel, J. J. Almena Perea, and P. Jones, *Tetrahedron*, **54**, 8275 (1998).
69. P. Knochel, M. C. P. Yeh, S. C. Berk, and J. Talbert, *J. Org. Chem.*, **53**, 2390 (1988); M. C. P. Yeh and P. Knochel, *Tetrahedron Lett.*, **29**, 2395 (1988); S. C. Berk, P. Knochel, and M. C. P. Yeh, *J. Org. Chem.*, **53**, 5789 (1988); H. G. Chou and P. Knochel, *J. Org. Chem.*, **55**, 4791 (1990).
70. B. H. Lipshutz, *Acc. Chem. Res.*, **30**, 277 (1997).
71. A. Alexakis, J. Vastra, and P. Mageney, *Tetrahedron Lett.*, **38**, 7745 (1997).
72. B. H. Lipshutz, M. R. Wood, and R. J. Tirado, *J. Am. Chem. Soc.*, **117**, 6126 (1995).



Ref. 73

Several examples of mixed organocopper-zinc reagents in synthesis are given in Scheme 8.5. Entries 1 and 2 show the use of functionalized reagents prepared from the corresponding iodides by reaction with zinc, followed by CuCN-LiCl. Entry 3 uses a similar reagent to prepare a prostaglandin precursor. Note the slightly different pattern from Entry 3 in Scheme 8.4; in the present case the addition is to an exocyclic methylene group rather than to an endocyclic cyclopentenone. Entry 4 involves generation of a mixed reagent directly from an iodide, followed by conjugate addition to methyl acrylate. Entries 5 and 6 are substitutions on allylic systems. The arylzinc reagent used in Entry 5 was prepared from 2-nitrophenyllithium, which was prepared by halogen-metal exchange, as discussed on p. 632. Entry 7 is a stereospecific S_N2' displacement on an allylic methanesulfonate. Entry 8 is a substitution on a β-sulfonyloxy enone. The zinc reagent is mixed dialkyl zinc. This reaction may proceed by conjugate addition to give the enolate, followed by elimination of the triflate group. Entry 9 shows the use of a tertiary mixed zinc reagent in the preparation of a ketone.

8.1.2.6. Carbometallation with Mixed Organocopper Compounds. Mixed copper-magnesium reagents analogous to the lithium cuprates can be prepared.[74] The precise structural nature of these compounds, often called *Normant reagents*, has not been determined. Individual species with differing Mg:Cu ratios may be in equilibrium.[75] These reagents undergo addition to terminal acetylenes to generate alkenylcopper reagents. The addition is stereospecifically *syn*.



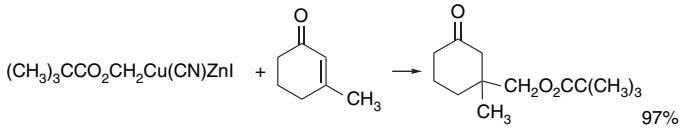
The alkenylcopper adducts can be worked up by protonolysis, or they can be subjected to further elaboration by alkylation or electrophilic substitution.

Mixed copper-zinc reagents also react with alkynes to give alkenylcopper species that can undergo subsequent electrophilic substitution.

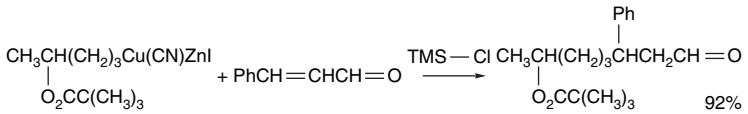
73. R. D. Rieke, M. V. Hanson, J. D. Brown, and Q. J. Niu, *J. Org. Chem.*, **61**, 2726 (1996).
74. J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2583 (1971); J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villieras, *Bull. Soc. Chim. Fr.*, 1656 (1974); H. Westmijze, J. Meier, H. J. T. Bos, and P. Vermeer, *Recl. Trav. Chim. Pays Bas*, **95**, 299, 304 (1976).
75. E. C. Ashby, R. S. Smith, and A. B. Goel, *J. Org. Chem.*, **46**, 5133 (1981); E. C. Ashby and A. B. Goel, *J. Org. Chem.*, **48**, 2125 (1983).

Scheme 8.5. Conjugate Addition and Substitution Reactions of Mixed Organocopper-Zinc Reagents

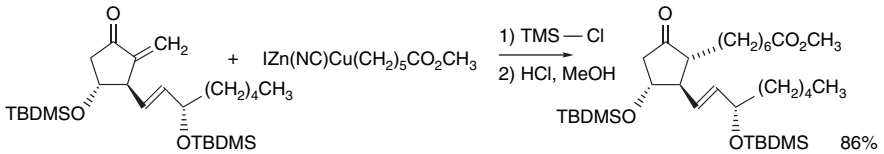
1[a]



2[b]

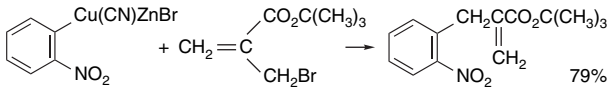


3[c]

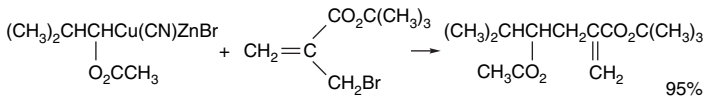


4[d]

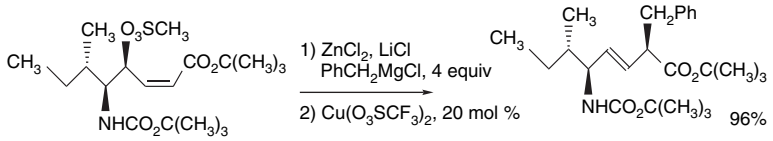
5[e]



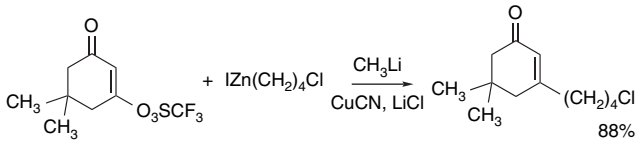
6[a]



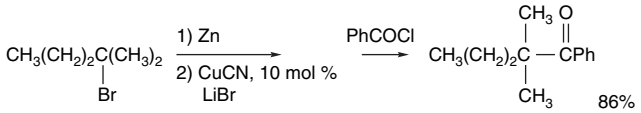
7[f]



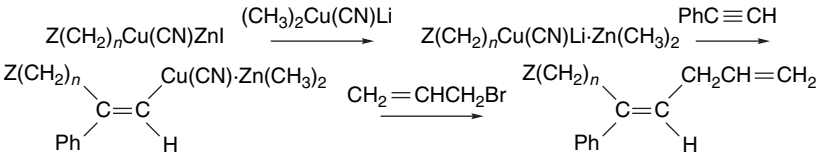
8[g]



9[h]

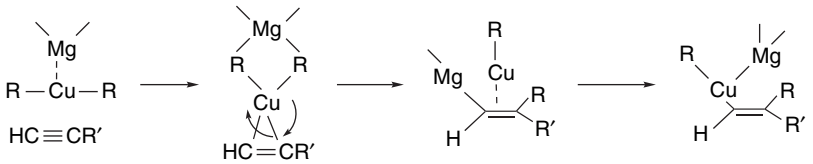


a. P. Knochel, T. S. Chou, C. Jubert, and D. Rajagopal, *J. Org. Chem.*, **58**, 588 (1993).
b. M. C. P. Yeh, P. Knochel, and L. E. Santa, *Tetrahedron*, **29**, 3887 (1988).
c. H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **31**, 4481 (1990).
d. J. P. Sestalo, J. L. Mascarenas, L. Castedo, and A. Mourina, *J. Org. Chem.*, **58**, 118 (1993).
e. C. Tucker, T. N. Majid, and P. Knochel, *J. Am. Chem. Soc.*, **114**, 3983 (1992).
f. N. Fujii, K. Nakai, H. Habashita, H. Yoshizawa, T. Ibuka, F. Garrido, A. Mann, Y. Chounann, and Y. Yamamoto, *Tetrahedron Lett.*, **34**, 4227 (1993).
g. B. H. Lipshutz and R. W. Vivian, *Tetrahedron Lett.*, **40**, 2871 (1999).
h. R. D. Rieke, M. V. Hanson, and Q. J. Niu, *J. Org. Chem.*, **61**, 2726 (1996).



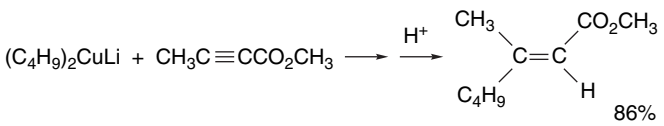
Ref. 76

The mechanism of carbometallation has been explored computationally.[77] The reaction consists of an oxidative addition to the triple bond forming a cyclic Cu(III) intermediate. The rate-determining step is reductive elimination to form a vinyl magnesium (or zinc) reagent, which then undergoes transmetallation to the alkenyl-copper product.



Some additional examples are given in Scheme 8.6. The electrophiles that have been used successfully include iodine (Entries 2 and 3) and cyanogen chloride (Entry 4). The adducts can undergo conjugate addition (Entry 5), alkylation (Entry 6), or epoxide ring opening (Entries 7 and 8). The latter reaction is an early step of a synthesis of epothilone B.

The lithium cuprate reagents are not as reactive toward terminal alkynes as mixed magnesium or zinc reagents. The stronger Lewis acid character of Mg^{2+}, as compared to Li^{+}, is believed to be the reason for the enhanced reactivity of the magnesium reagents. However, lithium dialkylcuprates do react with conjugated acetylenic esters, with *syn* addition being kinetically preferred.[78]

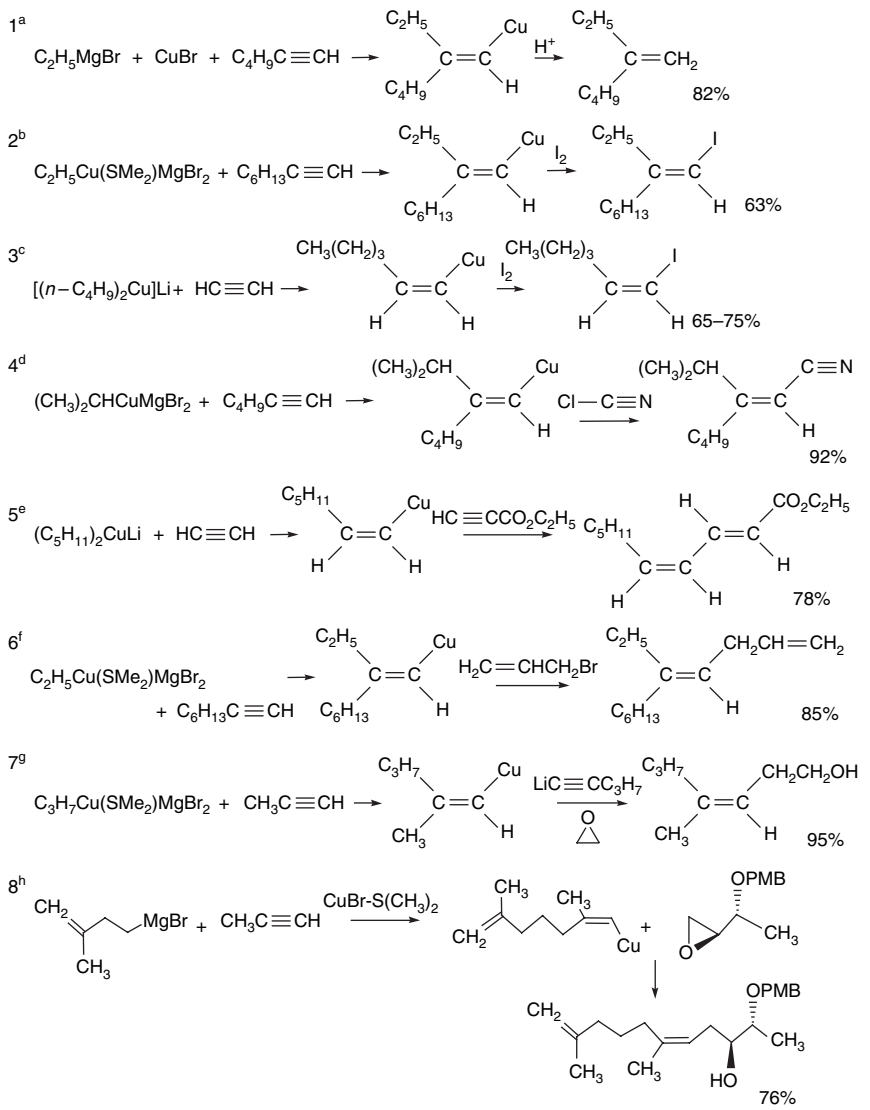


The intermediate adduct can be substituted at the α-position by a variety of electrophiles, including acyl chlorides, epoxides, aldehydes, and ketones.[79]

8.1.2.7. Mechanistic Interpretation of the Reactivity of Organocopper Compounds. The coupling with halides and tosylates, epoxide ring openings, and conjugate additions discussed in the preceding sections illustrate the nucleophilicity of the organocopper reagents. The nucleophilicity is associated with relatively high-energy filled *d* orbitals that are present in Cu(I), which has a $3d^{10}$ electronic configuration. The role of

76. S. A. Rao and P. Knochel, *J. Am. Chem. Soc.*, **113**, 5735 (1991).
77. S. Mori, A. Hirai, M. Nakamura, and E. Nakamura, *Tetrahedron*, **56**, 2805 (2000).
78. R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, **97**, 1197 (1975).
79. J. P. Marino and R. G. Linderman, *J. Org. Chem.*, **48**, 4621 (1983).

Scheme 8.6. Generation and Reactions of Alkenylcopper Reagents from Alkynes



a. J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villerias, *Bull. Chim. Soc. Fr.*, 1656 (1974).
b. N. J. LaLima, Jr., and A. B. Levy, *J. Org. Chem.*, **43**, 1279 (1978).
c. A. Alexakis, G. Cahiez, and J. F. Normant, *Org. Synth.*, **62**, 1 (1984).
d. H. Westmijze and P. Vermeer, *Synthesis*, 784 (1977).
e. A. Alexakis, J. Normant, and J. Villeras, *Tetrahedron Lett.*, 3461 (1976).
f. R. S. Iyer and P. Helquist, *Org. Synth.*, **64**, 1 (1985).
g. P. R. McGuirk, A. Marfat,and P. Helquist, *Tetrahedron Lett.*, 2465 (1978).
h. M. Valluri, R. M. Hindupur, P. Bijou, G. Labadie, J.-C. Jung, and M. A. Avery, *Org. Lett.*, **3**, 3607 (2001).

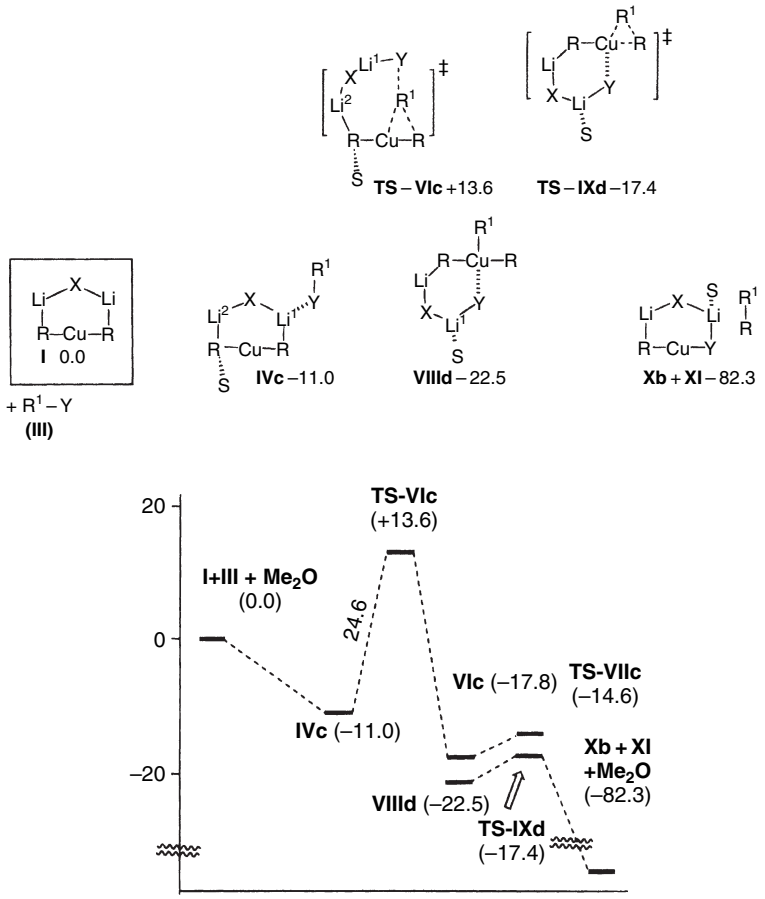


Fig. 8.2. Computational energy profile (B3LYP/631A) for reaction of $(CH_3)_2CuLi$-LiCl with CH_3Br including one solvent (CH_3OCH_3) molecule. Adapted from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

the copper-lithium clusters has been explored computationally (B3LYP/631A) for reactions with methyl bromide,[80] ethylene oxide,[80] acrolein,[81] and cyclohexenone.[82] In the case of methyl bromide, the reaction was studied both with and without a solvation model. The results in the case of inclusion of one molecule of solvent (CH_3OCH_3) are shown in Figure 8.2. The rate-determining step is the conversion of a complex of the reactant cluster, [$(CH_3)_2CuLi$-LiCl)-CH_3Br], to a tetracoordinate Cu(III) species. The calculated barrier is 13.6 kcal/mol. The reductive elimination step has a very low barrier (~5 kcal/mol).

The ring opening of ethylene oxide was studied with CH_3SCH_3 as the solvent molecule and is summarized in Figure 8.3. The crucial TS again involves formation of the C–Cu bond and occurs with assistance from Li^+. As with methyl bromide, the reductive elimination has a low barrier. Incorporation of BF_3 leads to a structure **TS-XXXi** (insert in Figure 8.3) in which BF_3 assists the epoxide ring opening. The

80. S. Mori, E. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **122**, 7294 (2000).
81. E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997).
82. S. Mori and E. Nakamura, *Chem. Eur. J.*, **5**, 1534 (1999).

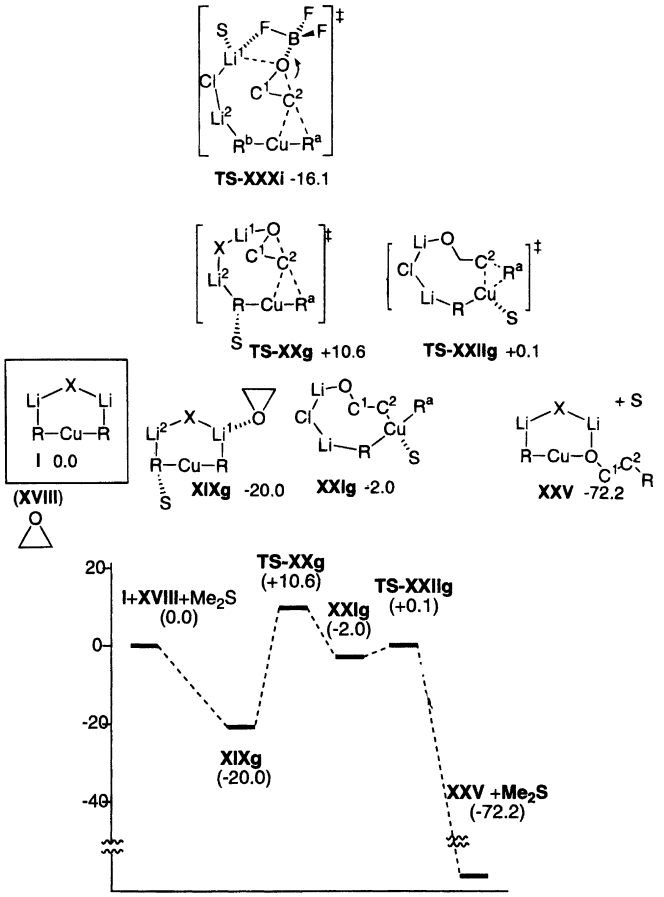


Fig. 8.3. Computational energy profile (B3LYP/631A) for reaction of $(CH_3)_2Cu$-LiCl-$(CH_3)_2S$ with ethylene oxide. The insert (**TS-XXXi**) is a TS that incorporates BF_3, but not $(CH_3)_2S$. Adapted from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

stabilization of the TS leads to a reduction of almost 37 kcal/mol in the computed E_a relative to **TSXXg**.

The nucleophilicity of the organocuprate cluster derives mainly from the filled copper $3d_z^2$ orbital, in combination with the carbon orbital associated with bonding to copper. These orbitals for the TS for reaction with methyl bromide and ethylene oxide are shown in Figure 8.4.

The conjugate addition reaction has also been studied computationally. B3LYP/631A calculations of the reaction of $[(CH_3)_2CuLi]_2$ with acrolein gives the TS and intermediates depicted in Figure 8.5.[81] Three intermediates and three TSs are represented. The first structure is a complex of the reactants (**CP1i**), which involves coordination of the acrolein oxygen to a lithium cation in the reactant. The second intermediate (**CPcl**) is a π complex in which the cluster is opened. A key feature of the mechanism is the third intermediate **CPop**, which involves interaction of *both* lithium ions with the carbonyl oxygen. Moreover, in contrast to the reactions with halides and epoxides, it is the *reductive elimination step that is rate determining*. The calculated barrier for this step is 10.4 kcal/mol.

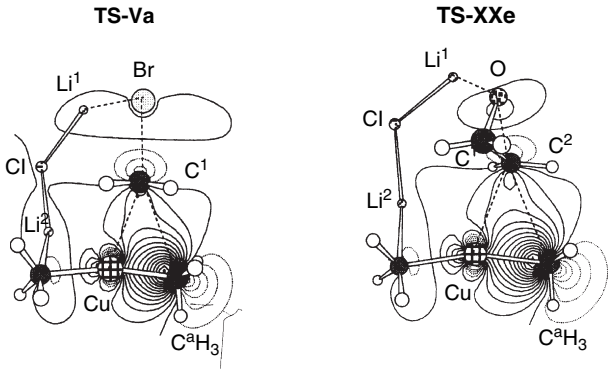


Fig. 8.4. Representation of the orbital involved in C–Cu bond formation in the reaction of $(CH_3)_2CuLi$-LiCl with methyl bromide (left) and ethylene oxide (right). Reproduced from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

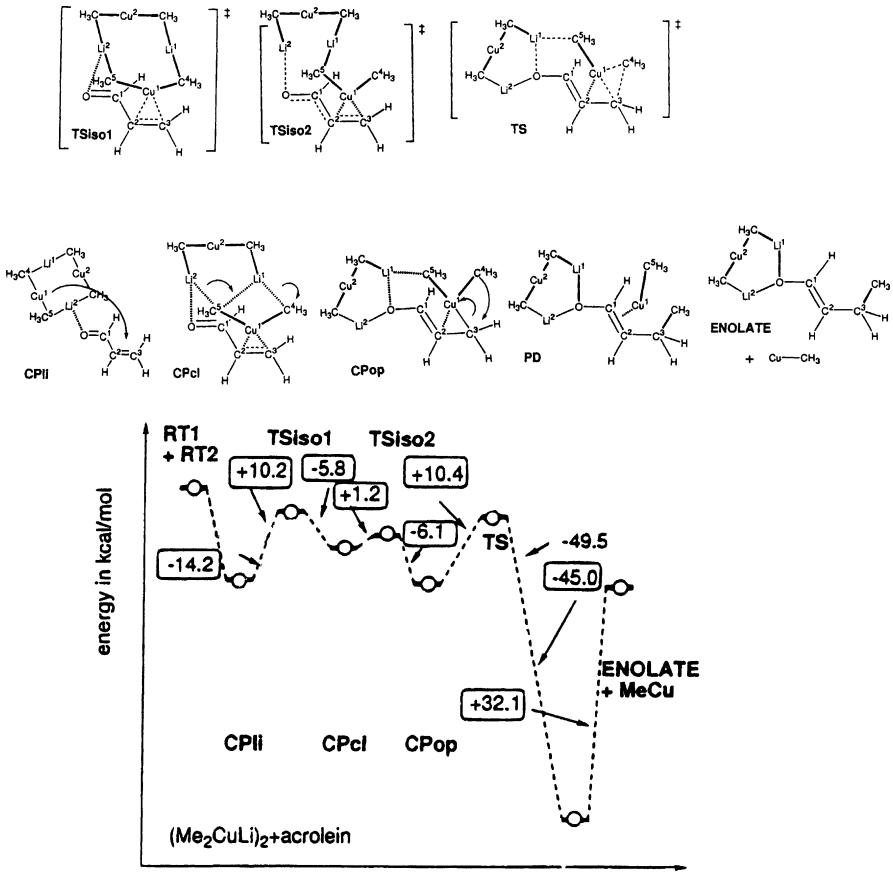
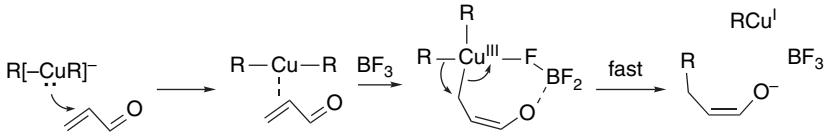


Fig. 8.5. Computational reaction profile (B3LYP/631A) for reaction of $[(CH_3)_2CuLi]_2$ with acrolein. Adapted from *J. Am. Chem. Soc.*, **119**, 4900 (1997), by permission of the American Chemical Society.

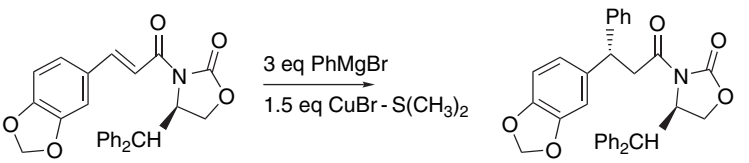
The role of BF_3 catalysis in the conjugate addition was also explored.[83] Inclusion of BF_3 results in a considerable stabilization of the reaction complex, but there is also a lowered barrier for the rate-determining reductive elimination. This suggests that BF_3 functions primarily at the Cu(III) stage by facilitating the decomposition of the Cu(III) intermediate.



A similar sequence of intermediates and TSs was found for the reaction of cyclohexenone.[82] In this case, both axial and equatorial approaches were examined. At the crucial rate- and product-determining TS for C−C bond formation, the axial pathway is favored by 1.7 kcal/mol, in agreement with experimental results from conformationally biased cyclohexenones. Nearly all of the difference is due to factors in the cyclohexenone ring and transferring methyl group. This result suggests that analysis of stereoselectivity of cuprate conjugate additions should focus on the relative energies of the competing TS for the C−C bond-forming step. These computational studies comport well with a variety of product, kinetic, and spectroscopic studies that have been applied to determining the mechanism of organocuprates and related reagents.[84]

Visual models and additional information on Organocuprate Intermediates can be found in the Digital Resource available at: Springer.com/carey-sundberg.

8.1.2.8. Enantioselective Reactions of Organocopper Reagents. Several methods have been developed for achieving enantioselectivity with organocopper reagents. Chiral auxiliaries can be used; for example, oxazolidinone auxiliaries have been utilized in conjugate additions. The outcome of these reactions can be predicted on the basis of steric control of reactant approach, as for other applications of the oxazolidinone auxiliaries.

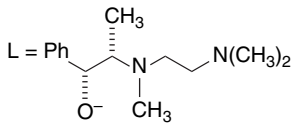


Ref. 85

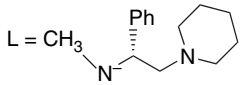
Conjugate addition reactions involving organocopper intermediates can be made enantioselective by using chiral ligands.[86] Several mixed cuprate reagents containing

83. E. Nakamura, M. Yamanaka, and S. Mori, *J. Am. Chem. Soc.*, **122**, 1826 (2000).
84. E. Nakamura and S. Mori, *Angew. Chem. Int. Ed. Engl.*, **39**, 3750 (2000).
85. M. P. Sibi, M. D. Johnson, and T. Punniyamurthy, *Can. J. Chem.*, **79**, 1546 (2001).
86. N. Krause and A. Gerold, *Angew. Chem. Int. Ed. Engl.*, **36**, 186 (1997); N. Krause, *Angew. Chem. Int. Ed. Engl.*, **37**, 283 (1998).

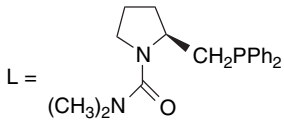
chiral ligands have been investigated to determine the degree of enantioselectivity that can be achieved. The combination of diethylzinc and cyclohexenone has been studied extensively, and several amide and phosphine ligands have been explored. Enantioselectivity can also be observed using Grignard reagents with catalytic amounts of copper. Scheme 8.7 shows some examples of these reactions using various chiral ligands.



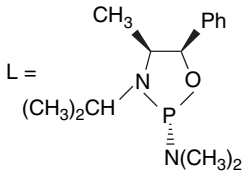
Ref. 87



Ref. 88

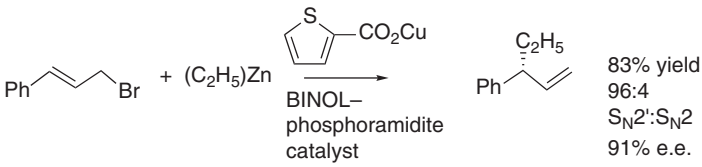


Ref. 89



Ref. 90

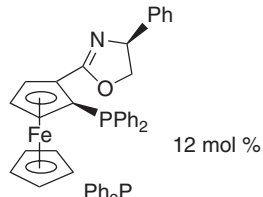
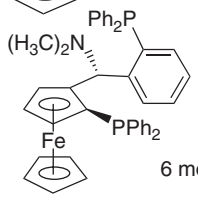
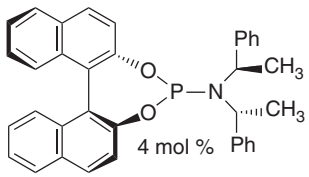
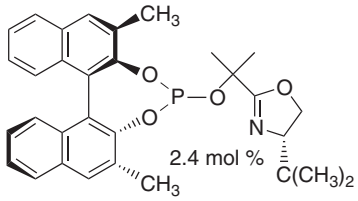
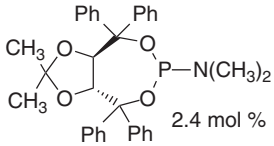
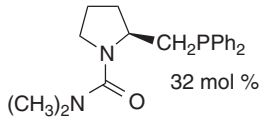
Enantioselective catalysis of S_N2' alkylation has been achieved.[91] A BINOL-phosphoramidite catalyst (*o*-methoxyphenyl analog) similar to that in Entry 3 in Scheme 8.7 gave good results.



8.1.2.9. Aryl-Aryl Coupling Using Organocopper Reagents. Organocopper intermediates are also involved in several procedures for coupling of two aromatic reactants to form a new carbon-carbon bond. A classic example of this type of reaction is the *Ullman coupling* of aryl halides, which is done by heating an aryl halide with a copper-bronze alloy.[92] Good yields by this method are limited to halides with EWG substituents.[93] Mechanistic studies have established the involvement of arylcopper

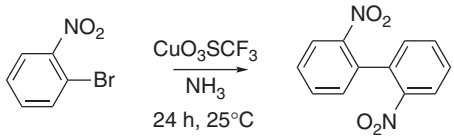
87. E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, **108**, 7144 (1986).
88. N. M. Swingle, K. V. Reddy, and B. L. Rossiter, *Tetrahedron*, **50**, 4455 (1994); G. Miao and B. E. Rossiter, *J. Org. Chem.*, **60**, 8424 (1995).
89. M. Kanai and K. Tomioka, *Tetrahedron Lett.*, **35**, 895 (1994); **36**, 4273, 4275 (1995).
90. A. Alexakis, J. Frutos, and P. Mageney, *Tetrahedron: Asymmetry*, **4**, 2427 (1993).
91. K. Tissot-Croset, D. Polet, and A. Alexakis, *Angew. Chem. Int. Ed. Engl.*, **43**, 2426 (2004).
92. P. E. Fanta, *Chem. Rev.*, **64**, 613 (1964); P. E. Fanta, *Synthesis*, 9 (1974).
93. R. C. Fuson and E. A. Cleveland, *Org. Synth.*, **III**, 339 (1955).

Scheme 8.7. Catalytic Enantioselective Conjugate Addition to Cyclohexenone

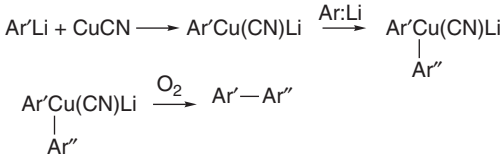
Entry	Reactant	Catalyst	Ligand	Yield	e.e.
1[a]	n-C_4H_9MgCl	CuI 10 mol %	 12 mol %	97	83
2[b]	C_2H_5MgBr	CuCl 3 mol %	 6 mol %	69	96
3[c]	$(C_2H_5)_2Zn$	$Cu(O_3SCF_3)_2$ 2 mol %	 4 mol %	94	>98
4[d]	$(C_2H_5)_2Zn$	$Cu(O_3SCF_3)_2$ 2 mol %	 2.4 mol %	96	90
5[e]	$(C_2H_5)_2Zn$	$Cu(O_3SCF_3)_2$ 1.2 mol %	 2.4 mol %	90	71
6[f]	n-C_4H_9MgCl	CuI 8 mol %	 32 mol %	92	90

a. E. L. Stangeland and T. Sammakia, *Tetrahedron*, **53**, 16503 (1997).
b. B. L. Feringa, R. Badorrey, D. Pena, S. R. Harutyunyan, and A. J. Minnaard, *Proc. Natl. Acad. Sci. USA*, **101**, 5834 (2004).
c. B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, and A. H. M. de Vries, *Angew. Chem. Int. Ed. Engl.*, **36**, 2620 (1997).
d. A. K. H. Knobel, I. H. Escher, and A. Pfaltz, *Synlett*, 1429 (1997); I. H. Escher and A. Pfaltz, *Tetrahedron*, **56**, 2879 (2000).
e. E. Keller, J. Maurer, R. Naasz, T. Schader, A Meetsma, and B. L. Feringa, *Tetrahedron: Asymmetry*, **9**, 2409 (1998).
f. M. Kanai, Y. Nakagawa, and K. Tomioka, *Tetrahedron*, **55**, 3843 (1999).

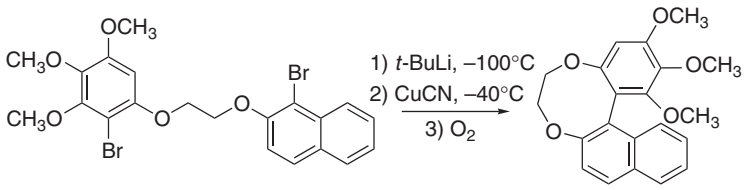
intermediates. Soluble Cu(I) salts, particularly the triflate, effect coupling of aryl halides at much lower temperatures and under homogeneous conditions.[94]



Arylcopper intermediates can be generated from organolithium compounds, as in the preparation of cuprates.[95] These compounds react with a second aryl halide to provide unsymmetrical biaryls in a reaction that is essentially a variant of the cuprate alkylation process discussed on p. 680. An alternative procedure involves generation of a mixed diarylcyanocuprate by sequential addition of two different aryllithium reagents to CuCN, which then undergo decomposition to biaryls on exposure to oxygen.[96] The second addition must be carried out at very low temperature to prevent equilibration with the symmetrical diarylcyanocuprates.



Intramolecular variations of this reaction have been achieved.

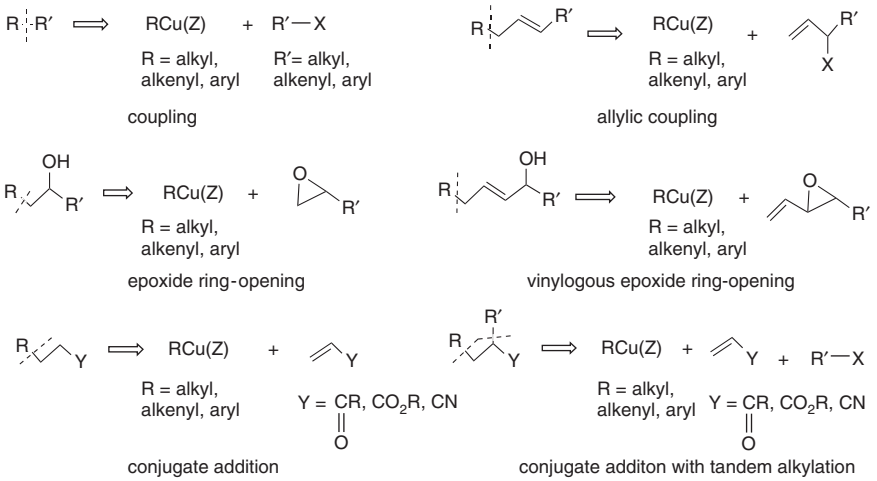


56% Ref. 97

8.1.2.10. Summary of Synthetic Reactions of Organocopper Reagents and Intermediates. The synthetic procedures involving organocopper reagents and intermediates offer a wide range of carbon-carbon bond-forming reactions. Coupling of alkyl, alkenyl, and aryl groups and the various mixed combinations can be achieved. The coupling of allylic reagents encompasses acetates, sulfonates, and phosphates, as well as halides. These reactions often occur with allylic transposition. Both direct and vinylogous

94. T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976).
95. F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, *J. Am. Chem. Soc.*, **102**, 790 (1980).
96. B. H. Lipshutz, K. Siegmann, and E. Garcia, *Tetrahedron*, **48**, 2579 (1992); B. H. Lipshutz, K. Siegmann, E. Garcia, and F. Kayser, *J. Am. Chem. Soc.*, **115**, 9276 (1993).
97. B. H. Lipshutz, F. Kayser, and N. Maullin, *Tetrahedron Lett.*, **35**, 815 (1994).

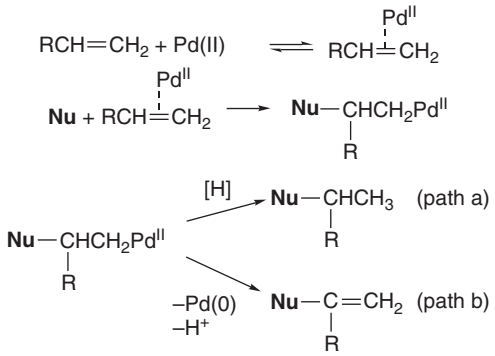
epoxide ring-opening reactions are available for the synthesis of alcohols. The reactants for conjugate addition include α, β-unsaturated ketones, esters, amides, and nitriles, and these reactions can be combined with tandem alkylation. These synthetic transformations are summarized below.



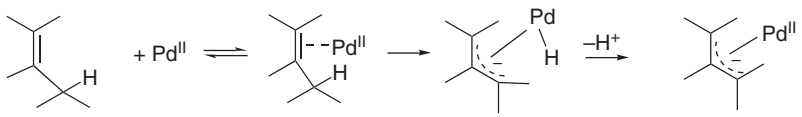
8.2. Reactions Involving Organopalladium Intermediates

Organopalladium intermediates are very important in synthetic organic chemistry. Usually, organic reactions involving palladium do not involve the preparation of stoichiometric organopalladium reagents. Rather, organopalladium species are generated in situ during the course of the reaction. In the most useful processes only a *catalytic amount* of palladium is used. The overall reaction mechanisms typically involve several steps in which organopalladium species are formed, react with other reagents, give product, and are regenerated in a catalytically active form. Catalytic processes have both economic and environmental advantages. Since, in principle, the catalyst is not consumed, it can be used to make product without generating by-products. Some processes use *solid phase catalysts*, which further improve the economic and environmental advantages of catalyst recovery. Reactions that involve chiral catalysts can generate enantiomerically enriched or pure materials from achiral starting materials. In this section we focus on carbon-carbon bond formation, but in Chapter 11 we will see that palladium can also catalyze aromatic substitution reactions.

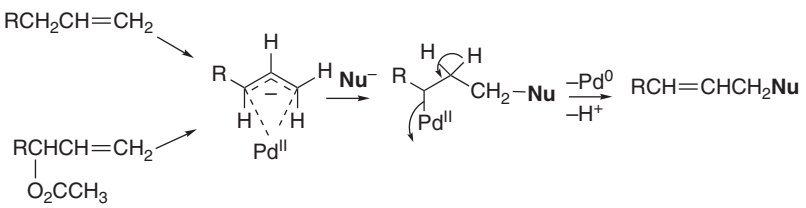
Several types of organopalladium intermediates are of primary importance in the reactions that have found synthetic applications. Alkenes react with Pd(II) to give π complexes that are subject to *nucleophilic attack*. These reactions are closely related to the solvomercuration reactions discussed in Section 4.1.3. The products that are formed from the resulting intermediates depend upon specific reaction conditions. The palladium can be replaced by hydrogen under reductive conditions (path a). In the absence of a reducing agent, elimination of Pd(0) and a proton occurs, leading to net substitution of a vinyl hydrogen by the nucleophile (path b). We return to specific examples of these reactions shortly.



A second major group of organopalladium intermediates are π-allyl complexes, which can be obtained from Pd(II) salts, allylic acetates, and other compounds having potential leaving groups in an allylic position.[98] The same type of π-allyl complex can be prepared directly from alkenes by reaction with $PdCl_2$ or $Pd(O_2CCF_3)_2$.[99] The reaction with alkenes occurs by electrophilic attack on the π electrons followed by loss of a proton. The proton loss probably proceeds via an unstable species in which the hydrogen is bound to palladium.[100]



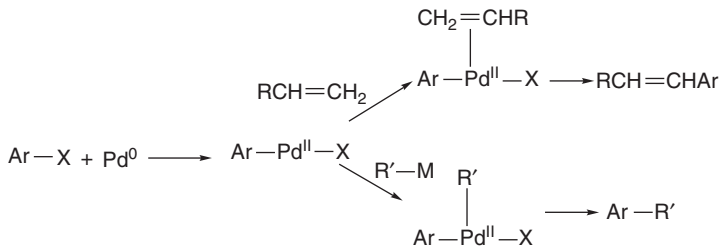
These π-allyl complexes are moderately *electrophilic* [101] in character and react with a variety of nucleophiles, usually at the less-substituted allylic terminus. After nucleophilic addition occurs, the resulting organopalladium intermediate usually breaks down by elimination of Pd(0) and H^+. The overall transformation is an allylic substitution.



Another general process involves the reaction of Pd(0) species with halides or sulfonates by *oxidative addition*, generating reactive intermediates having the organic group attached to Pd(II) by a σ bond. The oxidative addition reaction is very useful for aryl and alkenyl halides, but the products from saturated alkyl halides often decompose by β-elimination. The σ-bonded species formed by oxidative addition can react with alkenes and other unsaturated compounds to form new carbon-carbon bonds. The

98. R. Huttel, *Synthesis*, 225 (1970); B. M. Trost, *Tetrahedron*, **33**, 2615 (1977).
99. B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.*, **102**, 3572 (1980); B. M. Trost, P. E. Strege, L. Weber, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3407 (1978).
100. D. R. Chrisope, P. Beak, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **110**, 230 (1988).
101. O. Kuhn and H. Mayr, *Angew. Chem. Int. Ed. Engl.*, **38**, 343 (1998).

σ-bound species also react with a variety of organometallic reagents to give coupling products.



These are called *cross-coupling reactions* and usually involve three basic steps: oxidative addition, transmetallation, and reductive elimination. In the transmetallation step an organic group is transferred from the organometallic reagent to palladium.

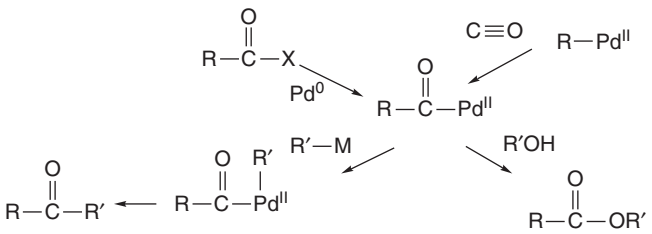
oxidative addition	$R{-}X + Pd^0 \longrightarrow R{-}Pd^{II}{-}X$
transmetallation	$R{-}Pd^{II}{-}X + R'{-}M \longrightarrow R{-}Pd^{II}{-}R' + M{-}X$
reductive elimination	$R{-}Pd^{II}{-}R' \longrightarrow R{-}R' + Pd^0$

The organometallic reagents that give such reactions include organomagnesium, organolithium, and organozinc compounds, stannanes, and even organoboron compounds. The reactions are very general for sp^2-sp^2 and sp^2-sp coupling and in some systems can also be applied to sp^2-sp^3 coupling. Most of these procedures involve phosphine or related ligands.

$$R{-}M + R'{-}X \xrightarrow{Pd(L)_y} R{-}R'$$

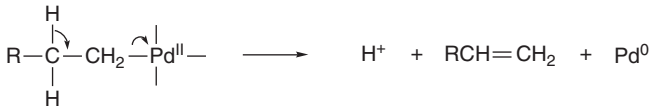
$M = Li, MgX, ZnX, SnR_3, BR_2$

Organopalladium intermediates are also involved in the synthesis of ketones and other carbonyl compounds. These reactions involve acylpalladium intermediates, which can be made from acyl halides or by reaction of an organopalladium species with carbon monoxide. A second organic group, usually arising from an organometallic reagent, can then form a ketone. Alternatively, the acylpalladium intermediate may react with nucleophilic solvents such as alcohols to form esters.

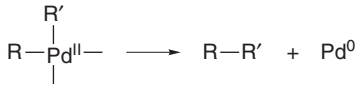


In considering the mechanisms involved in organopalladium chemistry, several general points should be kept in mind. Frequently, reactions involving organopalladium

intermediates are done in the presence of phosphine ligands, which play a key role by influencing the reactivity at palladium. Another general point concerns the relative weakness of the C–Pd bond and, especially, the instability of alkylpalladium species in which there is a β-hydrogen.

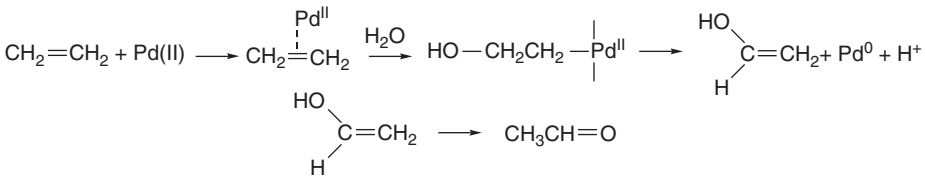


The final stage in many palladium-mediated reactions is the elimination of Pd(0) and H^+ to generate a carbon-carbon double bond. This tendency toward elimination distinguishes organopalladium species from most of the organometallic species we have discussed up to this point. Finally, organopalladium(II) species with two organic substituents show the same tendency to react with recombination of the organic groups by reductive elimination that is exhibited by copper(III) intermediates. This reductive elimination generates the new carbon-carbon bond.

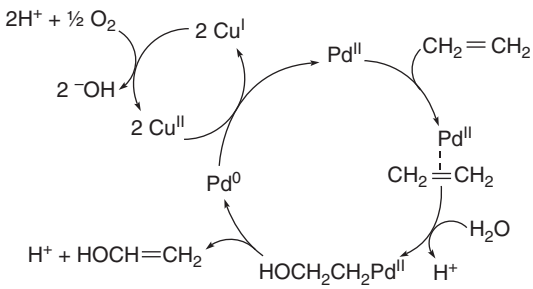


8.2.1. Palladium-Catalyzed Nucleophilic Addition and Substitution

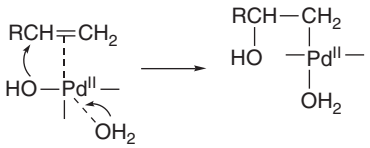
8.2.1.1. The Wacker Reaction and Related Oxidations. An important industrial process based on Pd-alkene complexes is the *Wacker reaction*, a catalytic method for conversion of ethene to acetaldehyde. The first step is addition of water to the Pd(II)-activated alkene. The addition intermediate undergoes the characteristic elimination of Pd(0) and H^+ to generate the enol of acetaldehyde.



The reaction is run with only a catalytic amount of Pd. The co-reagents $CuCl_2$ and O_2 serve to reoxidize the Pd(0) to Pd(II). The net reaction consumes only alkene and oxygen.

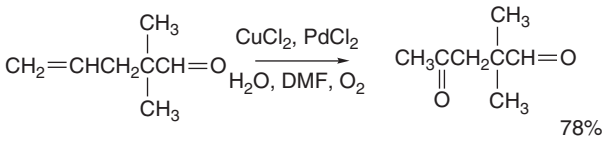


The relative reactivity profile of the simple alkenes toward Wacker oxidation is quite shallow and in the order ethene > propene > 1-butene > *E*-2-butene > *Z*-2-butene.[102] This order indicates that steric factors outweigh electronic effects and is consistent with substantial nucleophilic character in the rate-determining step. (Compare with oxymercuration; see Part A, Section 5.8.) The addition step is believed to occur by an internal ligand transfer through a four-center mechanism, leading to *syn* addition.

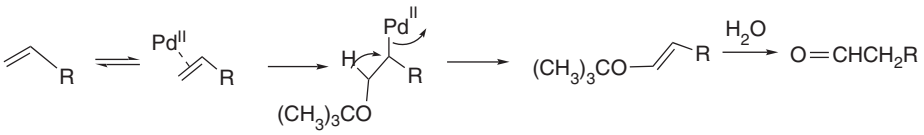


The stereochemistry, however, is sensitive to the concentration of chloride ion, shifting to *anti* when chloride is present.[103]

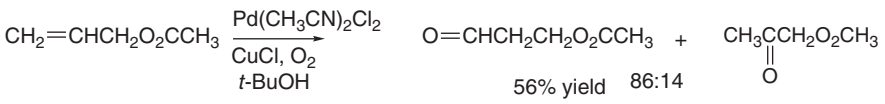
The Wacker reaction can also be applied to laboratory-scale syntheses.[104] When the Wacker conditions are applied to terminal alkenes, methyl ketones are formed.[105]



This regiochemistry is consistent with the electrophilic character of Pd(II) in the addition step. Solvent and catalyst composition can affect the regiochemistry of the Wacker reaction. Use of *t*-butanol as the solvent was found to increase the amount of aldehyde formed from terminal alkenes, and is attributed to the greater steric requirement of *t*-butanol. Hydrolysis of the enol ether then leads to the aldehyde.

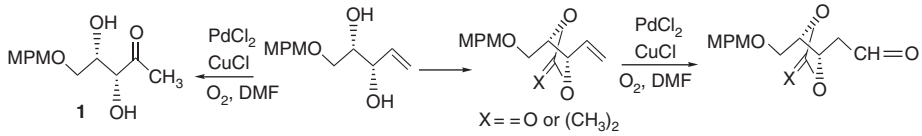


These conditions are particularly effective for allyl acetate.[106]

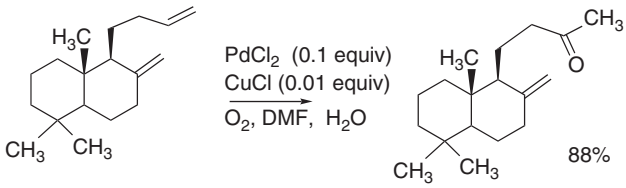


102. K. Zaw and P. M. Henry, *J. Org. Chem.*, **55**, 1842 (1990); A. Lambert, E. G. Derouane, and I. V. Kozhevnikov, *J. Catal.*, **211**, 445 (2002).
103. O. Hamed, P. M. Henry, and C. Thompson, *J. Org. Chem.*, **64**, 7745 (1999).
104. J. M. Takacs and X.-T. Jiang, *Current Org. Chem.*, **7**, 369 (2003).
105. (a) J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 2975 (1976); J. Tsuji, H. Nagashima, and H. Nemoto, *Org. Synth.*, **62**, 9 (1984); (c) D. Pauley, F. Anderson, and T. Hudlicky, *Org. Synth.*, **67**, 121 (1988); (d) K. Januszkiewicz and H. Alper, *Tetrahedron Lett.*, **25**. 5159 (1983); (e) K. Januszkiewicz and D. J. H. Smith, *Tetrahedron Lett.*, **26**, 2263 (1985).
106. B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 909 (1986); T. T. Wenzel, *J. Chem. Soc., Chem. Commun.*, 862 (1993).

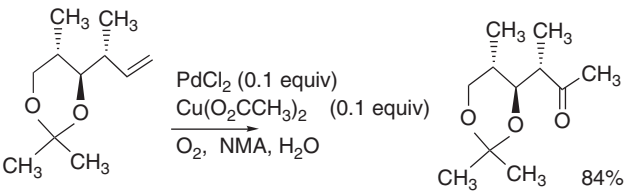
Both the regiochemistry and stereochemistry of Wacker oxidation can be influenced by substituents that engage in chelation with Pd. Whereas a single γ-alkoxy function leads to a mixture of aldehyde and ketone, more highly oxygenated systems such as the acetonide or carbonate of the diol **1** lead to dominant aldehyde formation.[107] The diol itself gives only ketone, which perhaps indicates that steric factors are also important.



The two reactions shown below are examples of the use of the Wacker reaction in multistep synthesis. In the first case, selectivity is achieved between two terminal alkene units on the basis of a difference in steric accessibility. Both reactions use a reduced amount of Cu(I) salt. In the second reaction this helps to minimize hydrolysis of the acid-sensitive dioxane ring.

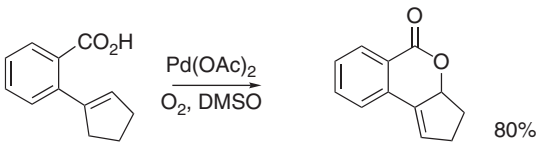


Ref. 108



Ref. 109

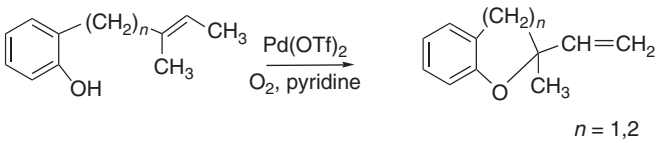
Palladium(II) like Hg(II) can induce intramolecular nucleophilic addition, but this is followed by elimination of Pd(0) and H^+. For example, γ, δ- and δ, ϵ-unsaturated carboxylic acids can be cyclized to unsaturated lactones by $Pd(OAc)_2$ in DMSO in the presence of O_2. Although $Cu(OAc)_2$ can be included as a catalyst for reoxidation of the Pd(0), it is not necessary.[110]



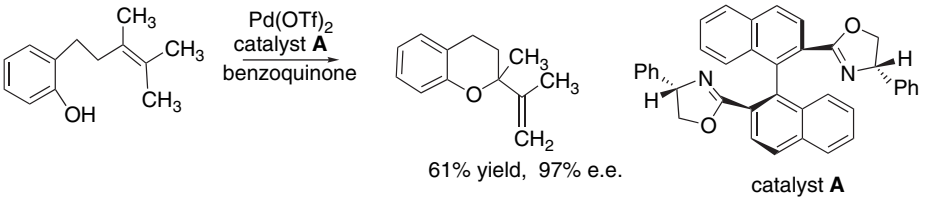
Similarly, phenols with unsaturated side chains can form five- and six-membered rings. In these systems the quaternary carbon imposes the β, γ-elimination. As with the above

107. S.-K. Kang, K.-Y. Jung, J.-U. Chung, E.-Y. Namkoong, and T.-H. Kim, *J. Org. Chem.*, **60**, 4678 (1995).
108. H. Toshima, H. Oikawa, T. Toyomasu, and T. Sassa, *Tetrahedron*, **56**, 8443 (2000).
109. A. B. Smith, III, Y. S. Cho, and G. K. Friestad, *Tetrahedron Lett.*, **39**, 8765 (1998).
110. R. C. Larock and T. R. Hightower, *J. Org. Chem.*, **58**, 5298 (1993).

cyclization, a copper co-oxidant is not needed. The pyridine is evidently involved in accelerating the oxidation of Pd(0) by O_2.[111]

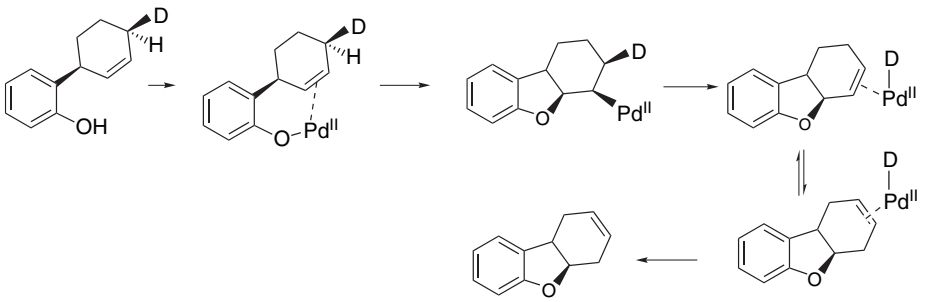


Cyclizations of this type can be carried out with high enantioselectivity using a chiral *bis*-oxazoline catalyst.



Ref. 112

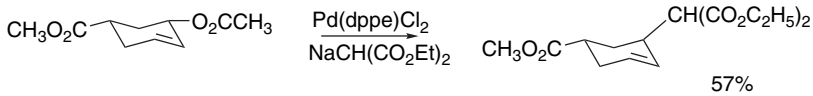
A deuterium-labeling study of a reaction of this type demonstrated *syn* stereoselectivity in both the oxypalladation and β-elimination, which indicates that the cyclization occurs by internal migration, rather than by an *anti* nucleophilic capture.[113] This particular system also gives products from double-bond migration that occurs by reversible Pd(II)–D addition-elimination.



8.2.1.2. Nucleophilic Substitution of π-Allyl Palladium Complexes. π-Allyl palladium species are subject to a number of useful reactions that result in allylation of nucleophiles.[114] The reaction can be applied to carbon-carbon bond formation using relatively stable carbanions, such as those derived from malonate esters and β-sulfonyl esters.[115] The π-allyl complexes are usually generated in situ by reaction of an allylic acetate with a catalytic amount of *tetrakis*-(triphenylphosphine)palladium

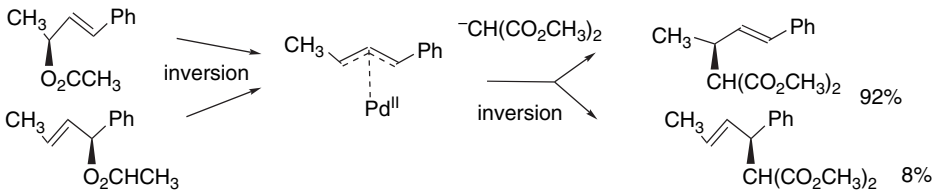
111. R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, and B. M. Stoltz, *Angew. Chem. Int. Ed. Engl.*, **42**, 2892 (2003).
112. Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, **119**, 5063 (1997).
113. T. Hayashi, K. Yamasaki, M. Mimura, and Y. Uozumi, *J. Am. Chem. Soc.*, **126**, 3036 (2004).
114. G. Consiglio and R. M. Waymouth, *Chem. Rev.*, **89**, 257 (1989).
115. B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, **96**, 7165 (1974); B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3416 (1978); B. M. Trost, *Acc. Chem. Res.*, **13**, 385 (1980).

or a chelated diphosphine complex.[116] The reactive Pd(0) species is regenerated in an elimination step.



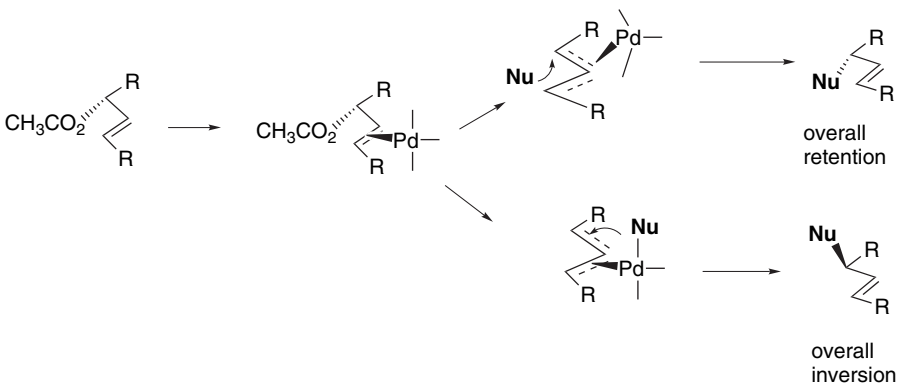
Ref. 117

For unsymmetrical allylic systems both the regiochemistry and stereochemistry of the substitution are critical issues. The palladium normally bonds *anti* to the acetate leaving group. The same products are obtained from 2-acetoxy-4-phenyl-3-butene and 1-acetoxy-1-phenyl-2-butene, indicating a common intermediate. The same product mixture is also obtained from the *Z*-reactants, indicating rapid *E*,Z-equilibration in the allylpalladium intermediate.[118]



In the presence of chiral phosphine ligands, there is also rapid epimerization to the most stable diastereomeric π-allyl complex. The stereoselectivity arises in the reaction with the nucleophile.[119]

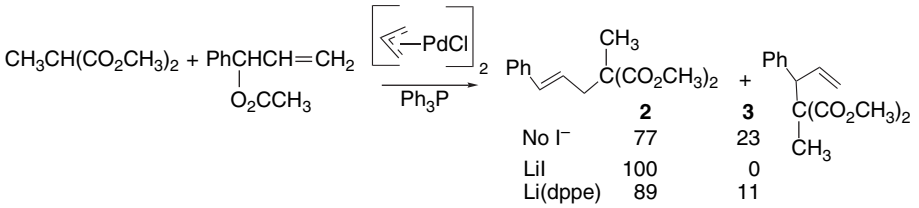
Mechanistically, the nucleophilic addition can occur either by internal ligand transfer or by external attack. Generally, softer more stable nucleophiles (e.g., malonate enolates) are believed to react by the external mechanism and give *anti* addition, whereas harder nucleophiles (e.g., hydroxide) are delivered by internal ligand transfer with *syn* stereochemistry.[120]



Both the regiochemistry and stereochemistry are influenced by reaction conditions. A striking example is a complete switch to 3-alkylation of dimethyl malonate

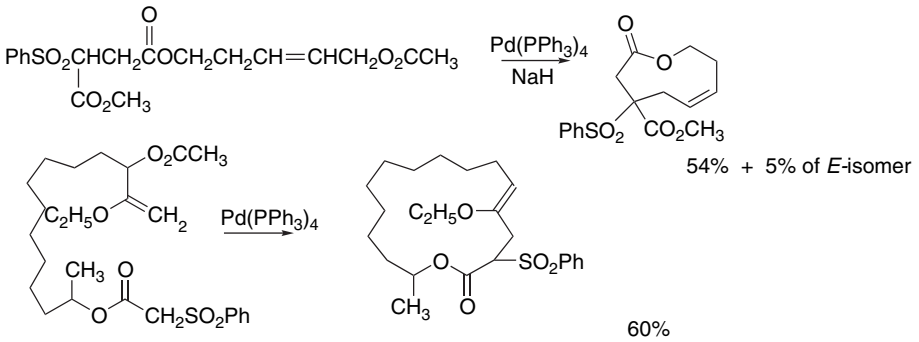
116. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4730 (1980).
117. B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **99**, 1649 (1977).
118. T. Hayashi, A. Yamamoto, and T. Hagihara, *J. Org. Chem.*, **51**, 723 (1986).
119. P. B. Mackenzie, J. Whelan, and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2046 (1985).
120. A. Heumann and M. Reglier, *Tetrahedron*, **51**, 975 (1995).

anion by 1-phenylprop-2-enyl acetate in the presence of iodide ion. In the absence of iodide, using 2 mol % catalyst, the ratio of **2** to **3** is about 4:1. When 2 mol % iodide is added, only **2** is formed. This change is attributed to the involvement of a catalytic species in which I^- is present as a Pd ligand. The effect is diminished when a chelating diphosphine ligand is used, presumably because addition of I^- to the Pd ligand sphere is prevented by the chelate.

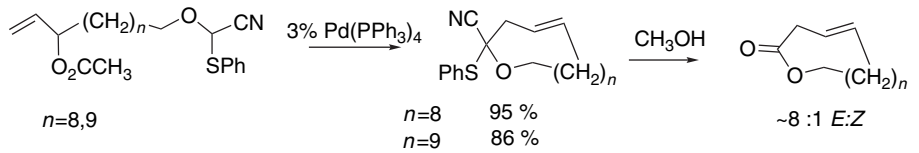


Ref. 121

The allylation reaction has also been used to form rings. β-Sulfonyl esters have proven particularly useful in this application for formation of both medium and large rings.[122] In some cases medium-sized rings are formed in preference to six- and seven-membered rings.[123]



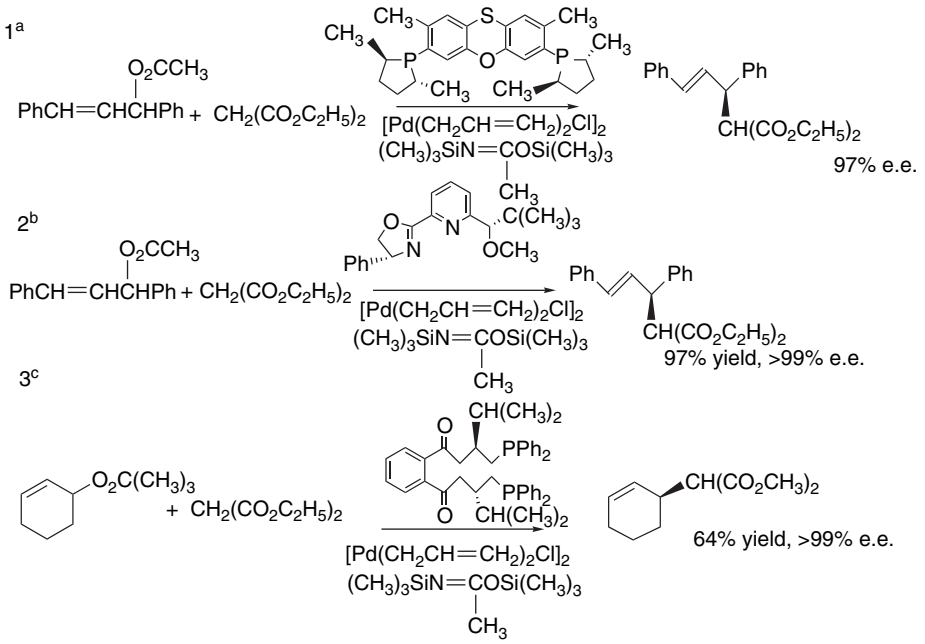
The sulfonyl substituent can be removed by reduction after the ring closure (see Section 5.6.2). Other appropriate reactants are α-phenylthio nitriles, which can be hydrolyzed to lactones.[124]



Allylation reactions can be made highly enantioselective by the use of various chiral phosphine ligands.[125] Examples are included in Scheme 8.8.

121. M. Kawatsura, Y. Uozumi, and T. Hayashi, *J. Chem. Soc., Chem. Commun.*, 217 (1998).
122. B. M. Trost, *Angew. Chem. Int. Ed. Engl.*, **28**, 1173 (1989).
123. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4743 (1980); B. M. Trost and S. J. Brickner, *J. Am. Chem. Soc.*, **105**, 568 (1983); B. M. Trost, B. A. Vos, C. M. Brzezowski, and D. P. Martina, *Tetrahedron Lett.*, **33**, 717 (1992).
124. B. M. Trost and J. R. Granja, *J. Am. Chem. Soc.*, **113**, 1044 (1991).
125. S. J. Sesay and J. M. J. Williams, in *Advances in Asymmetric Synthesis*, Vol. 3, A. Hassner, ed., JAI Press, Stamford, CT, 1998, pp. 235–271; G. Helmchen, *J. Organomet. Chem.*, **576**, 203 (1999).

Scheme 8.8. Enantioselective Allylation of Diethyl Malonate

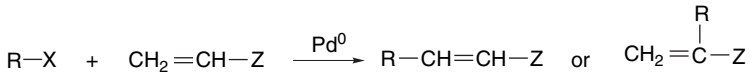


a. P. Dierks, S. Ramdeehul, L. Barley, A. DeCian, J. Fischer, P. C. J. Kramer, P. W. N. M. van Leeuwen, and J. A. Osborne, *Angew. Chem. Int. Ed. Engl.*, **37**, 3116 (1998).
b. K. Nordstrom, E. Macedo, and C. Moberg, *J. Org. Chem.*, **62**, 1604 (1997); U. Bremberg, F. Rahm, and C. Moberg, *Tetrahedron: Asymmetry*, **9**, 3437 (1998).
c. A Saitoh, M. Misawa, and T. Morimoto, *Tetrahedron: Asymmetry*, **10**, 1025 (1999).

8.2.2. The Heck Reaction

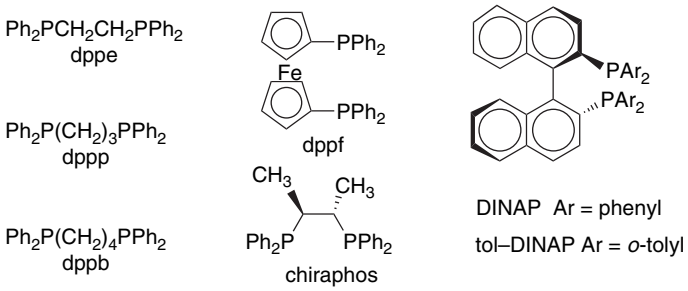
Another important type of reactivity of palladium, namely oxidative addition to Pd(0), is the foundation for several methods of forming carbon-carbon bonds. Aryl[126] and alkenyl[127] halides react with alkenes in the presence of catalytic amounts of palladium to give net substitution of the halide by the alkenyl group. The reaction, known as the *Heck reaction*,[128] is quite general and has been observed for simple alkenes, aryl-substituted alkenes, and substituted alkenes such as acrylate esters, vinyl ethers, and *N*-vinylamides.[129]

126. H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); R. F. Heck, *Acc. Chem. Res.*, **12**, 146 (1979); R. F. Heck, *Org. React.*, **27**, 345 (1982).
127. B. A. Patel and R. F. Heck, *J. Org. Chem.*, **43**, 3898 (1978); B. A. Patel, J. I. Kim, D. D. Bender, L. C. Kao, and R. F. Heck, *J. Org. Chem.*, **46**, 1061 (1981); J. I. Kim, B. A. Patel, and R. F. Heck, *J. Org. Chem.*, **46**, 1067 (1981).
128. I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, **100**, 3009 (2000); B. C. G. Soderberg, *Coord. Chem. Rev.*, **224**, 171 (2002); G. T. Crisp, *Chem. Soc. Rev.*, **27**, 427 (1998).
129. C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, **43**, 2941 (1978); W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.*, **43**, 2947 (1978); C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, **43**, 2949 (1978); H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); C. A. Busacca, R. E. Johnson, and J. Swestock, *J. Org. Chem.*, **58**, 3299 (1993).

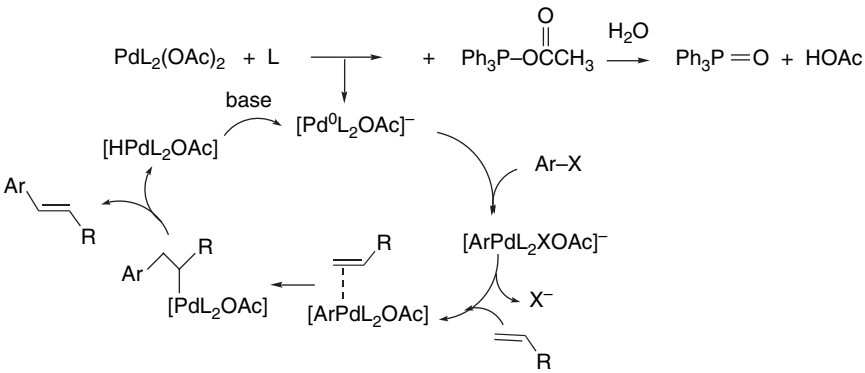


R = alkenyl, aryl
X = halide, sulfonate

Many procedures use $Pd(OAc)_2$ or other Pd(II) salts as catalysts with the catalytically active Pd(0) being generated in situ. The reactions are usually carried out in the presence of a phosphine ligand, with *tris-o*-tolylphosphine being preferred in many cases. *Tris*-(2-furyl)phosphine (tfp) is also used frequently. Several chelating diphosphines, shown below with their common abbreviations, are also effective. Phosphites are also good ligands.[130]



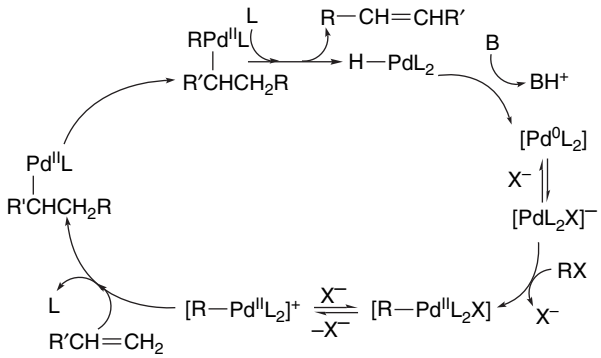
The reaction is initiated by oxidative addition of the halide or sulfonate to a Pd(0) species generated in situ from the Pd(II) catalyst. The arylpalladium(II) intermediate then forms a π complex with the alkene, which rearranges to a σ complex by carbon-carbon bond formation. The σ complex decomposes by β-elimination with regeneration of Pd(0). Both of these reactions occur with *syn* stereoselectivity. The Heck reaction often uses of $Pd(OAc)_2$ as the palladium source along with a triarylphosphine and a tertiary amine. Under these conditions it has been proposed that the initiation of the reaction involves formation of an anionic complex $[Pd(L)_2OAc]^-$.[131] This is a 16-electron species and is considered to be the active form of Pd for the oxidative addition. The base is crucial in maintaining the equilibrium in favor of the active anionic form after the reductive elimination. This is called the *anionic mechanism*. Note that the phosphine ligand is also the reducing agent for formation of the active Pd(0) species.



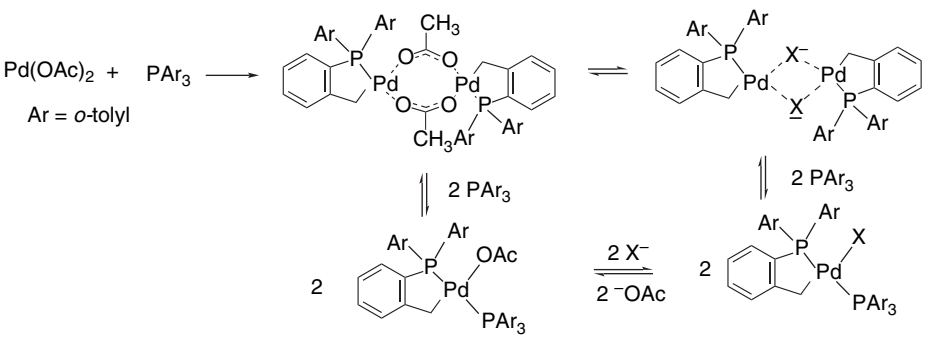
Anionic mechanism for Heck reaction

130. M. Beller and A. Zapt, *Synlett*, 792 (1998).
131. A. Amatore and A. Jutand, *Acc. Chem. Res.*, **33**, 314 (2000).

Several different Pd(0) species can be involved in both the oxidative addition and π-coordination steps, depending on the anions and ligands present. Because of the equilibria involving dissociation of phosphine ligands and anions, there is dependence on their identity and concentration.[132] High halide concentration promotes formation of the anionic species $[PdL_2X]^-$ by addition of a halide ligand. Use of trifluoromethanesulfonate anions promotes dissociation of the anion from the Pd(II) adduct and accelerates complexation with electron-rich alkenes. The presence of metal ions that bind the halide, e.g., Ag^+, also promotes dissociation. Reactions that proceed through a dissociated species are called *cationic* and are expected to have a more electrophilic interaction with the alkene. A base is included to neutralize the proton released in the β-elimination step. The catalytic cycle under these conditions is shown below.



It appears that a modified mechanism operates when *tris*-(*o*-tolyl)phosphine is used as the ligand,[133] and this phosphine has been found to form a *palladacycle*. Much more stable than noncyclic Pd(0) complexes, this compound is also more reactive toward oxidative addition. As with the other mechanisms, various halide adducts or halide-bridged compounds may enter into the overall mechanism.

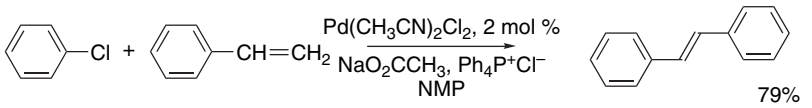


132. W. Cabri, I. Candiani, S. De Bernardinis, F. Francalanci, S. Penco, and R. Santi, *J. Org. Chem.*, **56**, 5796 (1991); F. Ozawa, A. Kubo, and T. Hayashi, *J. Am. Chem. Soc.*, **113**, 1417 (1991).

133. W. A. Hermann, C. Brossmer, K. Ofele, C.-P. Reisinger, T. Priermeier, M. Beller, and H. Fischer, *Angew. Chem. Int. Ed. Engl.*, **34**, 1844 (1995).

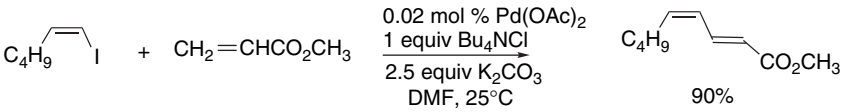
Several modified reaction conditions have been developed. One involves addition of silver salts, which activate the halide toward displacement.[134] Use of sodium bicarbonate or sodium carbonate in the presence of a phase transfer catalyst permits especially mild conditions to be used for many systems.[135] Tetraalkylammonium salts also often accelerate reaction.[136] Solid phase catalysts in which the palladium is complexed by polymer-bound phosphine groups have also been developed.[137]

Aryl chlorides are not very reactive under normal Heck reaction conditions but reaction can be achieved by inclusion of tetraphenylphosphonium salts with $Pd(OAc)_2$ or $PdCl_2$ as the catalysts.[138]



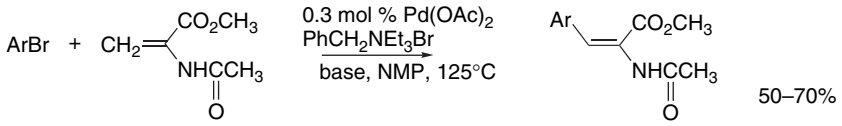
Pretreatment with nickel bromide causes normally unreactive aryl chlorides to undergo Pd-catalyzed substitution,[139] and aryl and vinyl triflates have been found to be excellent substrates for Pd-catalyzed alkenylations.[140]

Heck reactions can be carried out in the absence of phosphine ligands.[141] These conditions usually involve $Pd(OAc)_2$ as a catalyst, along with a base and a phase transfer salt such as tetra-*n*-butylammonium bromide. These conditions were originally applied to stereospecific coupling of vinyl iodides with ethyl acrylate and methyl vinyl ketone.



Several optimization studies have been carried out under these phosphine-free conditions. The reaction of bromobenzene and styrene was studied using $Pd(OAc)_2$ as the catalyst, and potassium phosphate and *N*,*N*-dimethylacetamide (DMA) were found to be the best base and solvent. Under these conditions, the Pd content can be reduced to as low as 0.025 mol %.[142] The reaction of substituted bromobenzenes with methyl α-acetamidoacrylate has also been studied carefully, since the products are potential precursors of modified amino acids. Good results were obtained using either *N*, *N*-diisopropylethylamine or NaOAc as the base.

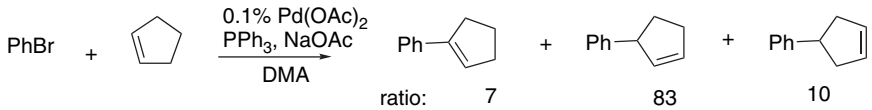
134. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, **52**, 4130 (1987); M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, **110**, 2328 (1988).
135. T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1287 (1984); T. Jeffery, *Tetrahedron Lett.*, **26**, 2667 (1985); T. Jeffery, *Synthesis*, 70 (1987); R. C. Larock and S. Babu, *Tetrahedron Lett.*, **28**, 5291 (1987).
136. A. de Meijere and F. E. Meyer, *Angew. Chem. Int. Ed. Engl.*, **33**, 2379 (1994); R. Grigg, *J. Heterocycl. Chem.*, **31**, 631 (1994); T. Jeffery, *Tetrahedron*, **52**, 10113 (1996).
137. C.-M. Andersson, K. Karabelas, A. Hallberg, and C. Andersson, *J. Org. Chem.*, **50**, 3891 (1985).
138. M. T. Reetz, G. Lehmer, and R. Schwickard, *Angew. Chem. Int. Ed.*, **37**, 481 (1998).
139. J. J. Bozell and C. E. Vogt, *J. Am. Chem. Soc.*, **110**, 2655 (1988).
140. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987); K. Karabelas and A. Hallberg, *J. Org. Chem.*, **53**, 4909 (1988).
141. T. Jeffery, *Tetrahedron Lett.*, **26**, 2667 (1985); T. Jeffery, *Synthesis*, 70 (1980).
142. Q. Yao, E. P. Kinney, and Z. Yang, *J. Org. Chem.*, **68**, 7528 (2003).



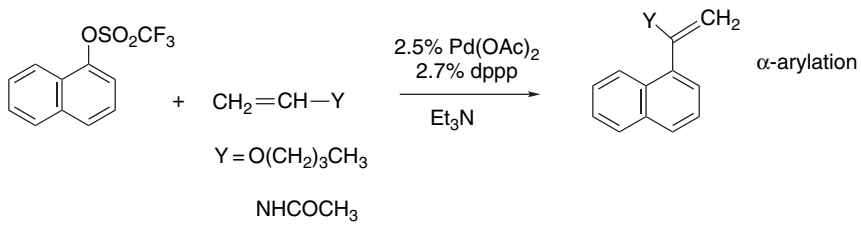
Ref. 143

Low Pd concentrations are beneficial in preventing precipitation of inactive Pd metal.[144] Small Pd clusters can be observed in phosphine-free systems,[145] and these particles may serve as catalysts or, alternatively, as reservoirs of Pd for formation of soluble reactive species.

The regiochemistry of the Heck reaction is determined by the competitive removal of the β-proton in the elimination step. Mixtures are usually obtained if more than one type of β-hydrogen is present. Often there is also double-bond migration that occurs by reversible Pd-H elimination-addition sequences. For example, the reaction of cyclopentene with bromobenzene leads to all three possible double-bond isomers.[146]



Substituents with stronger electronic effects can influence the competition between α- and β-arylation. Alkenes having EWG substituents normally result in β-arylation. However, alkenes with donor substituents give a mixture of α- and β-regioisomers. The regiochemistry can be controlled to some extent by specific reaction conditions. Bidentate phosphines such as dppp and dppf promote α-arylation of alkenes with donor substituents such as alkoxy, acetoxy, and amido. These reactions are believed to occur through the more electrophilic form of Pd(II) generated by dissociation of the triflate anion (cationic mechanism).[147] Electronic factors favor migration of the aryl group to the α-carbon. The combination of the bidentate ligand and triflate leaving group increases the importance of electronic effects on the regiochemistry.

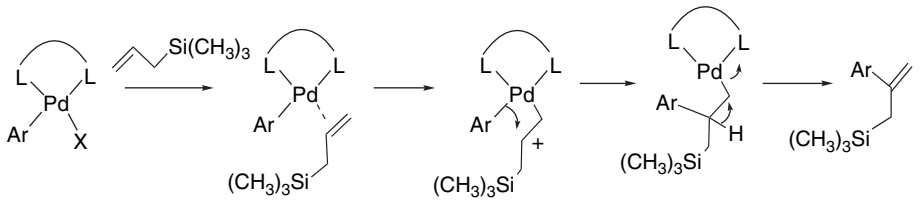


Substituents without strong donor or acceptor character (e.g., phenyl, succinimido) give mixtures. The reason for the increased electronic sensitivity is thought to be the

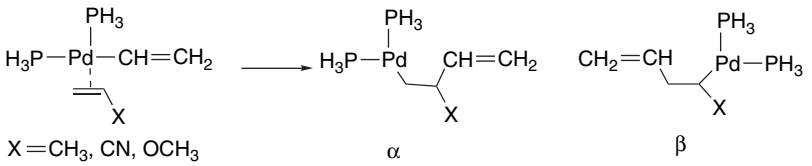
143. C. E. Williams, J. M. C. A. Mulders, J. G. de Vries, and A. H. M. de Vries, *J. Organomet. Chem.*, **687**, 494 (2003).
144. A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Hendrickx, and J. G. de Vries, *Org. Lett.*, **5**, 3285 (2003).
145. M. T. Reetz and E. Westermann, *Angew. Chem. Int. Ed. Engl.*, **39**, 165 (2000).
146. C. G. Hartung, K. Kohler, and M. Beller, *Org. Lett.*, **1**, 709 (1999).
147. W. Cabri, I. Cardiani, A. Bedeschi, and R. Santi, *J. Org. Chem.*, **55**, 3654 (1990); W. Cabri, I. Candiani, A. Bedeschi, and R. Santi, *J. Org. Chem.*, **57**, 3558 (1992). W. Cabri, I. Candiani, A. Bedeschi, S. Penco, and R. Santi, *J. Org. Chem.*, **57**, 1481 (1992).

involvement of a cationic, as opposed to a neutral, complex. The triflate anion is more likely to be dissociated than a halide.

Allylic silanes show a pronounced tendency to react at the α-carbon in the presence of bidentate ligands.[148] This regiochemistry is attributed to the preferential stabilization of cationic character by the silyl substituent. The bidentate ligands enhance the electrophilic character of the TS, and the cation stabilization of the silyl group becomes the controlling factor.



There have been several computational studies of electronic effects on the regioselectivity of the Heck reaction. Vinyl migration was studied for X = CH_3 CN, and OCH_3 using PH_3 as the ligand model.[149] Differences were calculated for the best α- and β-migration TS for each substituent. The differences were as follows: CH_3: α-migration favored by 0.1 kcal/mol; CN: β-migration favored by 4 kcal/mol; OCH_3: α-migration favored by 2 kcal/mol.



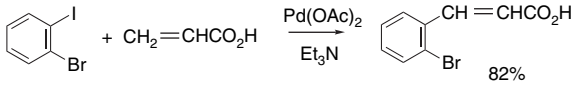
Examination of the HOMO and LUMO orbitals in these TSs indicates that the electronic effect operates mainly through the LUMO. The EWG cyano tends to localize the LUMO on the β-carbon, whereas ERG substituents have the opposite effect. Similar trends were found for Pd coordinated by diimine ligands.[150] These results indicate that the Markovnikov rule applies with the more electrophilic Pd complexes. When steric effects become dominant, the Pd adds to the less hindered position.

The Heck reaction has been applied to synthesis of intermediates and in multistage syntheses. Some examples are given in Scheme 8.9. Entries 1 and 2 illustrate both the β-regioselectivity and selectivity for aryl iodides over bromides. Entries 3 and 4 show conditions that proved favorable for cyclohexene. These examples also indicate preferential *syn* Pd-H elimination, since this accounts for formation of the 3-substituted cyclohexene as the major product.

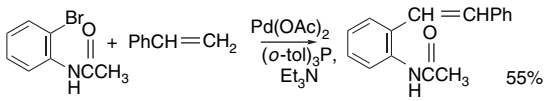
148. K. Olofsson, M. Larhed, and A. Hallberg, *J. Org. Chem.*, **63**, 5076 (1998).
149. R. J. Deeth, A. Smith, and J. M. Brown, *J. Am. Chem. Soc.*, **126**, 7144 (2004).
150. H. V. Schenck, B. Akermark, and M. Svensson, *J. Am. Chem. Soc.*, **125**, 3503 (2003).

Scheme 8.9. Palladium-Catalyzed Alkenylation of Aryl and Alkenyl Systems

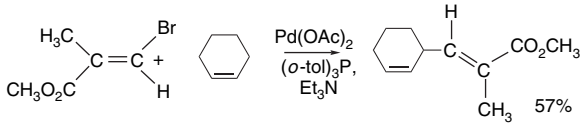
1[a]



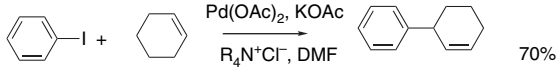
2[b]



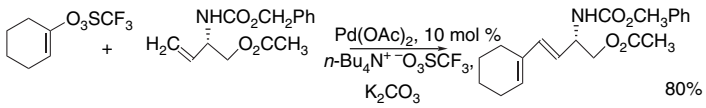
3[c]



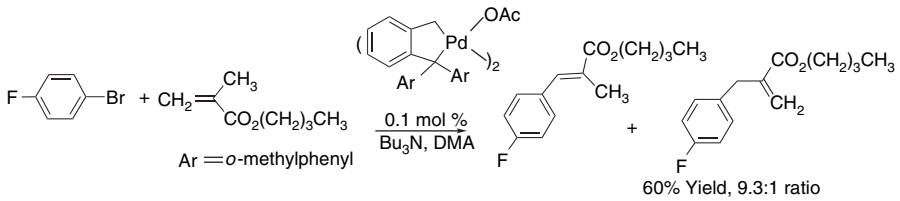
4[d]



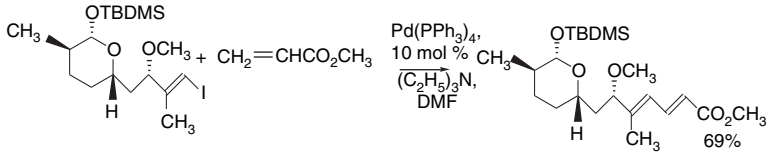
5[e]



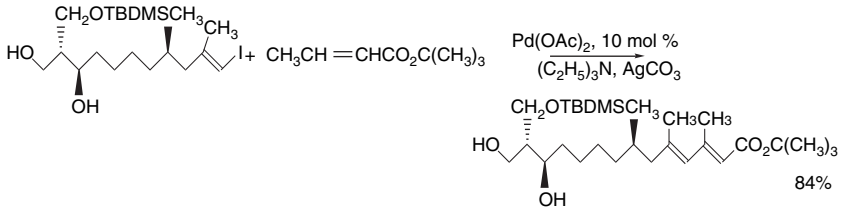
6[f]



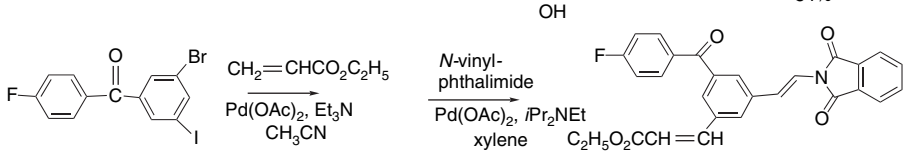
7[g]



8[h]



9[i]

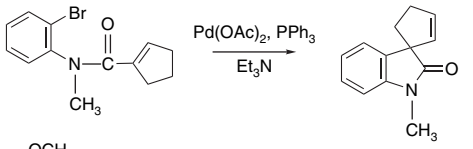


(*Continued*)

Scheme 8.9. (*Continued*)

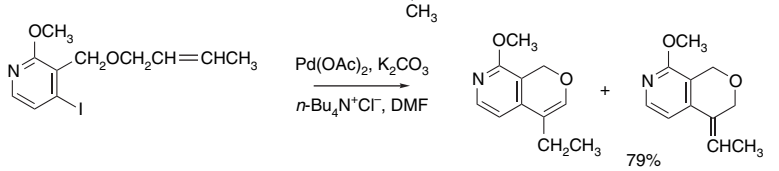
Intramolecular reactions

10[j]



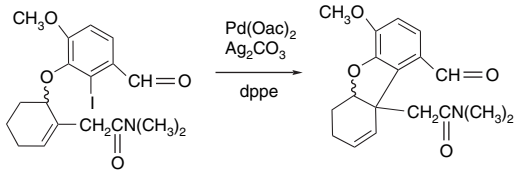
85%

11[k]



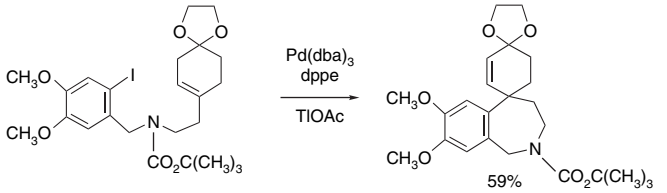
79%
11:1

12[l]



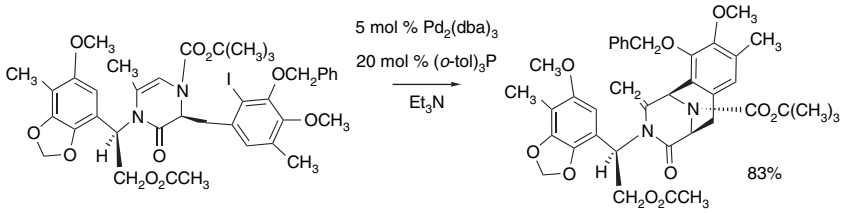
75%

13[m]



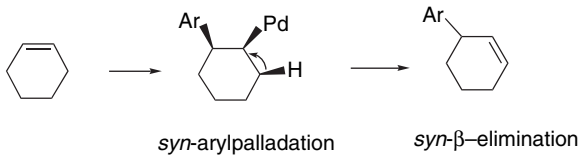
59%

14[n]



83%

a. J. E. Plevyak, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, **44**, 4078 (1979).
b. P. de Mayo, L. K. Sydnes, and G. Wenska, *J. Org. Chem.*, **45**, 1549 (1980).
c. J.-I. Kim, B. A. Patel, and R. F. Heck, *J. Org. Chem.*, **46**, 1067 (1981).
d. R. C. Larock and B. E. Baker, *Tetrahedron Lett.*, **29**, 905 (1988).
e. G. T. Crisp and M. G. Gebauer, *Tetrahedron*, **52**, 12465 (1996).
f. M. Beller and T. H. Riermeier, *Tetrahedron Lett.*, **37**, 6535 (1996).
g. L. Harris, K. Jarowicki, P. Kocienski, and R. Bell, *Synlett*, 903 (1996).
h. P. M. Wovkulich, K. Shankaran, J. Kiegel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993); T. Jeffery and J.-C. Galland, *Tetrahedron Lett.*, **35**, 4103 (1994).
i. D. C. Waite and C. P. Mason, *Org. Proc. Res. Devel.*, **2**, 116 (1998).
j. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, **59**, 4130 (1987).
k. F. G. Fang, S. Xie, and M. W. Lowery, *J. Org. Chem.*, **59**, 6142 (1994).
l. P. J. Parsons, M. D. Charles, D. M. Harvey, L. R. Sumoreeah, A. Skell, G. Spoors, A. L. Gill, and S. Smith, *Tetrahedron Lett.*, **42**, 2209 (2001).
m. C. Bru, C. Thal, and C. Guillou, *Org. Lett.*, **5**, 1845 (2003).
n. A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, and T. Fukuyama, *J. Am. Chem. Soc.*, **124**, 6552 (2002).



Entry 5 illustrates use of a vinyl triflate under the "phosphine-free" conditions. Entry 6 achieved exceptionally high catalyst efficiency by using a palladacycle-type catalyst. Entries 7 and 8 show the introduction of acrylate ester groups using functionalized alkenyl iodides. Entry 9 demonstrates two successive Heck reactions employed in a large-scale synthesis of a potential thromboxane receptor antagonist. These reactions were carried out in the absence of any phosphine ligand. The greater reactivity of the iodide over the bromide permits the sequential introduction of the two substituents.

There are numerous examples of intramolecular Heck reactions,[151] such as in Entries 10 to 14. Entry 11 is part of a synthesis of the antitumor agent camptothecin. The Heck reaction gives an 11:1 endocyclic-exocyclic mixture. Entries 12–14 are also steps in syntheses of biologically active substances. Entry 12 is part of a synthesis of maritidine, an alkaloid with cytotoxic properties; the reaction in Entry 13 is on a route to galanthamine, a potential candidate for treatment of Alzheimer's disease; and Entry 14 is a key step in the synthesis of a potent antitumor agent isolated from a marine organism.

8.2.3. Palladium-Catalyzed Cross Coupling

Palladium can catalyze carbon-carbon bond formation between aryl or vinyl halides and sulfonates and a wide range of organometallic reagents *in cross-coupling reactions*.[152] The organometallic reagents used include organolithium, organomagnesium, and organozinc reagents, as well as cuprates, stannanes, and organoboron compounds. The reaction is quite general for formation of sp^2-sp^2 and sp^2-sp bonds in biaryls, dienes, polyenes, and enynes. There are also some reactions that can couple alkyl organometallic reagents, but these are less general because of the tendency of alkylpalladium intermediates to decompose by β-elimination. Arylation of enolates also can be effected by palladium catalysts.

The basic steps in the cross-coupling reaction include oxidative addition of the aryl or vinyl halide (or sulfonate) to Pd(0), followed by transfer of an organic group from the organometallic to the resulting Pd(II) intermediate (*transmetallation*). The disubstituted Pd(II) intermediate then undergoes reductive elimination, which gives the product by carbon bond formation and regenerates the catalytically active Pd(0) oxidation level.

oxidative addition $\quad R{-}X + Pd^0 \longrightarrow R{-}Pd^{II}{-}X$

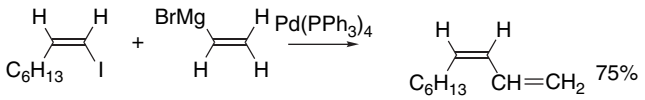
transmetallation $\quad R{-}Pd^{II}{-}X + R'{-}M \longrightarrow R{-}Pd^{II}{-}R' + M{-}X$

reductive elimination $\quad R{-}Pd^{II}{-}R' \longrightarrow R{-}R' + Pd^0$

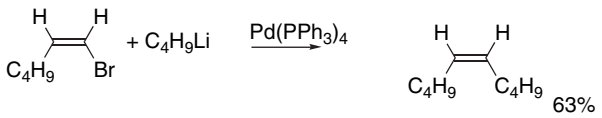
151. J. Link, *Org. React.*, **60**, 157 (2002).
152. F. Diederich and P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, 1998; S. P. Stanforth, *Tetrahedron*, **54**, 263 (1998).

Ligands and anions play a crucial role in determining the rates and equilibria of the various steps by controlling the detailed coordination environment at palladium.[153] In the next section we discuss coupling reactions involving organolithium, organomagnesium, organozinc, and organocopper reagents. We then proceed to arylation of enolates mediated by palladium catalysts. Subsequent sections consider cross coupling with stannanes (*Stille reaction*) and boron compounds (*Suzuki reaction*).

8.2.3.1. Coupling with Organometallic Reagents. Tetrakis-(triphenylphosphine) palladium catalyzes coupling of alkenyl halides with Grignard reagents and organolithium reagents. The reactions proceed with retention of configuration at the double bond.

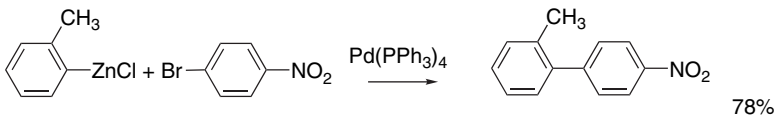


Ref. 154



Ref. 155

Organozinc compounds are also useful in palladium-catalyzed coupling with aryl and alkenyl halides. Procedures for arylzinc,[156] alkenylzinc,[157] and alkylzinc[158] reagents have been developed. The ferrocenyldiphosphine dppf has been found to be an especially good Pd ligand for these reactions.[159]



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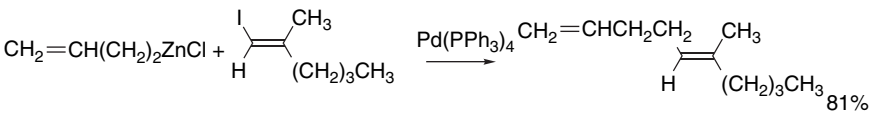


Ref. 158

153. P. J. Stang, M. H. Kowalski, M. D. Schiavelli, and D. Longford, *J. Am. Chem. Soc.*, **111**, 3347 (1989); P. J. Stang and M. H. Kowalski, *J. Am. Chem. Soc.*, **111**, 3356 (1989); M. Portnoy and D. Milstein, *Organometallics*, **12**, 1665 (1993).

154. M. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, 191 (1978).

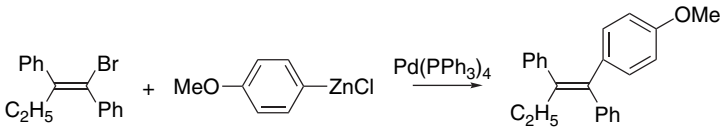
155. M. Yamamura, I. Moritani, and S. Murahashi, *J. Organometal. Chem.*, **91**, C39 (1975).

156 E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977); E. Negishi, T. Takahashi, and A. O. King, *Org. Synth.*, **66**, 67 (1987).

157 U. H. Lauk, P. Skrabal, and H. Zollinger, *Helv. Chim. Acta*, **68**, 1406 (1985); E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, and N. Okukado, *J. Am. Chem. Soc.*, **109**, 2393 (1987); J.-M. Duffault, J. Einhorn, and A. Alexakis, *Tetrahedron Lett.*, **32**, 3701 (1991).

158 E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, **102**, 3298 (1980).

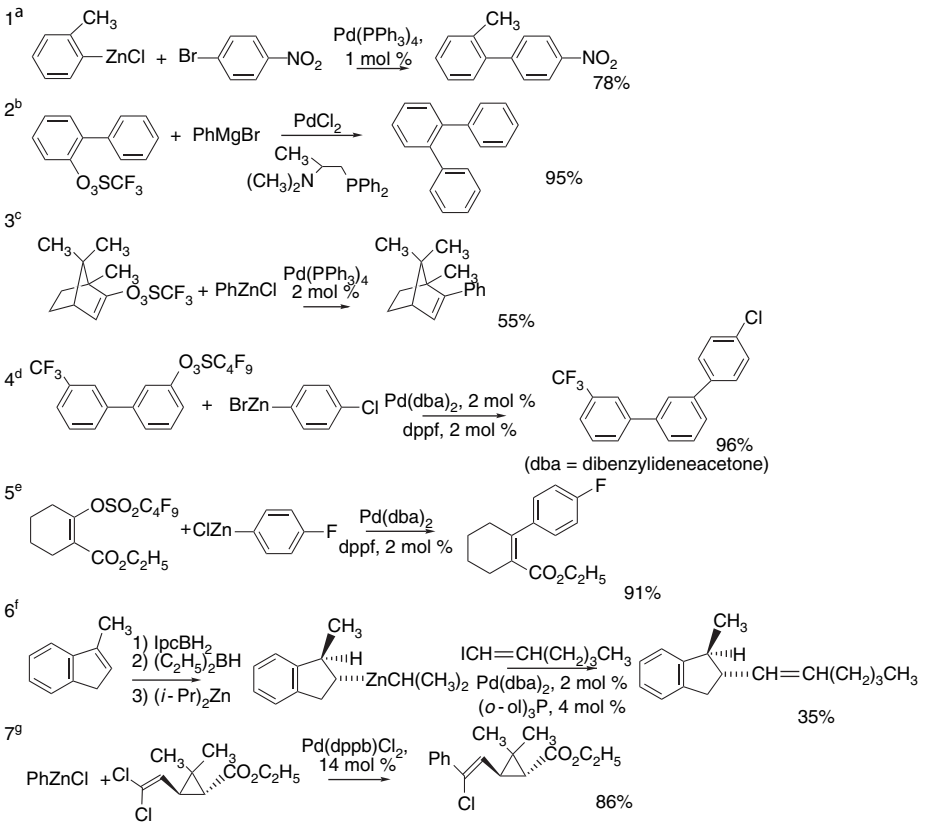
159 T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hirotsu, *J. Am. Chem. Soc.*, **106**, 158 (1984).



Ref. 160

Scheme 8.10 shows some representative coupling reactions with organomagnesium and organozinc reagents. Entry 1 shows a biaryl coupling accomplished using an arylzinc reagent. Entry 2 involves the use of a chelating ligand with an aryl triflate. The *bis*-phosphines dppe, dppp, and dppb were also effective for this coupling. Entry 3 is an example of use of a vinyl triflate. Entries 4 and 5 illustrate the use of perfluorobutanesulfonate (nonaflate) as an alternative leaving group to triflate. The organozinc

Scheme 8.10. Palladium-Catalyzed Cross Coupling of Organometallic Reagents with Halides and Sulfonates

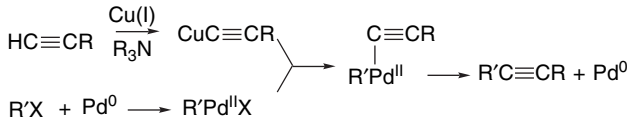


a. E. Negishi, T. Takahashi, and A. O. King, *Org. Synth.*, **VIII**, 430 (1993).
b. T. Kamikawa and T. Hayashi, *Synlett*, 163 (1997).
c. G. Stork and R. C. A. Issacs, *J. Am. Chem. Soc.*, **112**, 7399 (1990).
d. M. Rottlander and P. Knochel, *J. Org. Chem.*, **63**, 203 (1998).
e. F. Bellina, D. Ciucci, R. Rossi, and P. Vergamini, *Tetrahedron*, **55**, 2103 (1999).
f. A. Boudier and P. Knochel, *Tetrahedron Lett.*, **40**, 687 (1999).
g. A. Minato, *J. Org. Chem.*, **56**, 4052 (1991).

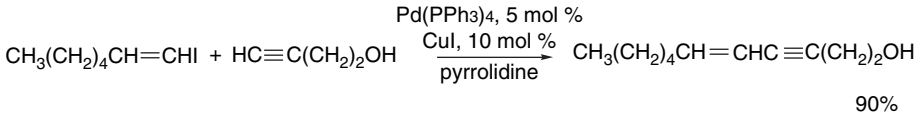
160. R. B. Miller and M. I. Al-Hassan, *J. Org. Chem.*, **50**, 2121 (1985).

reagent in Entry 4 was prepared by the hydroboration route (see Section 7.3.1.1). The reaction in Entry 7 was used to prepare analogs of the pyrethrin insecticides. There was a substantial difference in the reactivity of the two chlorides, permitting the stereoselective synthesis.

There are a number of procedures for coupling of terminal alkynes with halides and sulfonates, a reaction that is known as the *Sonogashira reaction*.[161] A combination of $Pd(PPh_3)_4$ and Cu(I) effects coupling of terminal alkynes with vinyl or aryl halides.[162] The reaction can be carried out directly with the alkyne, using amines for deprotonation. The alkyne is presumably converted to the copper acetylide, and the halide reacts with Pd(0) by oxidative addition. Transfer of the acetylide group to Pd results in reductive elimination and formation of the observed product.

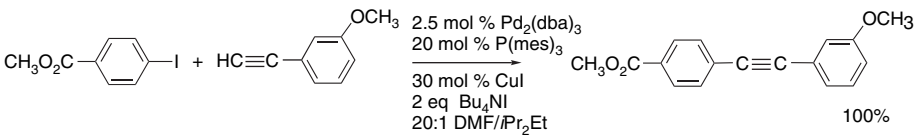


The original conditions used amines as solvents or cosolvents. Several other bases can replace the amine. Tetrabutylammonium hydroxide or fluoride can be used in THF (see Entry 1 in Scheme 8.11).[163] Tetrabutylammonium acetate is also effective with aryl iodides and EWG-substituted aryl bromides (Entry 2).[164] Use of alkenyl halides in this reaction has proven to be an effective method for the synthesis of enynes[165] (see also Entries 5 and 6 in Scheme 8.11).



Ref. 166

Several hindered phosphine ligands give enhanced reactivity. Aryl iodides can be coupled at low temperature using $Pd_2(dba)_3$ and *tris*-(mesityl)phosphine.

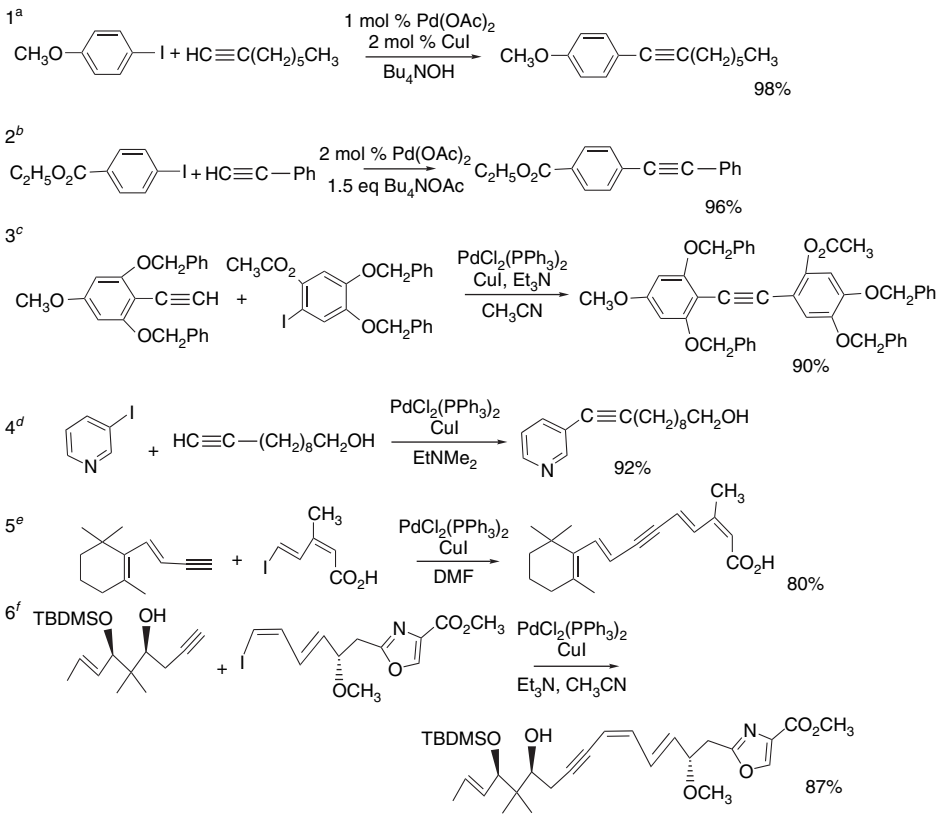


Ref. 167

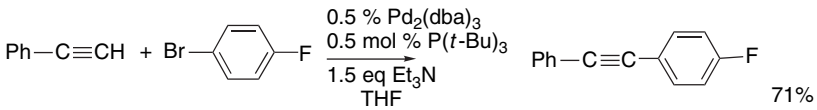
$Pd_2(dba)_3$ with *tris*-*t*-butylphosphine is an effective catalyst and functions in the absence of copper.[168]

161. R. R. Tykwinski, *Angew. Chem. Int. Ed. Engl.*, **42**, 1566 (2003).
162. K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 4467 (1975).
163. A. Mori, T. Shimada, T. Kondo, and A. Sekiguchi, *Synlett*, 649 (2001).
164. S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*, **69**, 5752 (2004).
165. V. Ratovelomana and G. Linstrumelle, *Synth. Commun.*, **11**, 917 (1981); L. Crombie and M. A. Horsham, *Tetrahedron Lett.*, **28**, 4879 (1987); G. Just and B. O'Connor, *Tetrahedron Lett.*, **29**, 753 (1988); D. Guillerm and G. Linstrumelle, *Tetrahedron Lett.*, **27**, 5857 (1986).
166. M. Alami, F. Ferri, and G. Linstrumelle, *Tetrahedron Lett.*, **34**, 6403 (1993).
167. K. Nakamura, H. Okubo, and M. Yamaguchi, *Synlett*, 549 (1999).
168. V. P. W. Bohm and W. A. Herrmann, *Eur. J. Org. Chem.*, 3679 (2000).

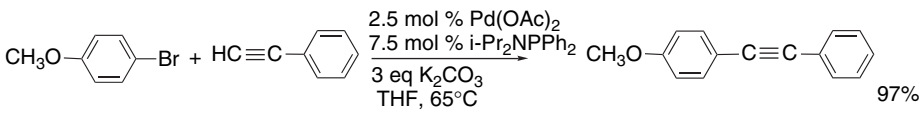
Scheme 8.11. Palladium-Catalyzed Coupling of Alkynes



a. S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*, **69**, 5752 (2004).
b. A. Mori, T. Shimada, T. Kondo, and A. Sekiguchi, *Synlett*, 649 (2001)
c. C. C. Li, Z. X. Xie, Y. D. Zhang, J. H. Chen, and Z. Yang, *Org. Lett.*, **5**, 3919 (2003).
d. J. Krauss and F. Bracher, *Arch. Pharm.*, **337**, 371 (2004).
e. M. Abarbri, J. Thibonnet, J.-L. Parrain, and A. Duchene, *Tetrahedron Lett.*, **43**, 4703 (2002).
f. M. C. Hillier, A. T. Price, and A. I. Meyers, *J. Org. Chem.*, **66**, 6037 (2001).

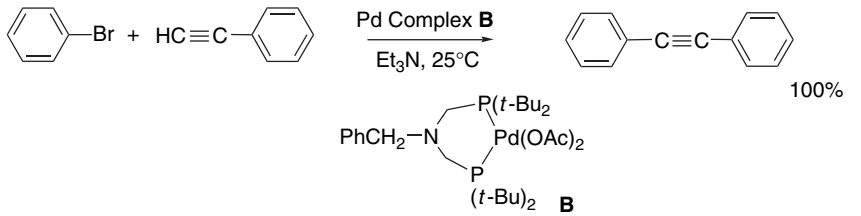


Various aminophosphines have also been found to catalyze coupling in the absence of copper.



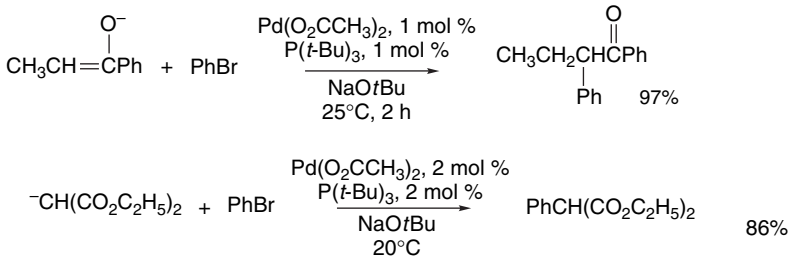
Ref. 169

169. J. Cheng, Y. Sun, F. Wang, M. Guo, J.-H. Xu, Y. Pan, and Z. Zhang, *J. Org. Chem.*, **69**, 5428 (2004).

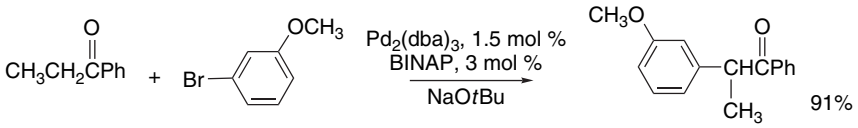


Ref. 170

8.2.3.2. Palladium-Catalyzed Arylation of Enolates. Very substantial progress has been made in the use of Pd-catalyzed cross coupling for arylation of enolates and enolate equivalents. This reaction provides an important method for arylation of enolates, which is normally a difficult transformation to accomplish.[171] A number of phosphine ligands have been found to promote these reactions. Bulky trialkyl phosphines such as *tris*-(*t*-butyl)phosphine with a catalytic amount of $Pd(OAc)_2$ results in phenylation of the enolates of aromatic ketones and diethyl malonate.[172]

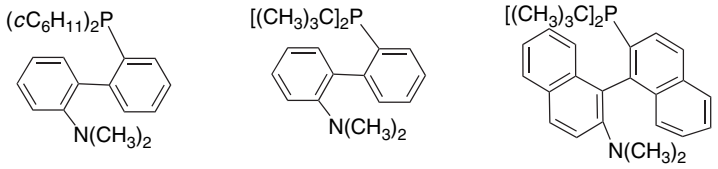


Phenylation has also been achieved with the diphosphine ligands BINAP and tol-BINAP.



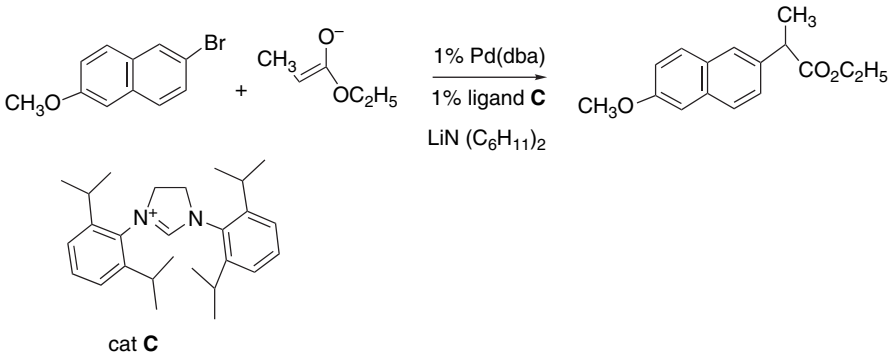
Ref. 173

Several biphenylphosphines with 2′-amino substituents are also effective in arylation of ester enolates.[174] Among the esters that were successfully arylated were *t*-butyl acetate, *t*-butyl propanoate, and ethyl phenylacetate. The ester enolates were generated with LiHMDS.

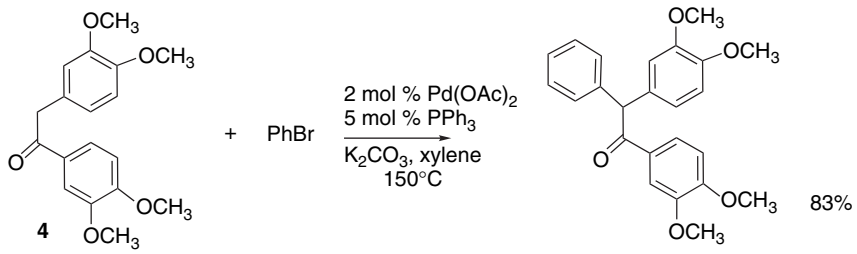


170. D. Mery, K. Heuze, and D. Astruc, *Chem. Commun.*, 1934 (2003).
171. D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, **36**, 234 (2003).
172. M. Kawatsura and J. E. Hartwig, *J. Am. Chem. Soc.*, **121**, 1473 (1999).
173. M. Palucki and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 11108 (1997).
174. W. A. Moradi and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 7996 (2001).

Carbenoid imidazolidene ligands such as **C** can also be used in conjunction with $Pd(dba)_2$, and this method has been applied to α-arylpropanoic acids (NSAIDS) such as naproxen.[175]

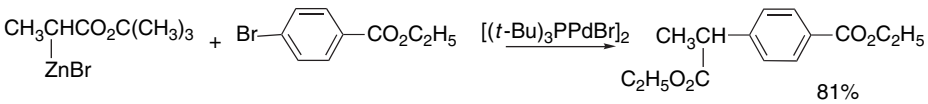


Highly arylated ketones have been prepared successfully. For example, arylation of the enolate of the deoxybenzoin **4** gives 1,1,2-triarylethanones that are related to substances such as tamoxifen.[176]



Similar reactions have been carried out using polymer-supported catalysts.[177]

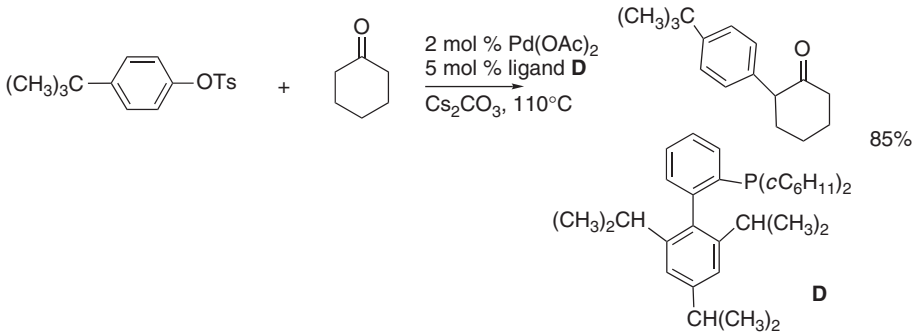
Arylations have also been extended to zinc enolates of esters (Reformatsky reagents).[178]



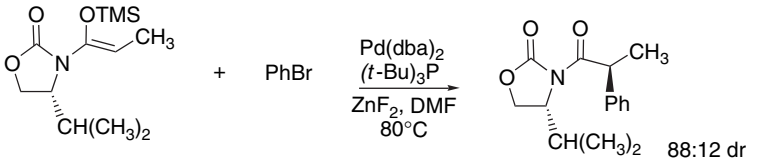
These conditions can also be applied to enolates prepared from α-halo amides.

175. M. Jorgensen, S. Lee, X. Liu, J. P. Wolkowski, and J. F. Hartwig, *J. Am. Chem. Soc.*, **124**, 12557 (2002).
176. F. Churruca, R. SanMartin, I. Tellitu, and E. Dominguez, *Org. Lett.*, **4**, 1591 (2002).
177. F. Churruca, R. SanMartin, M. Carrill, I. Tellitu, and E. Dominguez, *Tetrahedron*, **60**, 2393 (2004).
178. T. Hama, X. Liu, D. A. Culkin, and J. F. Hartwig, *J. Am. Chem. Soc.*, **125**, 11176 (2003).

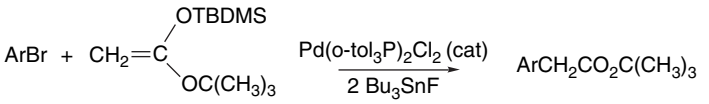
Enolate arylation has also been extended to aryl tosylates. The preferred catalyst includes a very bulky biphenyl phosphine **D**.[179]



Conditions for arylation of enolate equivalents have also been developed. In the presence of ZnF_2, silyl enol ethers, silyl ketene acetals, and similar compounds react. For example, the TMS derivatives of *N*-acyl oxazolidinones can be arylated.

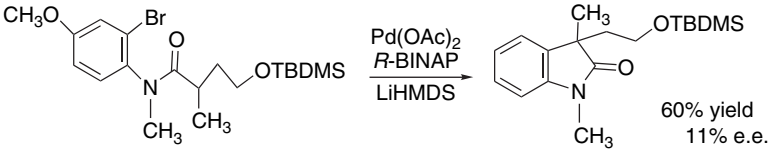


Arylacetate esters have been generated by coupling aryl bromides with stannyl enolates generated from silyl ketene acetals.



Ref. 180

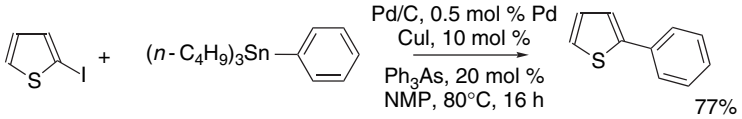
Intramolecular arylations are possible and several studies have examined the synthesis of biologically active compounds such as oxindoles.[181] For example, a synthesis of physovenine has been reported using this methodology.



Ref. 182

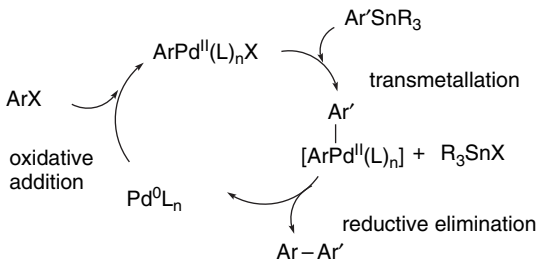
179. H. N. Nguyen, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 11818 (2003).
180. F. Agnelli and G. A. Sulikowski, *Tetrahedron Lett.*, **39**, 8807 (1998).
181. S. Lee and J. F. Hartwig, *J. Org. Chem.*, **66**, 3402 (2001).
182. T. Y. Zhang and H. Zhong, *Tetrahedron Lett.*, **43**, 1363 (2002).

8.2.3.3. Coupling with Stannanes. Another important group of cross-coupling reactions, known as *Stille reactions*, uses aryl and alkenyl stannanes as the organometallic component.[183] The reactions are carried out with Pd(0) catalysts in the presence of phosphine ligands and have proven to be very general with respect to the halides that can be used. Benzylic, aryl, alkenyl, and allylic halides can all be utilized,[184] and the groups that can be transferred from tin include alkyl, alkenyl, aryl, and alkynyl. The approximate order of the effectiveness of transfer of groups from tin is alkynyl > alkenyl > aryl > methyl > alkyl, so unsaturated groups are normally transferred selectively.[185] Subsequent studies have found better ligands, including *tris*-(2-furyl)phosphine[186] and triphenylarsine.[187] Aryl-aryl coupling rates are increased by the presence of a Cu(I) cocatalyst,[188] which has led to a simplified protocol in which Pd-C catalyst, along with CuI and Ph_3As, gives excellent yields of biaryls.



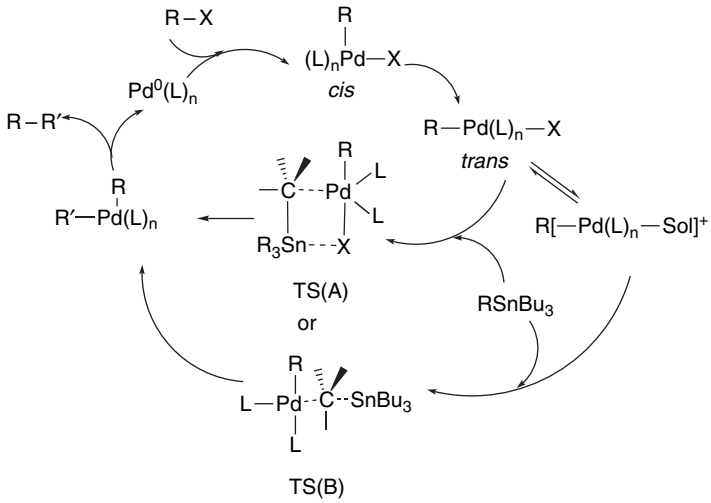
Ref. 189

The general catalytic cycle of the Stille reaction involves oxidative addition, transmetallation, and reductive elimination.



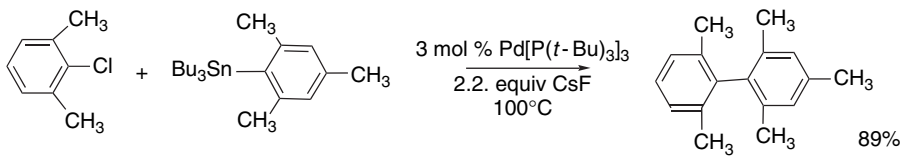
The role of the ligands is both to stabilize the Pd(0) state and to "tune" the reactivity of the palladium. The outline mechanism above does not specify many detailed aspects of the reaction that are important to understanding the effect of ligands, added salts, and solvents. Moreover, it does not address the stereochemistry, either in terms of the Pd center (tetracoordinate? pentacoordinate?, *cis*?, *trans*?) or of the reacting carbon groups (inversion?, retention?). Some of these issues are addressed by a more detailed mechanism.[190]

183. J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, **25**, 508 (1986); T. N. Mitchell, *Synthesis*, 803 (1992); V. Farina, V. Krishnamurthy, and W. J. Scott, *Org. React.*, **50**, 1 (1998).
184. F. K. Sheffy, J. P. Godschalx, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984); I. P. Beltskaya, *J. Organomet. Chem.*, **250**, 551 (1983); J. K. Stille and B. L. Groth, *J. Am. Chem. Soc.*, **109**, 813 (1987).
185. J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983).
186. V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, **113**, 9585 (1991).
187. V. Farina, B. Krishnan, D. R. Marshall, and G. P. Roth, *J. Org. Chem.*, **58**, 5434 (1993).
188. V. Farina, S. Kapadia, B. Krishnan, C. Wang, and L. S. Liebskind, *J. Org. Chem.*, **59**, 5905 (1994).
189. G. P. Roth, V. Farina, L. S. Liebeskind, and E. Pena-Cabrera, *Tetrahedron Lett.*, **36**, 2191 (1995).
190. P. Espinet and A. Echavarren, *Angew. Chem. Int. Ed. Engl.*, **43**, 4704 (2004).



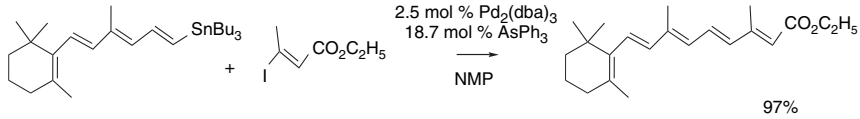
The oxidative addition is considered to give a *cis* Pd complex that can rearrange to the more stable *trans* complex. The mechanism also takes account of the possibility of exchange of the ligands by solvent (or anions that may be present). This mechanism suggests that the transmetallation can occur either with retention (TS-A) or inversion (TS-B), which is consistent with experimental observations of both outcomes. The reductive elimination is believed to occur from a *cis* complex, and the ligands can play a role in promoting this configuration. The ligands can also affect the rate and position of the off-on equilibria. Thus there are several factors that affect the detailed kinetics of the reaction and these can be manipulated in optimization of the reaction conditions. Especially when triflates are used as the electrophilic reactant, added LiCl can have a beneficial effect. The chloride is believed to facilitate the oxidative addition step by reversible formation of an anionic complex that is more nucleophilic than the neutral species. (Compare with the anionic mechanisms for the Heck reaction on p. 716.)[191] The harder triflate does not have this effect. Acetate ions can also accelerate the reaction.[192] Copper salts are believed to shift the extent of ligation at the palladium by competing for the phosphine ligand.[193] The kinetics of Stille reactions catalyzed by triphenylarsine have been studied in some detail.[194] In this system, displacement of an arsine ligand by solvent DMF precedes the transmetallation step.

Various phosphine ligands have been employed. *Tris*-(*t*-butyl)phosphine is an excellent ligand and is applicable to both vinyl and arylstannanes, including sterically hindered ones. Aryl chlorides are reactive under these conditions.[195]

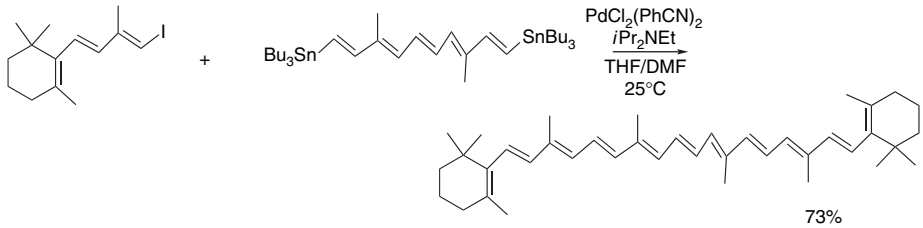


191. C. Amatore, A. Jutand, and A. Suarez, *J. Am. Chem. Soc.*, **115**, 9531 (1993); C. Amatore and A. Jutand, *Acc. Chem. Res.*, **33**, 314 (2000).
192. C. Amatore, E. Carre, A. Jutland, M. M'Barki, and G. Meyer, *Organometallics*, **14**, 5605 (1995).
193. A. L. Casado and P. Espinet, *Organometallics*, **22**, 1305 (2003).
194. C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, N. A. Ndedi, and L. Ricard, *J. Am. Chem. Soc.*, **125**, 4212 (2003).
195. A. F. Littke, L. Schwarz, and G. C. Fu, *J. Am. Chem. Soc.*, **124**, 6343 (2002).

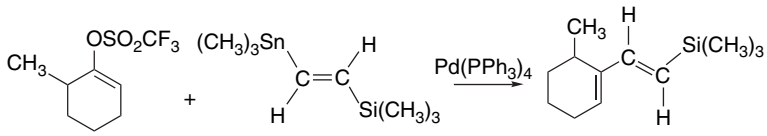
The Stille reaction can be used with alkenyl stannanes, alkenyl halides, and triflates,[196] and the reactions occur with retention of configuration at both the halide and stannane. These methods are applicable to stereospecific syntheses of materials such as the retinoids.[197]



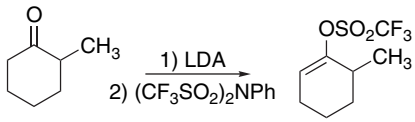
Carotene has been synthesized from a symmetrical 1,10-*bis*-(tri-*n*-butyl stannyl) decapentaene.[198]



The versatility of Pd-catalyzed coupling of stannanes has been extended by the demonstration that alkenyl triflates are also reactive.[199]

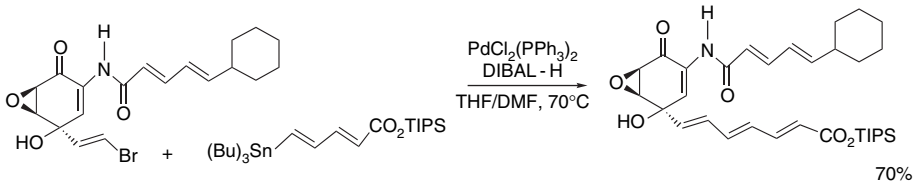


The alkenyl triflates can be prepared from ketones,[200] and methods are available for regioselective preparation of alkenyl triflates from unsymmetrical ketones.[201]



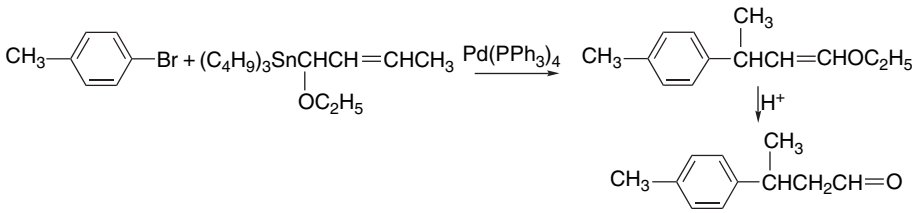
The coupling reaction can tolerate a number of functional groups, as illustrated by a step in the synthesis of the antibiotic nisamycin.

196. W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986).
197. B. Dominguez, B. Iglesias, and A. R. de Lera, *Tetrahedron*, **55**, 15071 (1999).
198. B. Vaz, R. Alvarez, and A. R. de Lera, *J. Org. Chem.*, **67**, 5040 (2002).
199. W. J. Scott, G. T. Crisp, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4630 (1984); W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, **21**, 47 (1988).
200. P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 85 (1982).
201. J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, **24**, 979 (1983).



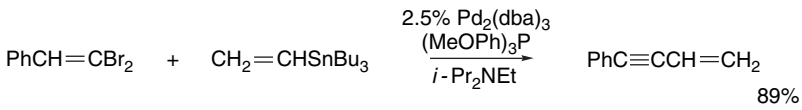
Ref. 202

The Stille coupling reaction is very versatile with respect to the functionality that can be carried in both the halide and the tin reagent. Groups such as ester, nitrile, nitro, cyano, and formyl can be present, which permits applications involving "masked functionality." For example, when the coupling reaction is applied to 1-alkoxy-2-butenylstannanes, the double-bond shift leads to a vinyl ether that can be hydrolyzed to an aldehyde.

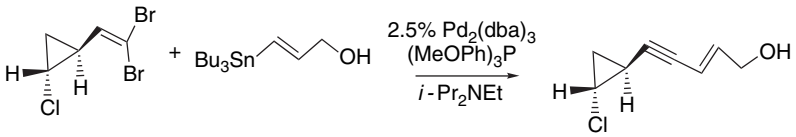


Ref. 203

Alkenylstannanes react with 1,1-dibromoalkenes to give enynes.[204] These reactions are thought to involve elimination of the elements of HBr prior to reductive elimination.



This reaction has been used in the synthesis of a portion of callipeltoside, a substance with anticancer activity.

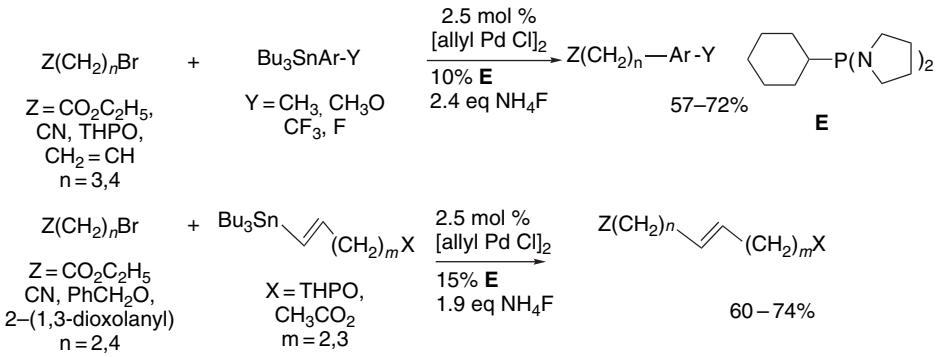


Ref. 205

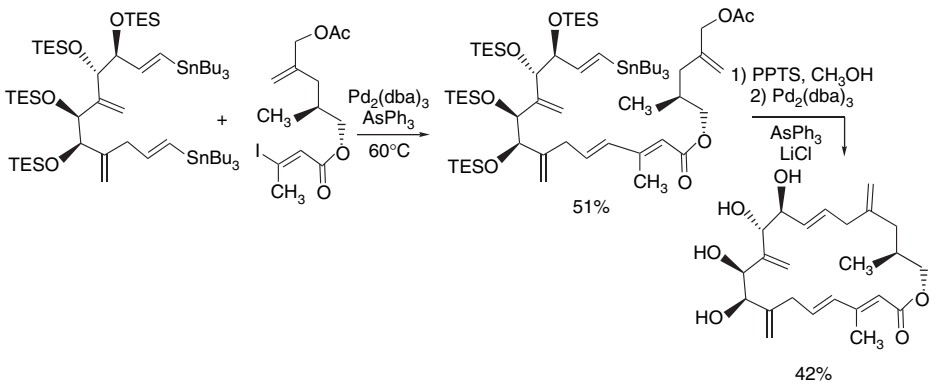
The most problematic cases for the Stille reaction involve coupling saturated systems. The tendency for β-elimination of alkylpalladium compounds requires special conditions. *Bis*-(dialkylamino)cyclohexylphosphines have shown considerable success

202. P. Wipf and P. D. G. Coish, *J. Org. Chem.*, **64**, 5053 (1999).
203. A. Duchene and J.-P. Quintard, *Synth. Commun.*, **15**, 873 (1987).
204. W. Shen and L. Wang, *J. Org. Chem.*, **64**, 8873 (1999).
205. H. F. Olivo, F. Velazquez, and H. C. Trevisan, *Org. Lett.*, **2**, 4055 (2000).

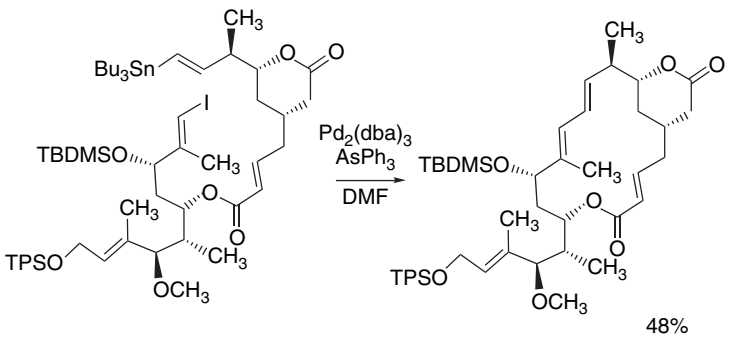
in promoting coupling of saturated primary bromides and iodides with alkenyl and aryl stannanes.[206]



The Stille reaction has been successfully applied to a number of macrocyclic ring closures.[207] In a synthesis of amphidinolide A, the two major fragments were coupled via a selective Stille reaction, presumably governed by steric factors. After deprotection the ring was closed by coupling the second vinyl stannane group with an allylic acetate.[208]

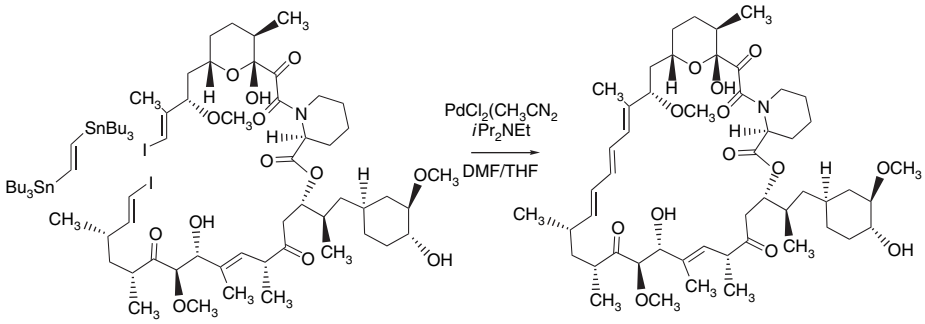


A similar cross-coupling reaction was used for macrocylization in the synthesis of rhizoxin A.[209]



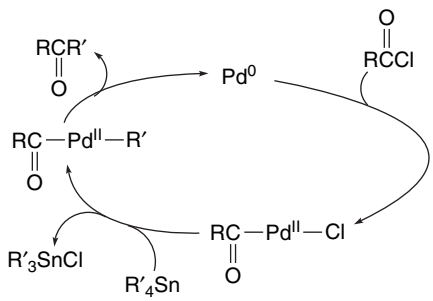
206. H. Tang, K. Menzel, and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **42**, 5079 (2003).
207. M. A. J. Duncton and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1235 (1999).
208. H. W. Lam and G. Pattenden, *Angew. Chem. Int. Ed. Engl.*, **41**, 508 (2002).
209. I. S. Mitchell, G. Pattenden, and J. P. Stonehouse, *Tetrahedron Lett.*, **43**, 493 (2002).

A striking example of a macrocyclic closure is found in the double "stitching" done in the final step of the synthesis of the immunosuppressant rapamycin. *Bis*-1,2-(tri-*n*-butylstannyl)ethene reacted with the diiodide to close a 31-membered ring in 28% yield at 70% conversion. The intermediate iodostannane (from a single coupling) was also isolated in about 30% yield and could be cyclized in a second step.[210]



Some other examples of Pd-catalyzed coupling of organostannanes with halides and triflates are given in Scheme 8.12. Entries 1 and 2 are early examples that show that the reaction can be done with either ERG or EWG substituents on the aromatic ring. Entry 3 is an example of the use of an aryl triflate. Entry 5 was developed in the exploration of the synthetic potential of cyclobutendiones. Entries 6 to 11 are various alkenyl-alkenyl and alkenyl-aryl couplings using iodides and triflates. Entries 12 to 14 involve heterocyclic structures in the synthesis of several antibiotics. Entry 15 involves coupling of a protected glycoside with a vinyl triflate and an α-oxystannane. Entry 16 involves an alkynylstannane and generates a deca-1,6-diyne ring. Entries 17 and 18 show the use of allylic and benzylic bromides.

Procedures for the synthesis of ketones based on coupling of organostannanes with acyl halides have also been developed.[211] The catalytic cycle is similar to that involved in coupling with aryl halides. The scope of compounds to which the reaction is applicable includes tetra-*n*-butylstannane. This example indicates that the reductive elimination step competes successfully with β-elimination.



Scheme 8.13 gives some examples of these reactions.

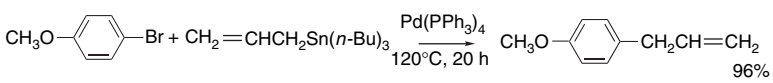
210. K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, and P. Bertinato, *J. Am. Chem. Soc.*, **115**, 4419 (1993).

211. D. Milstein and J. K. Stille, *J. Org. Chem.*, **44**, 1613 (1979); J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983).

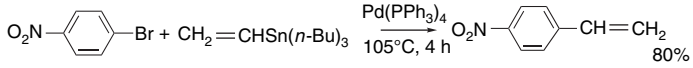
Scheme 8.12. Palladium-Catalyzed Coupling of Stannanes with Halides and Sulfonates

A. Aryl halides

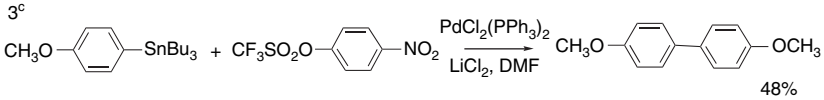
1[a]



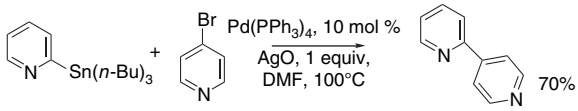
2[b]



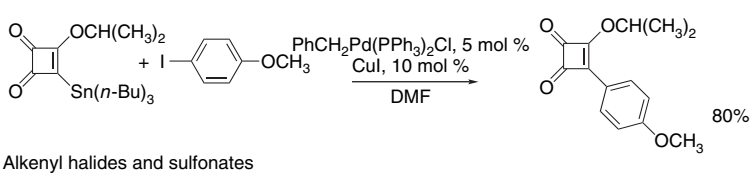
3[c]



4[d]

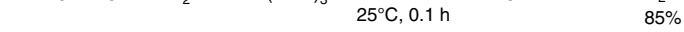


5[e]

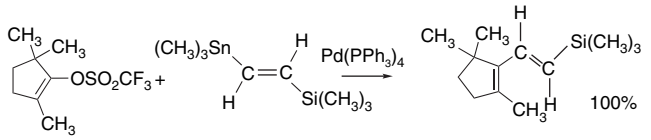


B. Alkenyl halides and sulfonates

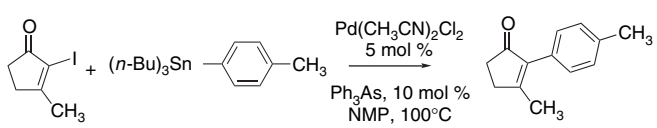
6[f]



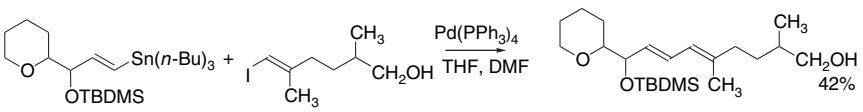
7[g]



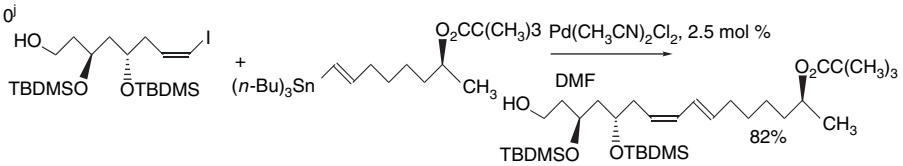
8[h]



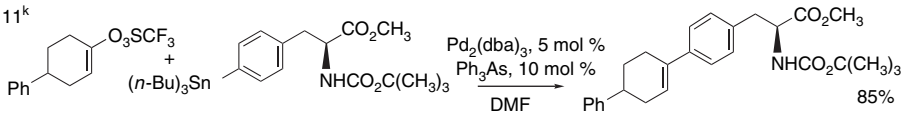
9[i]



10[j]



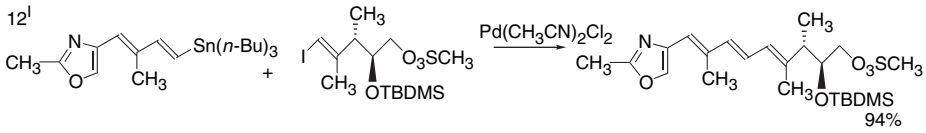
11[k]



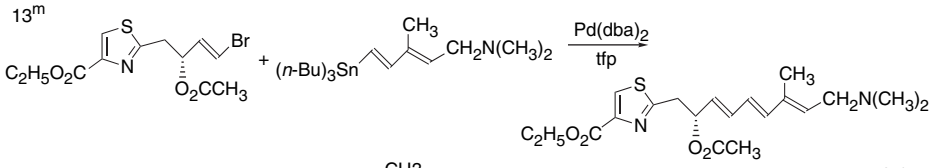
(*Continued*)

Scheme 8.12. (*Continued*)

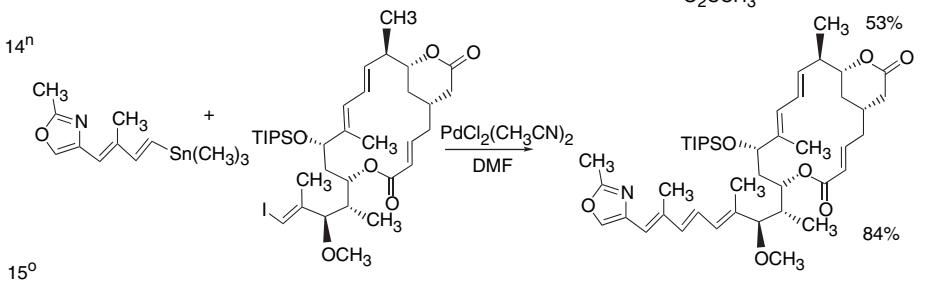
12[l]



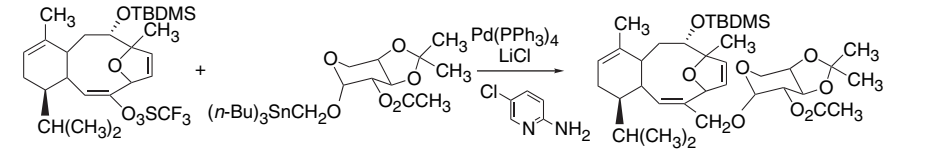
13[m]



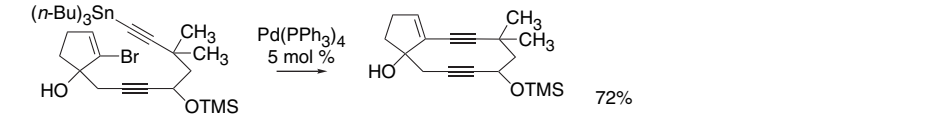
14[n]



15[o]

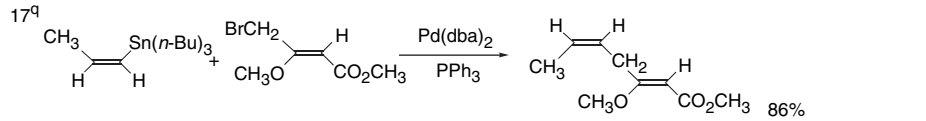


16[p]

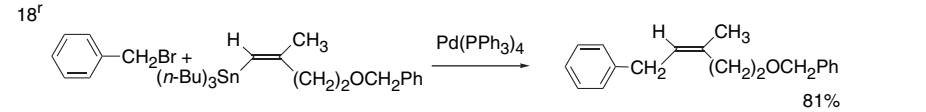


C. Allylic and benzylic halides

17[q]



18[r]



a. M. Kosugi, K. Sasazawa, Y. Shimizu, and T. Migata, *Chem. Lett.*, 301 (1977).
b. D. R. McKean, G. Parrinello, A. F. Renaldo, and J. K. Stille, *J. Org. Chem.*, **52**, 422 (1987).
c. J. K. Stille, A. M. Echavarren, R. M. Williams, and J. A. Hendrix, *Org. Synth.*, **IX**, 553 (1998).
d. J. Malm, P. Bjork, S. Gronowitz, and A.-B. Hornfeldt, *Tetrahedron Lett.*, **33**, 2199 (1992).
e. L. S. Liebeskind and R. W. Fengl, *J. Org. Chem.*, **55**, 5359 (1990).
f. J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, **109**, 813 (1987).
g. W. J. Scott, G. T. Crisp, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4630 (1984).
h. C. R. Johnson, J. P. Adams, M. P. Braun, and C. B. W. Senanayake, *Tetrahedron Lett.*, **33**, 919 (1992).
i. E. Claus and M. Kalesse, *Tetrahedron Lett.*, **40**, 4157 (1999).
j. A. B. Smith, III, and G. R. Ott, *J. Am. Chem. Soc.*, **120**, 3935 (1998).
k. E. Morera and G. Ortar, *Synlett*, 1403 (1997).
l. J. D. White, M. A. Holoboski, and N. J. Green, *Tetrahedron Lett.*, **38**, 7333 (1997).
m. D. Romo, R. M. Rzasa, H. E. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, and J. O. Liu, *J. Am. Chem. Soc.*, **120**, 12237 (1998).

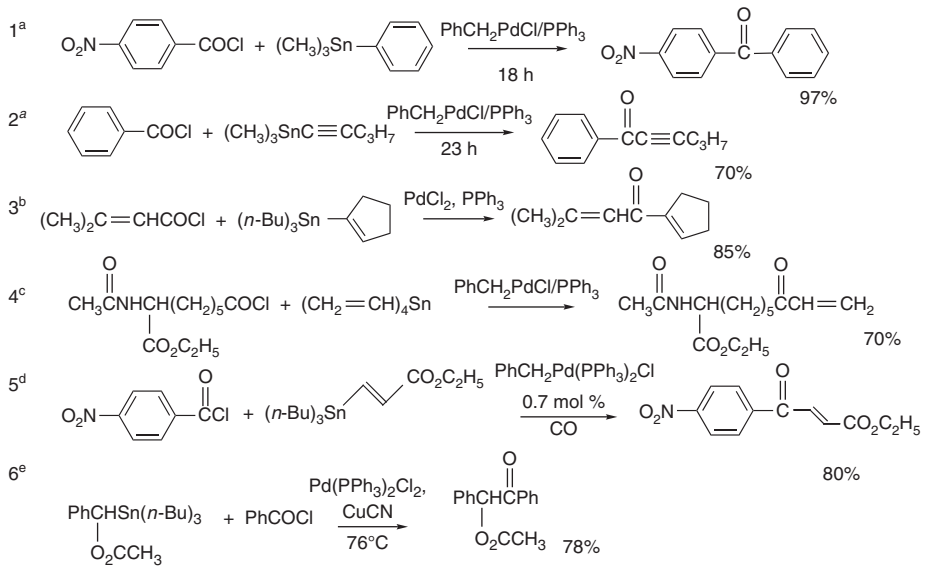
(*Continued*)

Scheme 8.12. (*Continued*)

n. J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. N. Kolz, and B. W. Phillips, *J. Org. Chem.*, **67**, 7750 (2002).
o. X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, and S. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 789 (1999).
p. M. Hirama, K. Fujiwara, K. Shigematu, and Y. Fukazawa, *J. Am. Chem. Soc.*, **111**, 4120 (1989).
q. F. K. Sheffy, J. P. Godschalx, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984).
r. J. Hibino, S. Matsubara, Y. Morizawa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **25**, 2151 (1984).

8.2.3.4. Coupling with Organoboron Reagents. The *Suzuki reaction* is a palladium-catalyzed cross-coupling reaction in which the organometallic component is a boron compound.[212] The organoboron compounds that undergo coupling include boronic acids,[213] boronate esters,[214] and boranes.[215] The overall mechanism is closely related to that of the other cross-coupling methods. The aryl halide or triflate reacts with the Pd(0) catalyst by oxidative addition. The organoboron compound serves as the source of the

Scheme 8.13. Synthesis of Ketones from Acyl Chlorides and Stannanes



a. J. W. Labadie, D. Tueting, and J. K. Stille, *J. Org. Chem.*, **48**, 4634 (1983).
b. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 6417 (1984).
c. D. H. Rich, J. Singh, and J. H. Gardner, *J. Org. Chem.*, **48**, 432 (1983).
d. A. F. Renaldo, J. W. Labadie, and J. K. Stille, *Org. Synth.*, **67**, 86 (1988).
e. J. Ye, R. K. Bhatt, and J. R. Falck, *J. Am. Chem. Soc.*, **116**, 1 (1994).

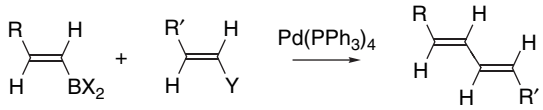
212. N. Miyaura, T. Yanagi, and A. Suzuki, *Synth. Commun.*, **11**, 513 (1981); A. Miyaura and A. Suzuki, *Chem. Rev.*, **95**, 2457 (1995); A. Suzuki, *J. Organomet. Chem.*, **576**, 147 (1999).
213. W. R. Roush, K. J. Moriarty, and B. B. Brown, *Tetrahedron Lett.*, **31**, 6509 (1990); W. R. Roush, J. S. Warmus, and A. B. Works, *Tetrahedron Lett.*, **34**, 4427 (1993); A. R. de Lera, A. Torrado, B. Iglesias, and S. Lopez, *Tetrahedron Lett.*, **33**, 6205 (1992).
214. T. Oh-e, N. Miyaura, and A. Suzuki, *Synlett*, 221 (1990); J. Fu, B. Zhao, M. J. Sharp, and V. Sniekus, *J. Org. Chem.*, **56**, 1683 (1991).
215. T. Oh-e, N. Miyauara, and A. Suzuki, *J. Org. Chem.*, **58**, 2201 (1993); Y. Kobayashi, T. Shimazaki, H. Taguchi, and F. Sato, *J. Org. Chem.*, **55**, 5324 (1990).

second organic group by transmetallation, and the disubstituted Pd(II) intermediate then undergoes reductive elimination. It appears that either the oxidative addition or the transmetallation can be rate determining, depending on reaction conditions.[216] With boronic acids as reactants, base catalysis is normally required and is believed to involve the formation of the more reactive boronate anion in the transmetallation step.[217]

$$\mathrm{ArX + Pd^0 \longrightarrow Ar{-}Pd^{II}{-}X}$$
$$\mathrm{Ar'B(OH)_2 + {}^{-}OH \rightleftharpoons [Ar'B(OH)_3]^-}$$
$$\mathrm{[Ar'B(OH)_3]^- + Ar{-}Pd^{II}{-}X \longrightarrow Ar{-}Pd^{II}{-}Ar' + B(OH)_3 + X^-}$$
$$\mathrm{Ar{-}Pd^{II}{-}Ar' \longrightarrow Ar{-}Ar' + Pd^0}$$

In some synthetic applications, specific bases such as Cs_2CO_3[218] or TlOH[219] have been found preferable to NaOH. Cesium fluoride can play a similar function by forming fluoroborate anions.[220] In addition to aryl halides and triflates, aryldiazonium ions can be the source of the electrophilic component in coupling with arylboronic acids.[221] Conditions for effecting Suzuki coupling in the absence of phosphine ligands have been developed.[222] One of the potential advantages of the Suzuki reaction, especially when boronic acids are used, is that the boric acid is a more innocuous by-product than the tin-derived by-products generated in Stille-type couplings.

Alkenylboronic acids, alkenyl boronate esters, and alkenylboranes can be coupled with alkenyl halides by palladium catalysts to give dienes.[223]

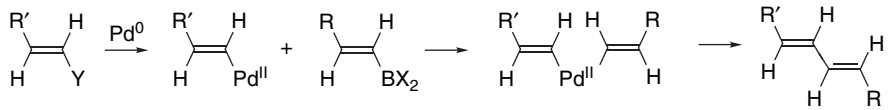


X = OH, OR, R
Y = Br. I

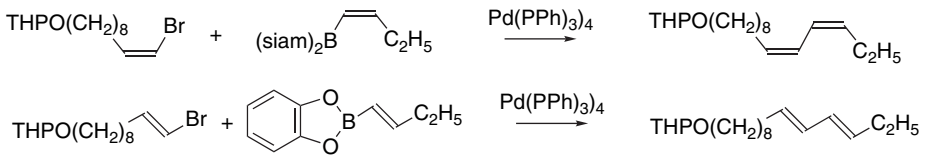
These reactions proceed with retention of double-bond configuration in both the boron derivative and the alkenyl halide. The oxidative addition by the alkenyl halide, transfer

216. G. B. Smith, G. C. Dezeny, D. L. Hughes, A. D. King, and T. R. Verhoeven, *J. Org. Chem.*, **59**, 8151 (1994).
217. K. Matos and J. B. Soderquist, *J. Org. Chem.*, **63**, 461 (1998).
218. A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **37**, 3387 (1998).
219. J. Uenishi, J.-M. Beau, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, **109**, 4756 (1987); J. C. Anderson, H. Namli, and C. A. Roberts, *Tetrahedron*, **53**, 15123 (1997).
220. S. W. Wright, D. L. Hageman, and L. D. McClure, *J. Org. Chem.*, **59**, 6095 (1994).
221. S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer, and J.-P. Demoute, *Tetrahedron Lett.*, **37**, 3857 (1996); S. Darses, T. Jeffery, J.-L. Brayer, J.-P. Demoute, and J.-P. Genet, *Bull. Soc. Chim. Fr.*, **133**, 1095 (1996); S. Sengupta and S. Bhattacharyya, *J. Org. Chem.*, **62**, 3405 (1997).
222. T. L. Wallow and B. M. Novak, *J. Org. Chem.*, **59**, 5034 (1994); D. Badone, M. B. R. Cardamone, A. Ielmini, and U. Guzzi, *J. Org. Chem.*, **62**, 7170 (1997).
223. (a) N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985); (b) N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986); (c) F. Bjorkling, T. Norin, C. R. Unelius, and R. B. Miller, *J. Org. Chem.*, **52**, 292 (1987).

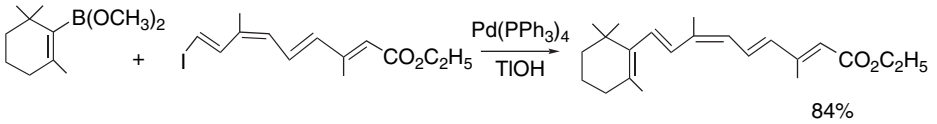
of an alkenyl group from boron to palladium, and reductive elimination all occur with retention of configuration.



Both alkenyl disiamylboranes and *B*-alkenylcatecholboranes also couple stereospecifically with alkenyl bromides.[224]

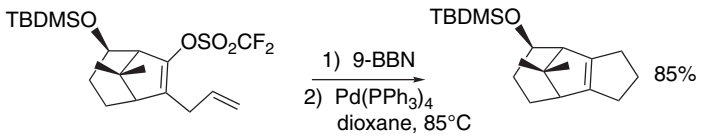


Boronate esters have been used for the preparation of polyunsaturated systems such as retinoic acid esters.



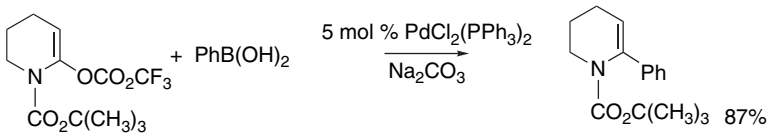
Ref. 225

Intramolecular Suzuki reactions have been done by hydroboration followed by coupling.



Ref. 226

Triflates prepared from *N*-alkoxycarbonyllactams can be coupled with aryl and alkenylboronic acids.[227]



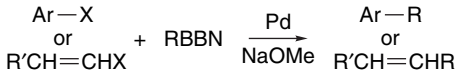
224. (a) N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985); (b) N. Miyaura, T. Ishiyama, M. Ishikawa, and A. Suzuki, *Tetrahedron Lett.*, **27**, 6369 (1986); (c) N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986); (d) Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, and A. Suzuki, *Tetrahedron Lett.*, **29**, 1811 (1988).

225. Y. Pazos, B. Iglesias, and A. R. de Lera, *J. Org. Chem.*, **66**, 8483 (2001).

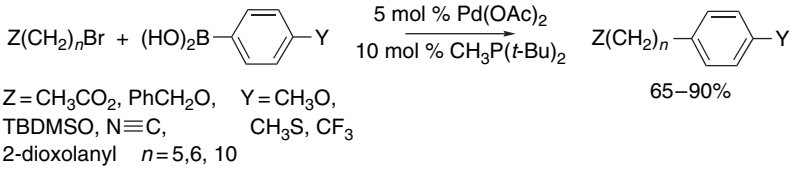
226. K. Shimada, M. Nakamura, T. Suzuka, J. Matsui, R. Tatsumi, K. Tsutsumi, T. Morimoto, H. Kurosawa, and K. Kakiuchi, *Tetrahedron Lett.*, **44**, 1401 (2003).

227. E. G. Occhiato, A. Trabocchi, and A. Guarna, *J. Org. Chem.*, **66**, 2459 (2001).

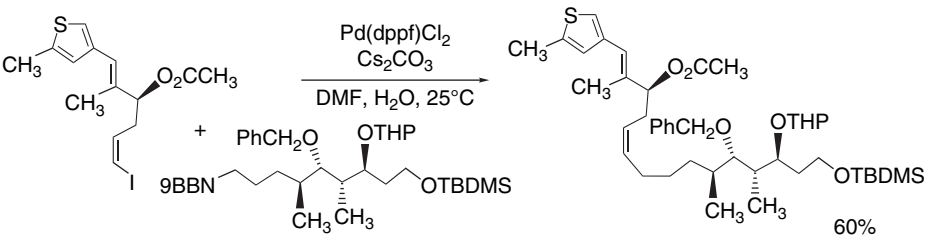
Alkyl substituents on boron in 9-BBN derivatives can be coupled with either vinyl or aryl halides through Pd catalysts.[224b] This is an especially interesting reaction because of its ability to effect coupling of saturated alkyl groups. Palladium-catalyzed couplings of alkyl groups by most other methods often fail because of the tendency for β-elimination



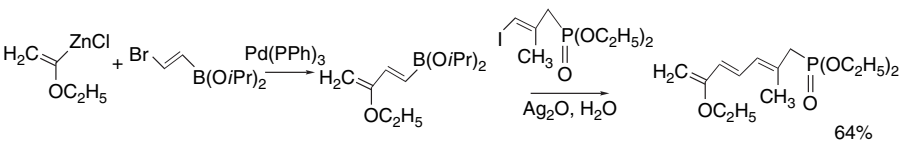
One catalyst that has been found amenable to alkyl systems is $CH_3P(t\text{-Bu})_2$ or the corresponding phosphonium salt.[228] A range of substituted alkyl bromides were coupled with arylboronic acids.



Suzuki couplings have been used in the synthesis of complex molecules. For example, coupling of two large fragments of the epothilone A structure was accomplished in this way.[229]



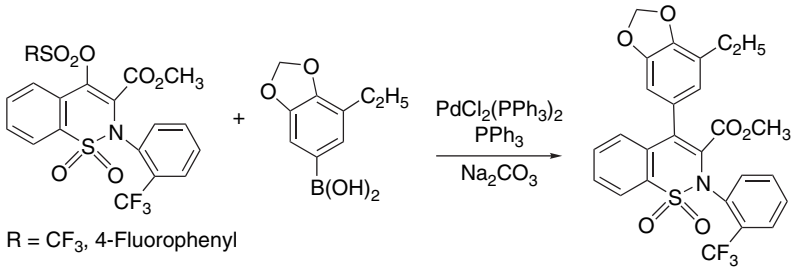
A portion of the side chain of calyculin was prepared by a tandem reaction sequence that combined an alkenylzinc reagent with 2-bromoethenylboronate, followed by Suzuki coupling with a vinyl iodide in the same pot.[230]



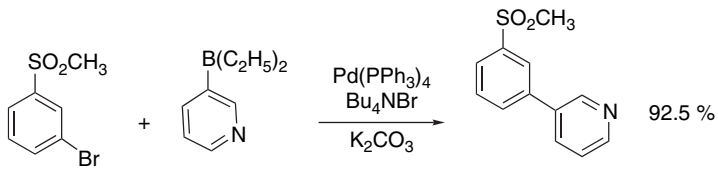
There are also several examples of the use of Suzuki reactions in scale-up synthesis of drug candidates. In the synthesis of CI-1034, an endothelin antagonist, a triflate,

228. J. H. Kirchoff, M. R. Netherton, I. D. Hills, and G. C. Fu, *J. Am. Chem. Soc.*, **124**, 13662 (2002).
229. B. Zhu and J. S. Panek, *Org. Lett.*, **2**, 2575 (2000); see also A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **35**, 2801 (1996).
230. A. B. Smith, III, G. K. Friestad, J. Barbosa, E. Bertounesque, J. J.-W. Duan, K. G. Hull, M. Iwashima, Y. Qui, P. G. Spoors, and B. A. Salvatore, *J. Am. Chem. Soc.*, **121**, 10478 (1999).

and boronic acid were coupled in 95% yield on an 80-kg scale.[231] For reasons of cost, a replacement was sought for the triflate group, and the most promising was the 4-fluorobenzenesulfonate.

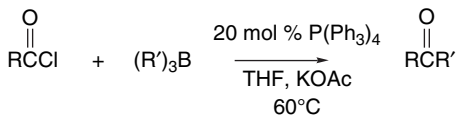


A coupling of a 3-pyridylborane was used in the synthesis of a potential CNS agent.[232] The product (278 kg) was isolated in 92.5% yield as the methanesulfonate salt.



Scheme 8.14 gives some examples of cross coupling using organoboron reagents. Entries 1 to 3 illustrate biaryl coupling. The conditions in Entry 1 are appropriate for the relatively unreactive chlorides. The conditions in Entries 2 and 3 involve no phosphine ligands. The reactions in Entries 4 and 5 illustrate the use of diazonium ions as reactants. Entry 6 illustrates the use of highly substituted reactants. Entry 7 involves use of a cyclic boronate ester. Entries 8 and 9 pertain to heteroaromatic rings. Entry 10 shows the use of a solid-supported reactant. Part B of Scheme 8.14 illustrates several couplings of alkenylboron reagents including catecholboranes (Entries 11 and 12), boronate esters (Entry 13), and boronic acids (Entries 14 and 15). The latter reaction was applied to the synthesis of a retinoate ester. Entry 16 employs a lactone-derived triflate. Entries 17 to 20 are examples of the use of Suzuki couplings in multistage synthesis. Entries 21 to 24 illustrate the applicability of the reaction to alkylboranes. Entry 25 applies phosphine-free conditions to an allylic bromide.

Ketones can also be prepared by palladium-catalyzed reactions of boranes or boronic acids with acyl chlorides. Both saturated and aromatic acyl chlorides react with trialkylboranes in the presence of $Pd(PPh_3)_4$.[233]



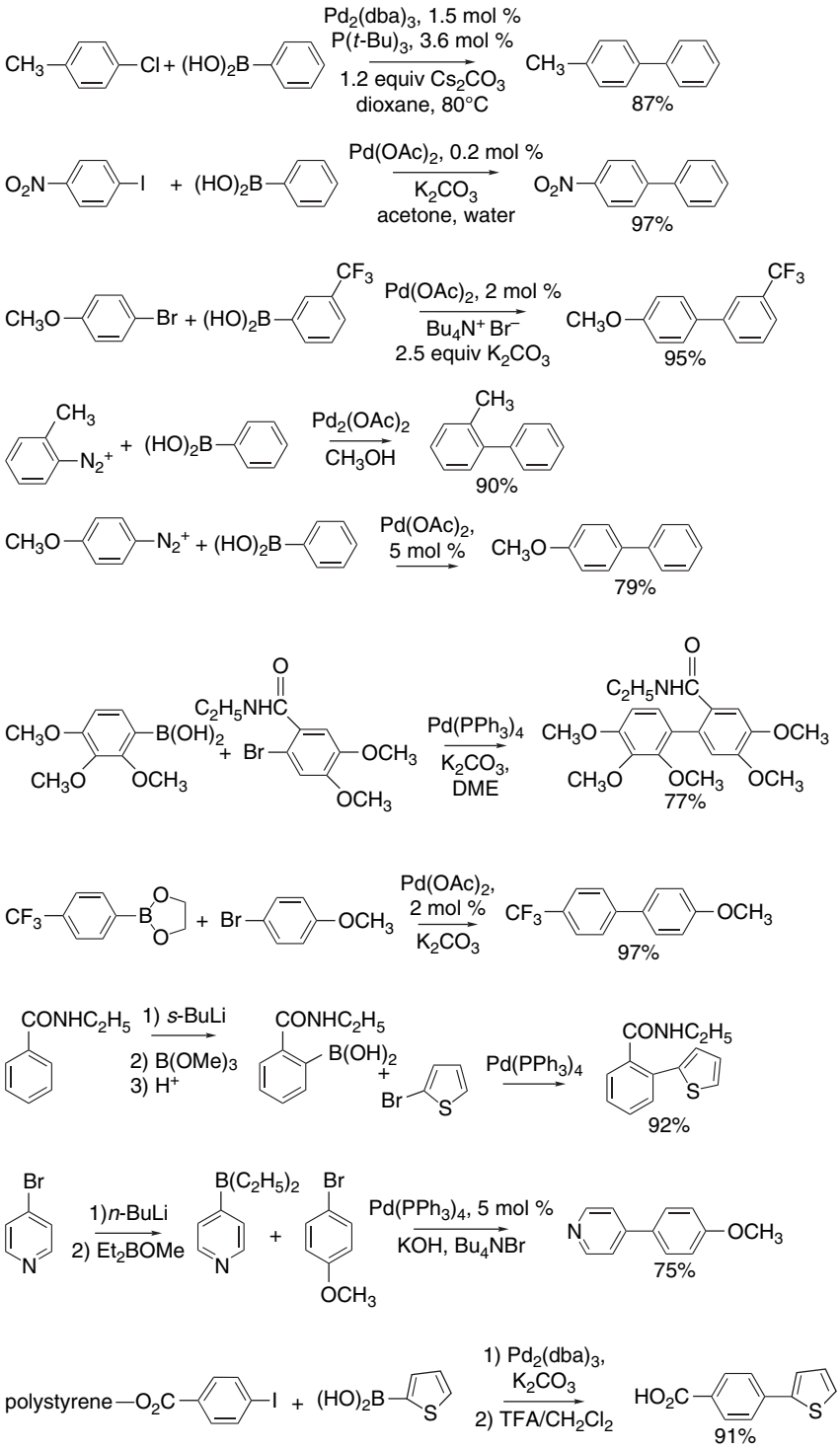
231. T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanniga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Dev.*, **8**, 201 (2004).

232. M. F. Lipton, M. A. Mauragis, M. T. Maloney, M. F. Veley, D. W. Vander Bor, J. J. Newby, R. B. Appell, and E. D. Daugs, *Org. Proc. Res. Dev.*, **7**, 385 (2003).

233. G. W. Kabalka, R. R. Malladi, D. Tejedor, and S. Kelly, *Tetrahedron Lett.*, **41**, 999 (2000).

Scheme 8.14. Palladium-Catalyzed Cross Coupling of Organoboron Reagents

A. Biaryl formation

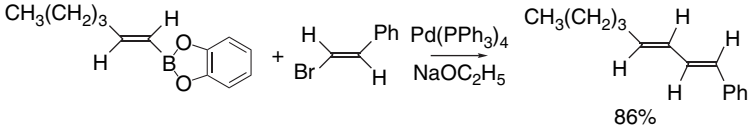


(*Continued*)

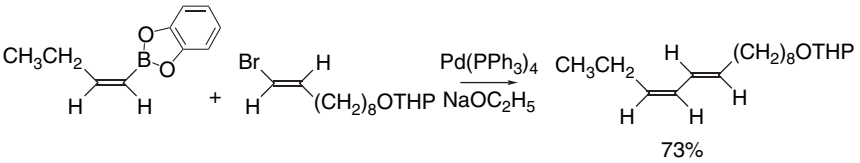
Scheme 8.14. (*Continued*)

B. Alkenylboranes and alkylboronic acids

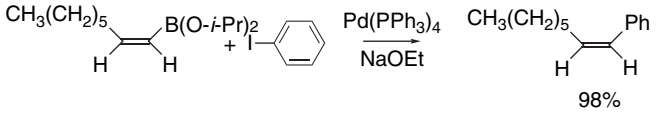
11[j]



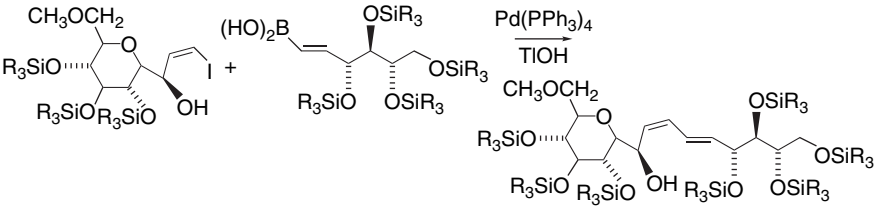
12[k]



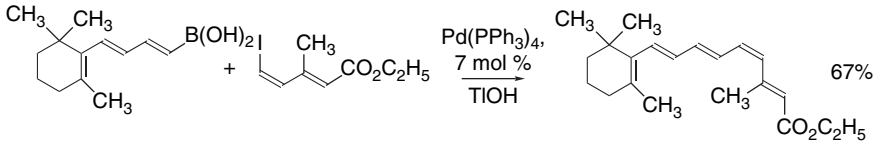
13[l]



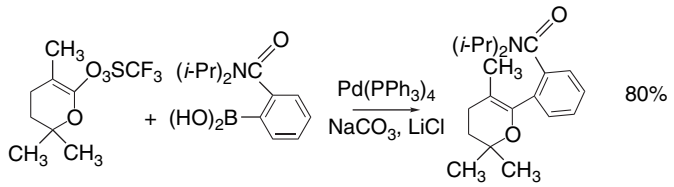
14[m]



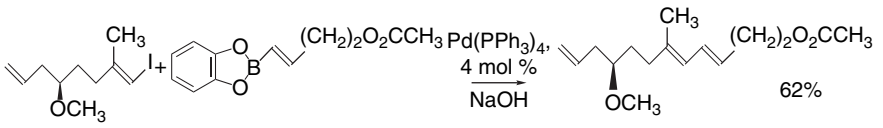
15[n]



16[o]



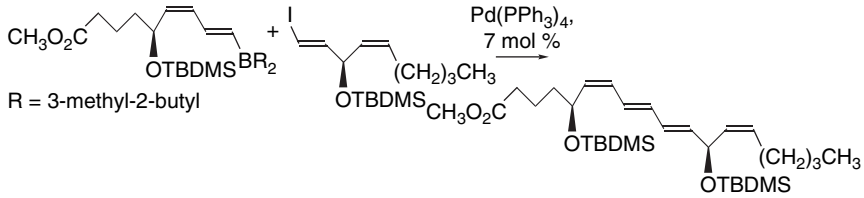
17[p]



(*Continued*)

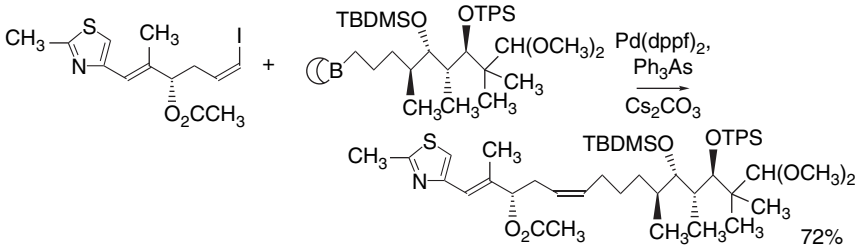
Scheme 8.14. (*Continued*)

18[q]



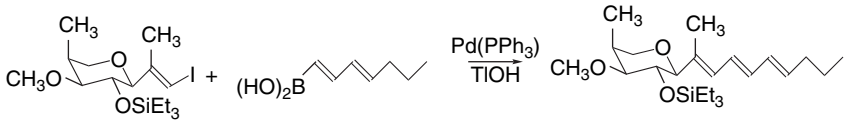
76%

19[r]



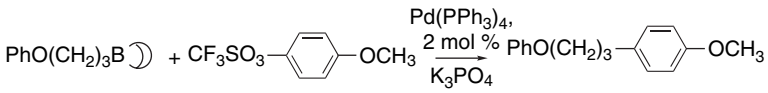
72%

20[s]



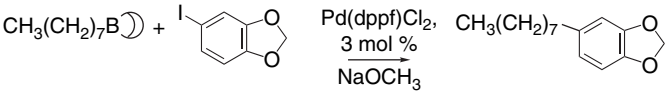
C. Alkyl–aryl coupling

21[t]



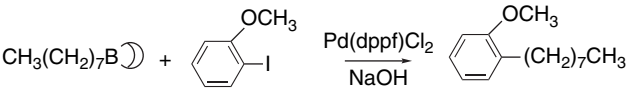
92%

22[u]



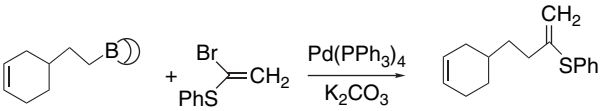
78%

23[v]



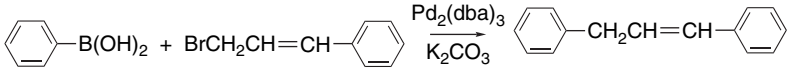
90%

24[w]



73–81%

25[x]



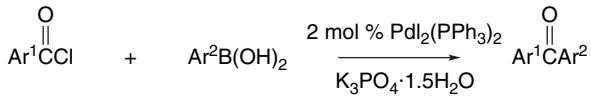
73%

(*Continued*)

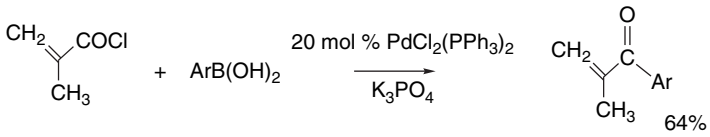
Scheme 8.14. (*Continued*)

a. F. Little and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **37**, 3387 (1998).
b. T. L. Wallow and B. M. Novak, *J. Org. Chem.*, **59**, 5034 (1994).
c. D. Badone, M. Baroni, R. Cardamone, A Ielmini, and U. Guzzi, *J. Org. Chem.*, **62**, 7170 (1997).
d. S. Darses, T. Jeffery, J.-L. Brayer, J.-P. Demoute, and J.-P. Genet, *Bull. Soc. Chim. Fr.* **133**, 1095 (1996); S. Sengupta and S. Bhattacharyya, *J. Org. Chem.*, **62**, 3405 (1997).
e. S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer, and J.-P. Demoute, *Tetrahedron Lett.*, **37**, 3857 (1996).
f. B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, and V. Snieckus, *J. Org. Chem.*, **56**, 3763 (1991).
g. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **26**, 5997 (1985).
h. M. Ishikura, T. Ohta, and M. Terashima, *Chem. Pharm. Bull.*, **33**, 4755 (1985).
i. J. W. Guiles, S. G. Johnson, and W. V. Murray, *J. Org. Chem.*, **61**, 5169 (1996).
j. N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985).
k. F. Bjorkling, T. Norin, C. R. Unelius, and R. B. Miller, *J. Org. Chem.*, **52**, 292 (1987).
l. N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986).
m. J. Uenishi, J.-M. Beau, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, **109**, 4756 (1987).
n. A. R. de Lera, A. Torrado, B. Iglesias, and S. Lopez, *Tetrahedron Lett.*, **33**, 6205 (1992).
o. M. A. F. Brandao, A. B. de Oliveira, and V. Snieckus, *Tetrahedron Lett.*, **34**, 2437 (1993).
p. J. D. White, T. S. Kim, and M. Nambu, *J. Am. Chem. Soc.*, **119**, 103 (1997).
q. Y. Kobayashi, T. Shimazaki, H. Taguchi, and F. Sato, *J. Org. Chem.*, **55**, 5324 (1990).
r. D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997).
s. A. G. M. Barrett, A. J. Bennett, S. Menzer, M. L. Smith, A. J. P. White, and D. J. Williams, *J. Org. Chem.*, **64**, 162 (1999).
t. T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.*, **58**, 2201 (1993).
u. N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, and A. Suzuki, *J. Am. Chem. Soc.*, **111**, 314 (1989).
v. N. Miyaura, T. Ishiyama, M. Ishikawa, and A. Suzuki, *Tetrahedron Lett.*, **27**, 6369 (1986).
w. T. Ishiyama, N. Miyaura, and A. Suzuki, *Org. Synth.*, **71**, 89 (1993).
x. M. Moreno-Manas, F. Pajuelo, and R. Pleixarts, *J. Org. Chem.*, **60**, 2396 (1995).

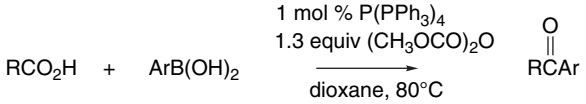
Aromatic acyl chlorides also react with arylboronic acids to give ketones.[234]



α, β-Unsaturated acyl chlorides can also be converted to ketones by reaction with arylboronic acids.[235]



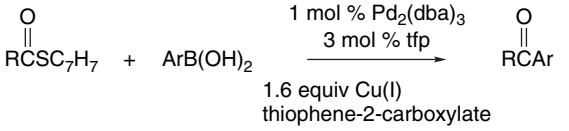
Ketones can also be prepared directly from carboxylic acids by activation as mixed anhydrides by dimethyl dicarbonate.[236] These conditions were used successfully with alkanoic and alkanedioic acids, as well as aromatic acids.



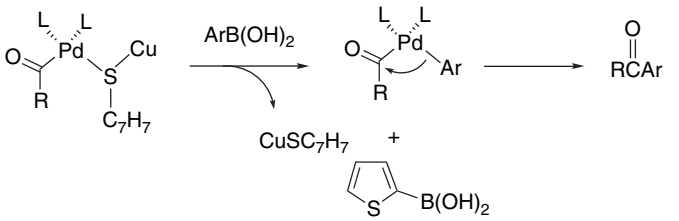
In all these reactions, the acylating reagent reacts with the active Pd(0) catalyst to give an acyl Pd(II) intermediate. Transmetallation by the organoboron derivative and reductive elimination generate the ketone.

234. Y. Urawa and K. Ogura, *Tetrahedron Lett.*, **44**, 271 (2003).
235. Y. Urawa, K. Nishiura, S. Souda, and K. Ogura, *Synthesis*, 2882 (2003).
236. R. Kakino, H. Narahashi, I. Shimizu, and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **75**, 1333 (2002).

Ketones can also be prepared from 4-methylphenylthiol esters. These reactions require a stoichiometric amount of a Cu(I) salt and the thiophene-2-carboxylate was used.[237]



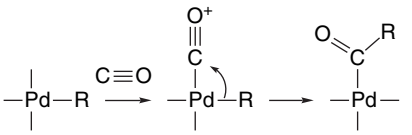
The copper salt is believed to function by promoting the transmetallation stage.



These reaction conditions were applicable to the thiol esters of alkanoic, heteroaromatic, and halogenated acetic acids.

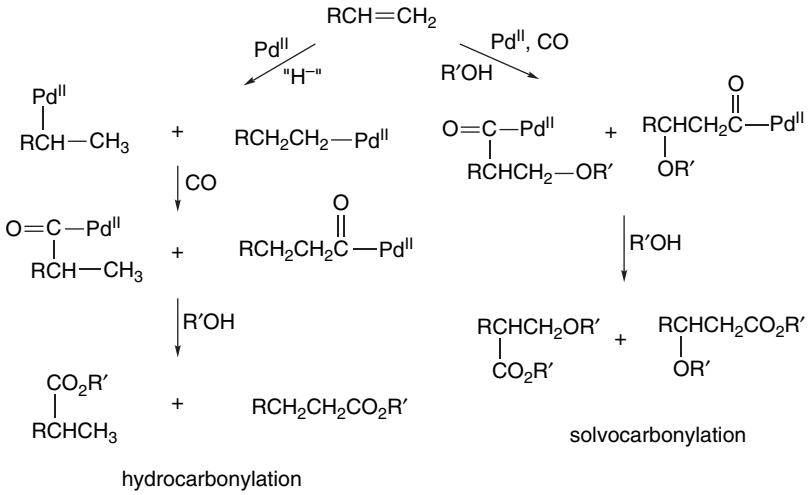
8.2.4. Carbonylation Reactions

Carbonylation reactions involve coordination of carbon monoxide to palladium and a transfer of an organic group from palladium to the coordinated carbon monoxide.

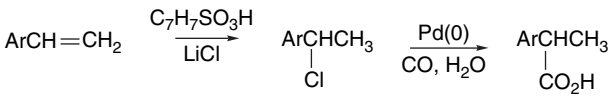


Carbonylation reactions have been observed using both Pd(II)-alkene complexes and σ-bonded Pd(II) species formed by oxidative addition. Under reductive conditions, the double bond can be *hydrocarbonylated*, resulting in the formation of a carboxylic acid or ester.[238] In nucleophilic solvents, the intermediate formed by *solvopalladation* is intercepted by carbonylation and addition of nucleophilic solvent. In both types of reactions, regioisomeric products are possible.

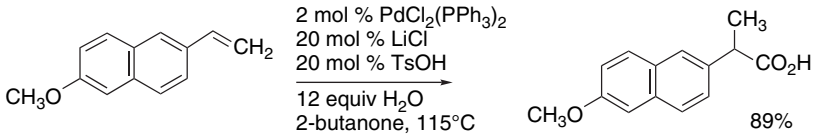
237. L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, **122**, 11260 (2000).
238. B. El Ali and H. Alper, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 2, E. Negishi and A. de Meijere, eds., Wiley-Interscience, New York, 2000, pp. 2333–2349.



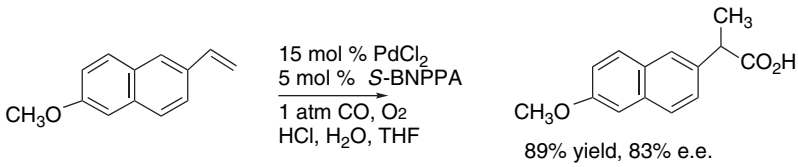
8.2.4.1. Hydrocarbonylation. The hydrocarbonylation reaction can be applied to the synthesis of α-arylpropanoic acids of the NSAIDS type.[239] For this synthesis to be effective, selective carbonylation of the more-substituted sp^2 carbon is required. Although many carbonylation conditions are unselective, $PdCl_2(PPh_3)_2$ with *p*-toluenesulfonic acid and LiCl achieves excellent selectivity, which is thought to involve the formation of a benzylic chloride intermediate.



Naproxen can be synthesized in 89% yield with 97.5% regioselectivity under these conditions.

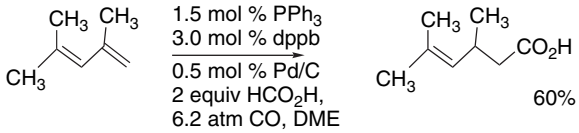


This reaction has been done with good enantioselectivity using 1, 1′-binaphthyl-2, 2′-diyl hydrogen phosphate (BNPPA) as a chiral ligand.[240]

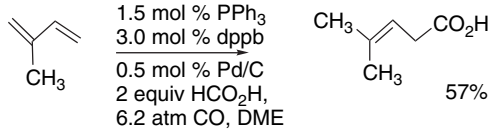


When conducting hydrocarbonylations with dienes, it was found that a mixture of nonchelating and bidentate phosphine ligands was beneficial.[241]

239. A Seayad, S. Jayasree, and R. V. Chaudhari, *Org. Lett.*, **1**, 459 (1999).
240. H. Alper and N. Hamel, *J. Am. Chem. Soc.*, **112**, 2803 (1990).
241. G. Vasapollo, A. Somasunderam, B. El Ali, and H. Alper, *Tetrahedron Lett.*, **35**, 6203 (1994).

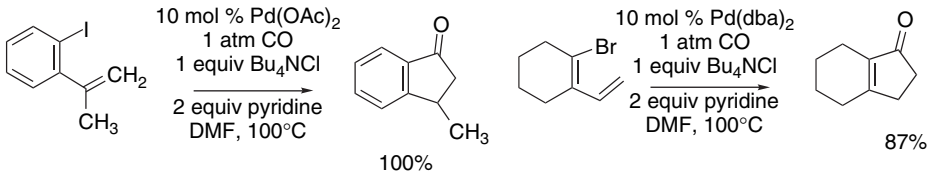


In some cases double-bond migration was noted, as for isoprene.

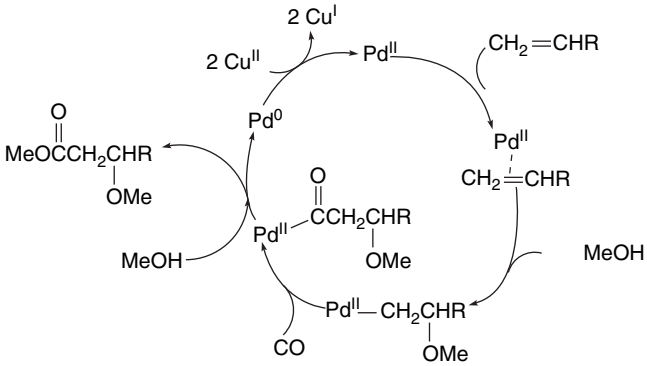


Esters can be formed when the hydrocarbonylation reaction is carried out in an alcohol.[242] Although hydrocarbonylation is the basis for conversion of alkenes to carboxylic acids on an industrial scale, it has seen only limited application in laboratory synthesis.

Olefin hydrocarbonylation can be used in conjunction with oxidative addition to prepare indanones and cyclopentenones, but the reaction is limited to terminal alkenes.[243]

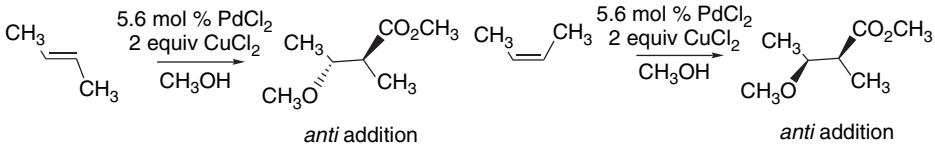


8.2.4.2. Solvocarbonylation. In solvocarbonylation, a substituent is introduced by a nucleophilic addition to a π complex of the alkene. The acylpalladium intermediate is then captured by a nucleophilic solvent such as an alcohol. A catalytic process that involves Cu(II) reoxidizes Pd(0) to the Pd(II) state.[244]

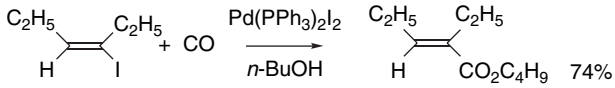


242. S. Oi, M. Nomura, T. Aiko, and Y. Inoue, *J. Mol. Catal. A.*, **115**, 289 (1997).
243. S. V. Gagnier and R. C. Larock, *J. Am. Chem. Soc.*, **125**, 4804 (2003).
244. D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1810 (1976).

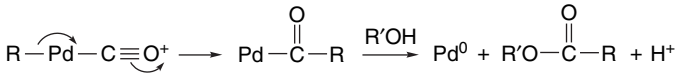
This reaction has been shown to proceed with overall *anti* addition in the case of *E*- and *Z*-butene.[245]



Organopalladium(II) intermediates generated from halides or triflates by oxidative addition react with carbon monoxide in the presence of alcohols to give carboxylic acids[246] or esters.[247]

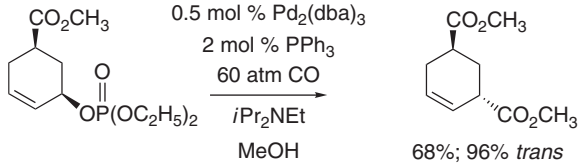


The carbonyl insertion step takes place by migration of the organic group from the metal to the coordinated carbon monoxide, generating an acylpalladium species. This intermediate can react with nucleophilic solvent, releasing catalytically active Pd(0).

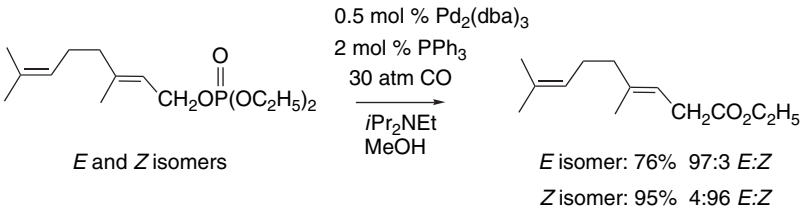


The detailed mechanisms of such reactions have been shown to involve addition and elimination of phosphine ligands. The efficiency of individual reactions can often be improved by careful choice of added ligands.

Allylic acetates and phosphates can be readily carbonylated.[248] Carbonylation usually occurs at the less-substituted end of the allylic system and with inversion of configuration in cyclic systems.

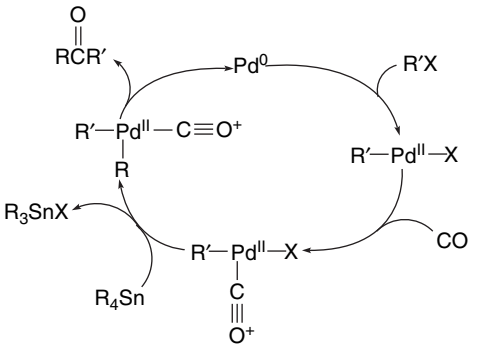


The reactions are accelerated by bromide salts, which are thought to exchange for acetate in the π-allylic complex. The reactions of acyclic compounds occur with minimal *E:Z* isomerization. This result implies that the π-allyl intermediate is captured by carbonylation faster than *E:Z* isomerization occurs.

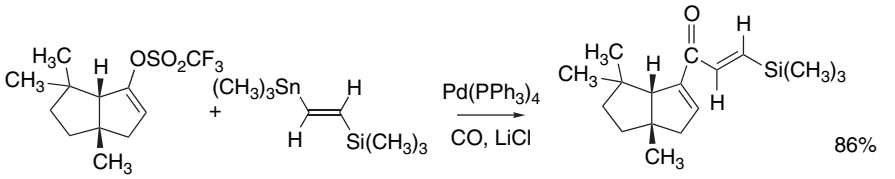


245. D. E. James, L. F. Hines, and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1806 (1976).
246. S. Cacchi and A. Lupi, *Tetrahedron Lett.*, **37**, 3939 (1992).
247. A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974); S. Cacchi, E. Morena, and G. Ortar, *Tetrahedron Lett.*, **26**, 1109 (1985).
248. S. Murahashi, Y. Imada, Y. Taniguchi, and S. Higashiura, *J. Org. Chem.*, **58**, 1538 (1993).

Coupling of organostannanes with halides in a carbon monoxide atmosphere leads to ketones by incorporation of a carbonylation step.[249] The catalytic cycle is similar to that involved in the coupling of alkyl or aryl halides. These reactions involve a migration of one of the organic substituents to the carbonyl carbon, followed by reductive elimination.



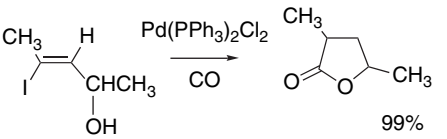
This method can also be applied to alkenyl triflates.



Ref. 250

Carbonylation reactions can be carried out with a boronic acid as the nucleophilic component.[251]

Application of the carbonylation reaction to halides with appropriately placed hydroxy groups leads to lactone formation. In this case the acylpalladium intermediate is trapped intramolecularly.



Ref. 252

Carbonylation can also be carried out as a tandem reaction in intramolecular Heck reactions.

249. M. Tanaka, *Tetrahedron Lett.*, 2601 (1979); D. Milstein and J. K. Stille, *J. Org. Chem.*, **44**, 1613 (1979); J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983); A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **110**, 1557 (1988).

250. G. T. Crisp, W. J. Scott, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 7500 (1984).

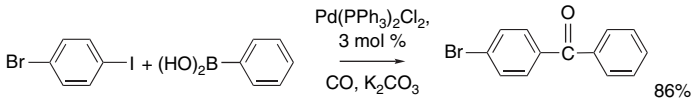
251. T. Ishiyama, H. Kizaki, N. Miyaura, and A. Suzuki, *Tetrahedron Lett.*, **34**, 7595 (1993); T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, and N. Miyaura, *J. Org. Chem.*, **63**, 4726 (1998).

252. A. Cowell and J. K. Stille, *J. Am. Chem. Soc.*, **102**, 4193 (1980).

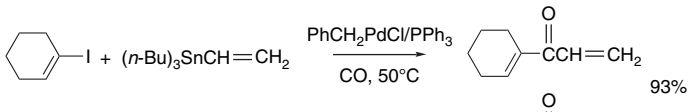
Scheme 8.15. Synthesis of Ketones, Esters, Carboxylic Acids, and Amides by Palladium-Catalyzed Carbonylation and Acylation

A. Ketones by carbonylation

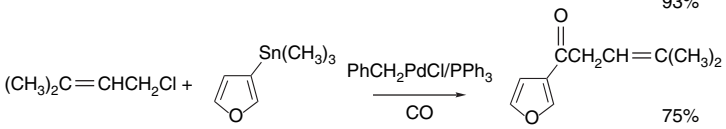
1[a]



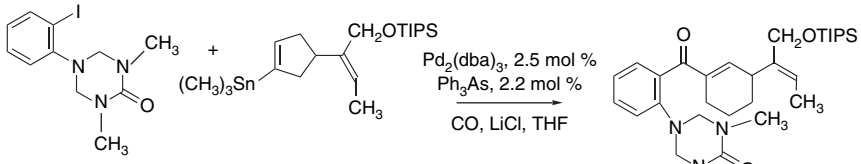
2[b]



3[c]

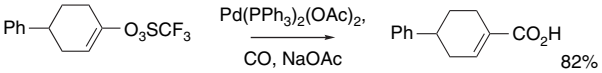


4[d]

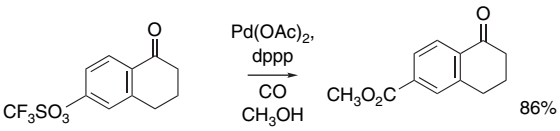


B. Esters, acids and amides

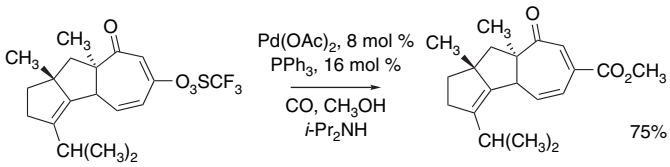
5[e]



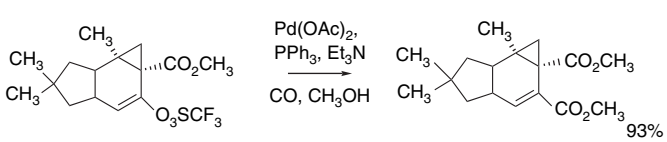
6[f]



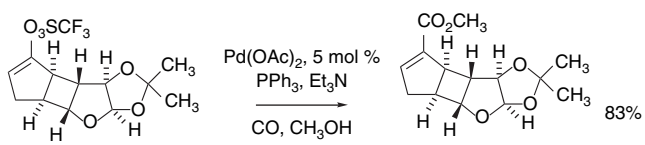
7[g]



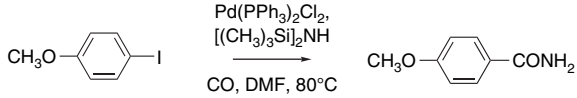
8[h]



9[i]



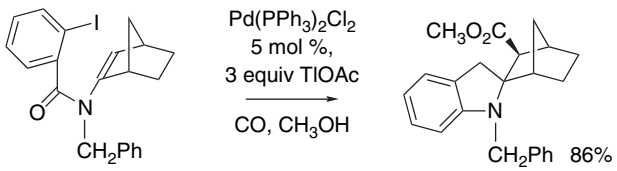
10[j]



(*Continued*)

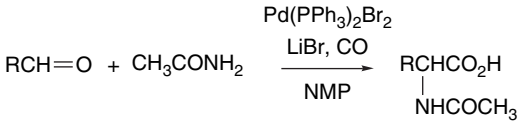
Scheme 8.15. (*Continued*)

a. T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, and N. Miyaura, *J. Org. Chem.*, **63**, 4726 (1998).
b. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 6417 (1984).
c. F. K. Sheffy, J. P. Godschalx, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984).
d. S. R. Angle, J. M. Fervig, S. D. Knight, R. W. Marquis, Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 3966 (1993).
e. S. Cacchi and A. Lupi, *Tetrahedron Lett.*, **33**, 3939 (1992).
f. U. Gerlach and T. Wollmann, *Tetrahedron Lett.*, **33**, 5499 (1992).
g. B. B. Snider, N. H. Vo, and S. V. O'Neill, *J. Org. Chem.*, **63**, 4732 (1998).
h. S. K. Thompson and C. H. Heathcock, *J. Org. Chem.*, **55**, 3004 (1990).
i. A. B. Smith III, G. A. Sulikowski, M. M. Sulikowski, and K. Fujimoto, *J. Am. Chem. Soc.*, **114**, 2567 (1992).
j. E. Morea and G. Ortar, *Tetrahedron Lett.*, **39**, 2835 (1998).



Ref. 253

It can also be done by in situ generation of other types of electrophiles. For example, good yields of *N*-acyl α-amino acids are formed in a process in which an amide and aldehyde combine to generate a carbinolamide and, presumably, an acyliminium ion. The organopalladium intermediate is then carbonylated prior to reaction with water.[254]



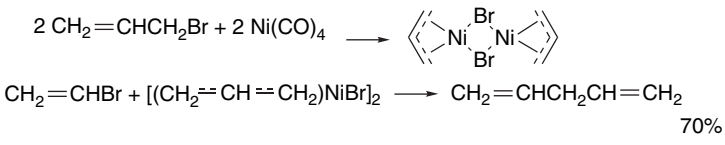
Scheme 8.15 gives some examples of carbonylations and acylations involving stannane reagents. Entry 1 illustrates synthesis of diaryl ketones from aryl halides and arylboronic acids. Entries 2 and 3 use stannanes as the nucleophilic reactant. Entry 4 was carried out as part of the synthesis of the *Strychnos* alkaloid akuammicine. The triazinone ring serves to protect the aromatic amino group. Entries 5 and 6 introduce carboxy groups using vinyl and aryl triflates, respectively. Entries 8 and 9 are similar reactions carried out during the course of multistage syntheses. Entry 10 illustrates direct formation of an amide by carbonylation.

8.3. Reactions Involving Other Transition Metals

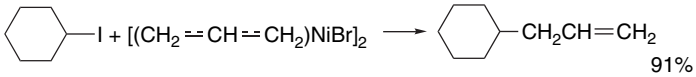
8.3.1. Organonickel Compounds

The early synthetic processes using organonickel compounds involved the coupling of allylic halides, which react with nickel carbonyl, $Ni(CO)_4$, to give π-allyl complexes. These complexes react with a variety of halides to give coupling products.[255]

253. R. Grigg, P. Kennewall, and A. J. Teasdale, *Tetrahedron Lett.*, **33**, 7789 (1992).
254. M. Beller, M. Eckert, F. M. Vollmuller, S. Bogdanovic, and H. Geissler, *Angew. Chem. Int. Ed. Engl.*, **36**, 1494 (1997); M. Beller, W. A. Maradi, M. Eckert, and H. Neumann, *Tetrahedron Lett.*, **40**, 4523 (1999).
255. M. F. Semmelhack, *Org. React.*, **19**, 115 (1972).

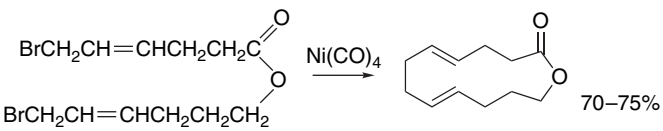


Ref. 256



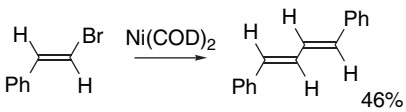
Nickel carbonyl effects coupling of allylic halides when the reaction is carried out in very polar solvents such as DMF or DMSO. This coupling reaction has been used intramolecularly to bring about cyclization of *bis*-allylic halides and was found useful in the preparation of large rings.

Ref. 257

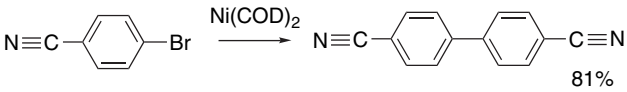


Ref. 258

Nickel carbonyl is an extremely toxic substance, but a number of other nickel reagents with generally similar reactivity can be used in its place. The Ni(0) complex of 1,5-cyclooctadiene, $Ni(COD)_2$, can effect coupling of allylic, alkenyl, and aryl halides.



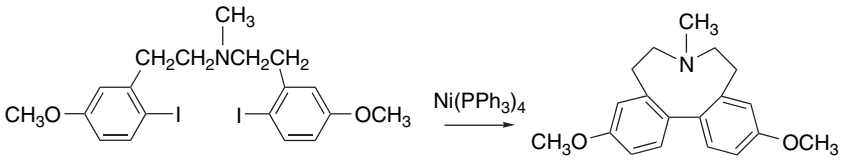
Ref. 259



Ref. 260

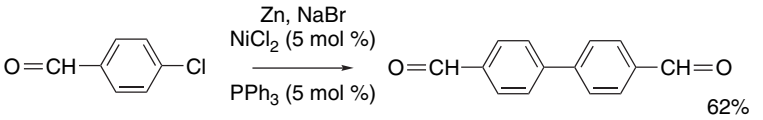
Tetrakis-(triphenylphosphine)nickel(0) is an effective reagent for coupling aryl halides,[261] and medium rings can be formed in intramolecular reactions.

256. E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).
257. E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, **89**, 2757 (1967).
258. E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972).
259. M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.*, **94**, 9234 (1972).
260. M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5908 (1971).
261. A. S. Kende, L. S. Liebeskind, and D. M. Braitsch, *Tetrahedron Lett.*, 3375 (1975).

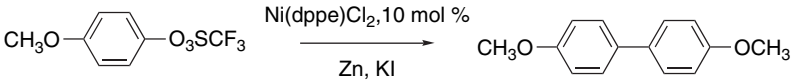


Ref. 262

The homocoupling of aryl halides and triflates can be made catalytic in nickel by using zinc as a reductant for in situ regeneration of the active Ni(0) species.



Ref. 263



Ref. 265

Mechanistic study of the aryl couplings has revealed the importance of the changes in redox state that are involved in the reaction.[265] Ni(I), Ni(II), and Ni(III) states are believed to be involved. Changes in the degree of coordination by phosphine ligands are also thought to be involved, but these have been omitted in the mechanism shown here. The detailed kinetics of the reaction are inconsistent with a mechanism involving only formation and decomposition of a biarylnickel(II) intermediate. The key aspects of the mechanism are: (1) the oxidative addition involving a Ni(I) species, and (2) the reductive elimination that occurs via a diaryl Ni(III) intermediate and regenerates Ni(I).

initiation by electron transfer $\quad ArNi(II)X + ArX \longrightarrow ArNi(III)X^+ + Ar\cdot + X^-$

propagation

$$ArNi(III)X^+ + ArNi(II)X \longrightarrow Ar_2Ni(III)X + Ni(II)^+ + X^-$$

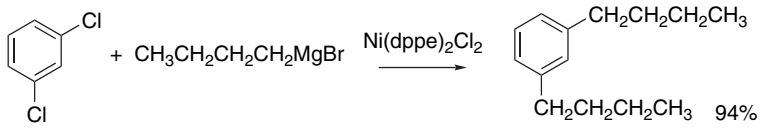
$$Ar_2Ni(III)X \longrightarrow Ar\text{-}Ar + Ni(I)X$$

$$Ni(I)X + ArX \longrightarrow ArNi(III)X^+ + X^-$$

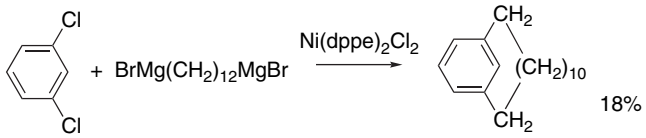
Nickel(II) salts are able to catalyze the coupling of Grignard reagents with alkenyl and aryl halides. A soluble *bis*-phosphine complex, $Ni(dppe)_2Cl_2$, is a particularly effective catalyst.[266] The main distinction between this reaction and Pd-catalyzed cross

262. S. Brandt, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2193 (1979).
263. M. Zembayashi, K. Tamao, J. Yoshida, and M. Kumada, *Tetrahedron Lett.*, 4089 (1977); I. Colon and D. R. Kelly, *J. Org. Chem.*, **51**, 2627 (1986).
265. A. Jutand and A. Mosleh, *J. Org. Chem.*, **62**, 261 (1997).
265. T. T. Tsou and J. K. Kochi, *J. Am. Chem. Soc.*, **101**, 7547 (1979); L. S. Hegedus and D. H. P. Thompson, *J. Am. Chem. Soc.*, **107**, 5663 (1985); C. Amatore and A. Jutand, *Organometallics*, **7**, 2203 (1988).
266. K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972).

coupling is that the nickel reaction can be more readily extended to saturated alkyl groups because of a reduced tendency toward β-elimination.

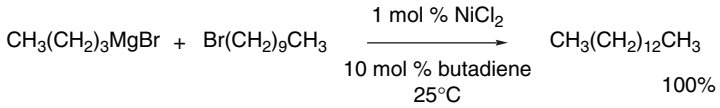


The reaction has been applied to the synthesis of cyclophane-type structures by use of dihaloarenes and Grignard reagents from α, ω-dihalides.

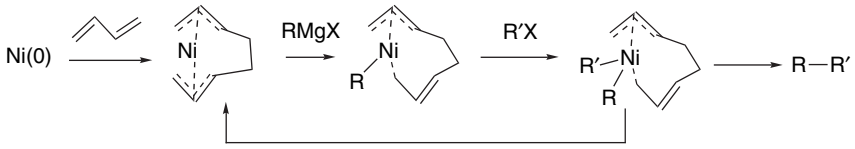


Ref. 267

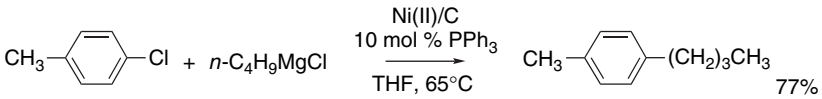
Recent discoveries have expanded the utility of nickel-catalyzed coupling reactions. Inclusion of butadiene greatly improves the efficiency of the reactions.[268]



These reaction conditions are applicable to primary chlorides, bromides, and tosylates. The active catalytic species appears to be a *bis*-π-allyl complex formed by dimerization of butadiene.

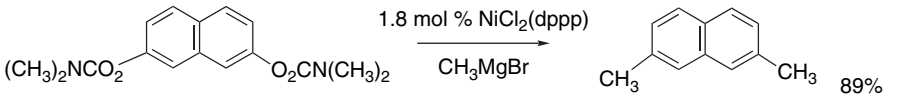


A preparation of Ni(II) on charcoal can also be used as the catalyst. It serves as a reservoir of active Ni(0) formed by reduction by the Grignard reagent.[269]



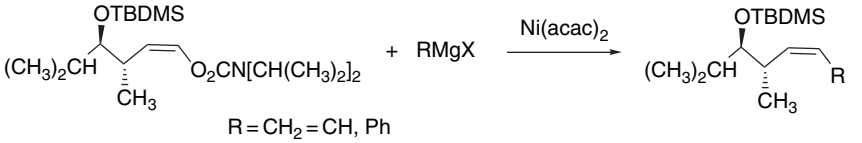
Aryl carbamates are also reactive toward nickel-catalyzed coupling.[270] Since the carbamates can be readily prepared from phenols, they are convenient starting materials.

267. K. Tamno, S. Kodama, T. Nakatsuka, Y. Kiso, and A. Kumada, *J. Am. Chem. Soc.*, **97**, 4405 (1975).
268. J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, and N. Kambe, *J. Am. Chem. Soc.*, **124**, 4222 (2002).
269. S. Tasler and R. H. Lipshutz, *J. Org. Chem.*, **68**, 1190 (2003).
270. S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle, and V. Snieckus, *J. Org. Chem.*, **57**, 4066 (1992).



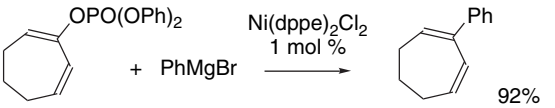
Ref. 271

Vinyl carbamates are also reactive.

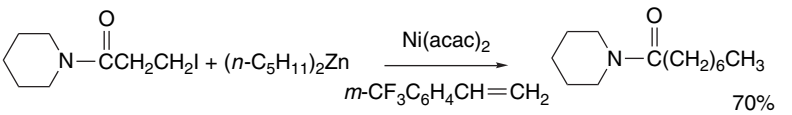


Ref. 272

Similarly, nickel catalysis permits the extension of cross coupling to vinyl phosphates, which are in some cases more readily obtained and handled than vinyl triflates.[273]

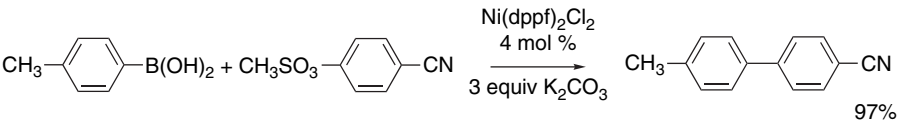


Nickel acetylacetonate, $Ni(acac)_2$, in the presence of a styrene derivative promotes coupling of primary alkyl iodides with organozinc reagents. The added styrene serves to stabilize the active catalytic species, and of the derivatives examined, *m*-trifluoromethylstyrene was the best.[274]



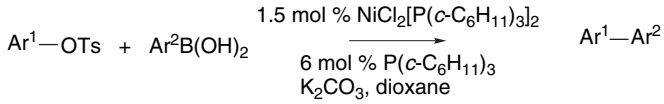
This method can extend Ni-catalyzed cross coupling to functionalized organometallic reagents.

Nickel can also be used in place of Pd in Suzuki-type couplings of boronic acids. The main advantage of nickel in this application is that it reacts more readily with aryl chlorides[275] and methanesulfonates[276] than do the Pd systems. These reactants may be more economical than iodides or triflates in large-scale syntheses.

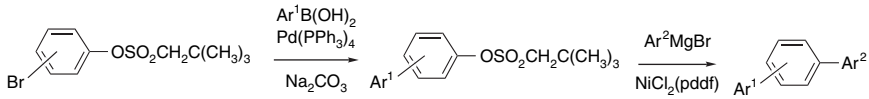


271. C. Dallaire, I. Kolber, and M. Gringas, *Org. Synth.*, **78**, 42 (2002).
272. F.-H. Poree, A. Clavel, J.-F. Betzer, A. Pancrazi, and J. Ardisson, *Chem. Eur. J.*, 7553 (2003).
273. A. Sofia, E. Karlstom, K. Itami, and J.-E. Backvall, *J. Org. Chem.*, **64**, 1745 (1999); Y. Nan and Z. Yang, *Tetrahedron Lett.*, **40**, 3321 (1999).
274. R. Giovannini, T. Studemann, G. Dussin, and P. Knochel, *Angew. Chem. Int. Ed. Engl.*, **37**, 2387 (1998); R. Giovannini, T. Studemann, A. Devasagayaraj, G. Dussin, and P. Knochel, *J. Org. Chem.*, **64**, 3544 (1999).
275. S. Saito, M. Sakai, and N. Miyaura, *Tetrahedron Lett.*, **37**, 2993 (1996); S. Sato, S. Oh-tani, and N. Miyaura, *J. Org. Chem.*, **62**, 8024 (1997).
276. V. Percec, J.-Y. Bae, and D. H. Hill, *J. Org. Chem.*, **60**, 1060 (1995); M. Ueda, A. Saitoh, S. Oh-tani, and N. Miyaura, *Tetrahedron*, **54**, 13079 (1998).

$NiCl_2[P(c\text{-}C_6H_{11})_3]_2$ is an effective catalyst for coupling aryl tosylates with arylboronic acids.[277]

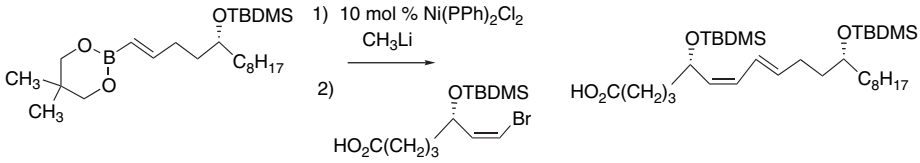


Nickel catalysis has been used in a sequential synthesis of terphenyls, starting with 2-, 3-, or 4-bromophenyl neopentanesulfonates. Conventional Pd-catalyzed Suzuki conditions were used for the first step involving coupling of the bromide and then nickel catalysis was utilized for coupling the sulfonate.



Ref. 278

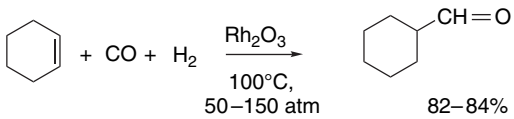
These coupling reactions can also be done with boronate esters activated by conversion to "ate" reagents by reaction with alkyllithium compounds.[279] For example, analogs of leukotrienes have been synthesized in this way.



Ref. 280

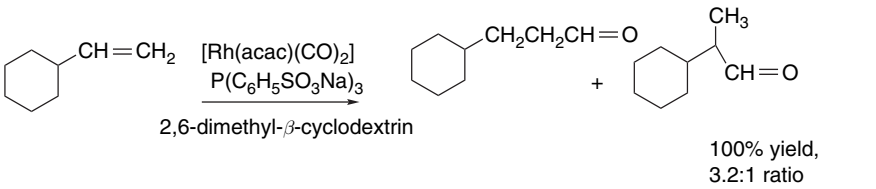
8.3.2. Reactions Involving Rhodium and Cobalt

Rhodium and cobalt participate in several reactions that are of value in organic syntheses. Rhodium and cobalt are active catalysts for the reaction of alkenes with hydrogen and carbon monoxide to give aldehydes, known as *hydroformylation*.[281]



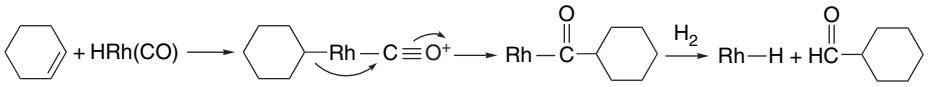
Ref. 282

277. D. Zim, V. R. Lando, J. Dupont, and A. L. Monteiro, *Org. Lett.*, **3**, 3049 (2001).
278. C.-H. Cho, I.-S. Kim, and K. Park, *Tetrahedron*, **60**, 4589 (2004).
279. Y. Kobayashi, Y. Nakayama, and R. Mizojiri, *Tetrahedron*, **54**, 1053 (1998).
280. Y. Nakayama, G. B. Kumar, and Y. Kobayashi, *J. Org. Chem.*, **65**, 707 (2000).
281. R. L. Pruett, *Adv. Organometal. Chem.*, **17**, 1 (1979); H. Siegel and W. Himmele, *Angew. Chem. Int. Ed. Engl.*, **19**, 178 (1980); J. Falbe, *New Syntheses with Carbon Monoxide*, Springer Verlag, Berlin, 1980.
282. P. Pino and C. Botteghi, *Org. Synth.*, **57**, 11 (1977).

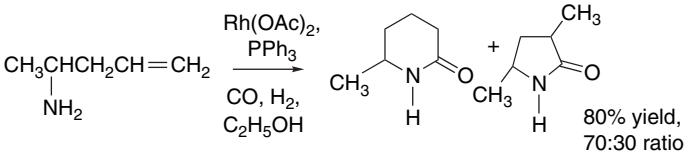


Ref. 283

The key steps in the reaction are addition of hydridorhodium to the double bond of the alkene and migration of the alkyl group to the complexed carbon monoxide. Hydrogenolysis then leads to the aldehyde.

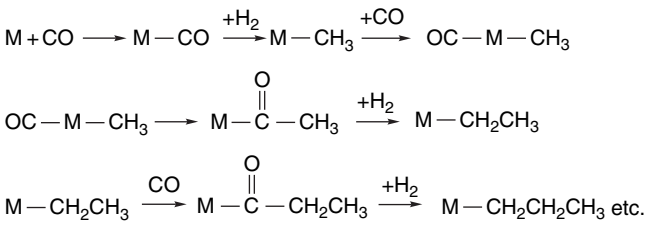


Carbonylation can also be carried out under conditions in which the acylrhodium intermediate is trapped by internal nucleophiles.



Ref. 284

The steps in the hydroformylation reaction are closely related to those that occur in the *Fischer-Tropsch process*, which is the reductive conversion of carbon monoxide to alkanes and occurs by a repetitive series of carbonylation, migration, and reduction steps that can build up a hydrocarbon chain.

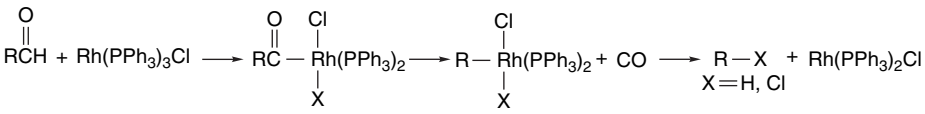


The Fischer-Tropsch process is of considerable economic interest because it is the basis of conversion of carbon monoxide to synthetic hydrocarbon fuels, and extensive work has been done on optimization of catalyst systems.

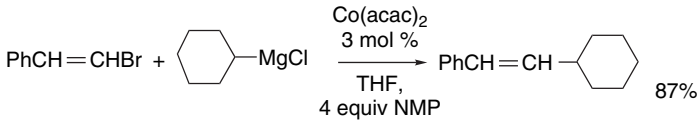
The carbonylation step that is involved in both hydroformylation and the Fischer-Tropsch reaction can be reversible. Under appropriate conditions, rhodium catalyst can be used for the decarbonylation of aldehydes[285] and acyl chlorides.[286]

283. E. Monflier, S. Tilloy, G. Fremy, Y. Castanet, and A. Mortreux, *Tetrahedron Lett.*, **36**, 9481 (1995).
284. D. Anastasiou and W. R. Jackson, *Tetrahedron Lett.*, **31**, 4795 (1990).
285. J. A. Kampmeier, S. H. Harris, and D. K. Wedgaertner, *J. Org. Chem.*, **45**, 315 (1980); J. M. O'Connor and J. Ma, *J. Org. Chem.*, **57**, 5074 (1992).
286. J. K. Stille and M. T. Regan, *J. Am. Chem. Soc.*, **96**, 1508 (1974); J. K. Stille and R. W. Fries, *J. Am. Chem. Soc.*, **96**, 1514 (1974).

An acylrhodium intermediate is involved in both cases. The elimination of the hydrocarbon or halide occurs by reductive elimination.[287]

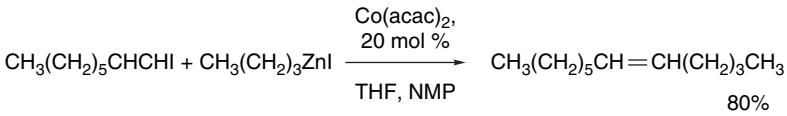


Although the very early studies of transition metal–catalyzed coupling of organometallic reagents included cobalt salts, the use of cobalt for synthetic purposes is quite limited. Vinyl bromide and iodides couple with Grignard reagents in good yield, but a good donor ligand such as NMP or DMPU is required as a cocatalyst.



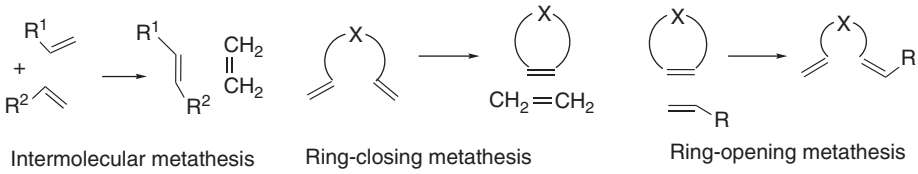
Ref. 288

$Co(acac)_2$ also catalyzes cross coupling of organozinc reagents under these conditions.[289]



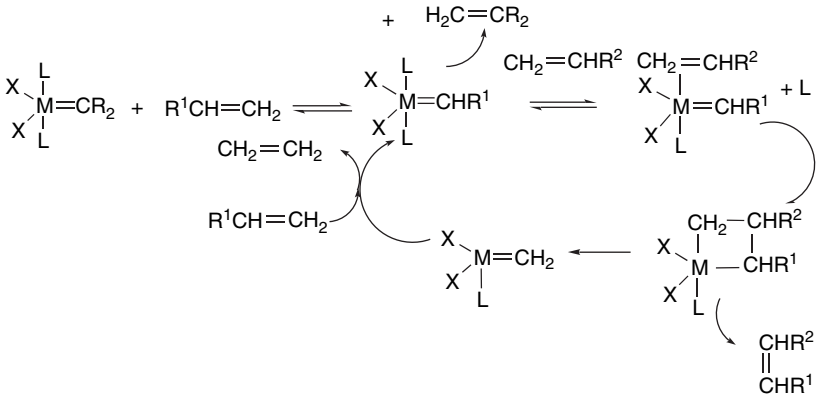
8.4. The Olefin Metathesis Reaction

Several transition metal complexes can catalyze the exchange of partners of two double bonds. Known as the *olefin metathesis reaction*, this process can be used to close or open rings, as well to interchange double-bond components.

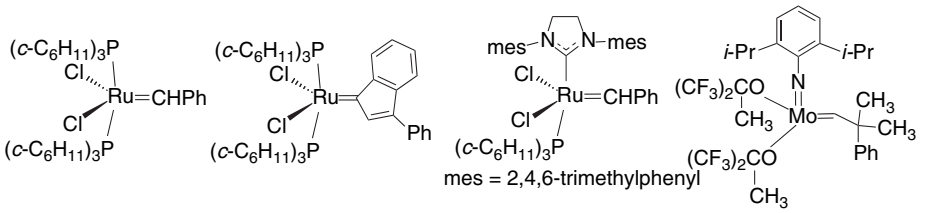


287. J. E. Baldwin, T. C. Barden, R. L. Pugh, and W. C. Widdison, *J. Org. Chem.*, **52**, 3303 (1987).
288. G. Cahiez and H. Avedissian, *Tetrahedron Lett.*, **39**, 6159 (1998).
289. H. Avedissian, L. Berillon, G. Cahiez, and P. Knochel, *Tetrahedron Lett.*, **39**, 6163 (1998).

The catalysts are metal-carbene complexes that react with the alkene to form a metallocyclobutane intermediate.[290] If the metallocyclobutane breaks down in the alternative path from its formation, an exchange of the double-bond components occurs.

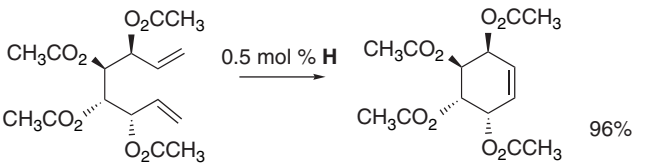


The most commonly used catalyst is the benzylidene complex of $RuCl_2[P(c-C_6H_{11})_3]_2$, **F**, which is called the *Grubbs catalyst*, but several other catalysts are also reactive. Catalyst **H**, which is known as the *second-generation Grubbs catalyst*, is used extensively.



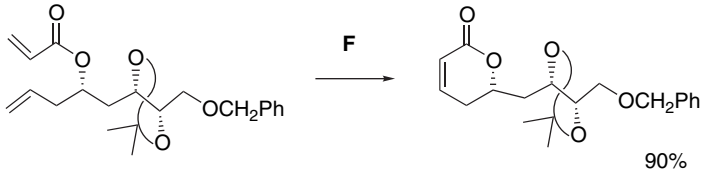
F[291] **G**[292] **H**[293] **I**[294]

In laboratory synthesis, these catalysts have been utilized primarily to form both common and large rings by coupling two terminal alkenes.[295] For example, catalyst **H** has been used to synthesize the highly oxygenated cyclohexenes known as conduritols.



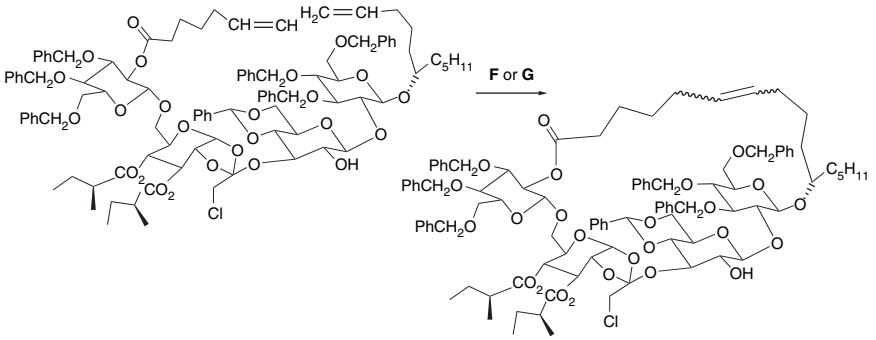
290. J.-L. Herisson and Y. Chauvin, *Makromol. Chem.*, **141**, 161 (1971).
291. P. Schwab, R. H. Grubbs, and J. W. Ziller, *J. Am. Chem. Soc.*, **118**, 100 (1996).
292. A. Furstner, M. Liebl, A. F. Hill, and J. D. E. T. Winton-Ely, *Chem. Commun.*, 601 (1999); A. Furstner, O. Guth, A. Duffels, G. Seidel, M. Liebl, B. Gabor, and R. Mynott, *Chem. Eur. J.*, **7**, 4811 (2001).
293. M. Scholl, T. M. Trnka, J. P. Morgan, and R. H. Grubbs, *Tetrahedron Lett.*, **40**, 2247 (1999); J. A. Love, M. S. Sanford, M. W. Day, and R. H. Grubbs, *J. Am. Chem. Soc.*, **125**, 10103 (2003).
294. R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. Di Mare, and M. O'Regan, *J. Am. Chem. Soc.*, **112**, 3875 (1999).
295. D. L. Wright, *Curr. Org. Chem.*, **3**, 211 (1999); A. Deiters and S. F. Martin, *Chem. Rev.*, **104**, 2199 (2004).

Various heterocyclic rings can be closed, as in the formation of an α, β-unsaturated lactone ring in the synthesis of peloruside A (see also Entries 3 and 5 of Scheme 8.16).



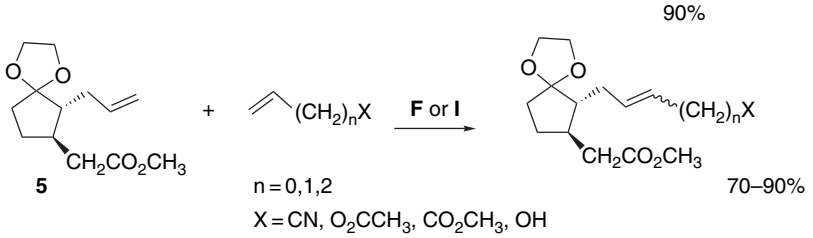
Ref. 296

Some of the most impressive successes have come in the synthesis of large rings. Several research groups employed the ring-closing metathesis reaction in the synthesis of epothilone and analogs (see Entry 8 of Scheme 8.14).[297] A large ring incorporating a tetrasaccharide unit was synthesized in essentially quantitative yield using either catalyst **F** or **G**. The newly formed double bond is 9:1 *E:Z*.



Ref. 298

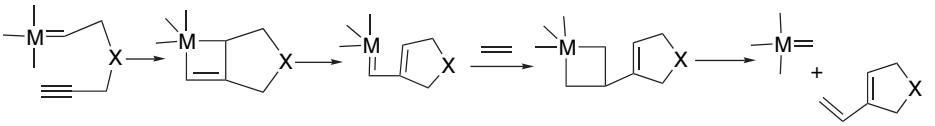
Olefin metathesis can also be used in intermolecular reactions.[299] For example, a variety of functionally substituted side chains were introduced by exchange with the terminal double bond in **5**.[300] These reactions gave *E:Z* mixtures.



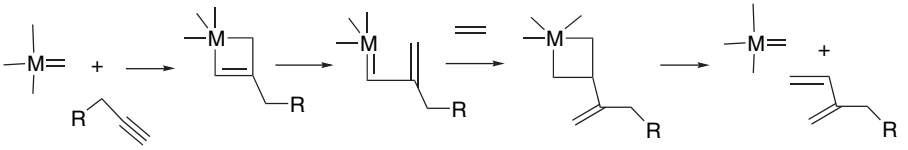
The effectiveness of these intermolecular reactions depends on the relative reactivity of the two components, since self-metathesis leading to dimeric products will occur if one compound is more reactive than the other.

296. A. K. Ghosh and J.-H. Kim, *Tetrahedron Lett.*, **44**, 3967 (2003).
297. K. C. Nicolaou, H. Vallberg, N. P. King, F. Roschangar, Y. He, D. Vourloumis, and C. G. Nicoloau, *Chem. Eur. J.*, **3**, 1957 (1997); D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997); K. Biswas, H. Lin, J. T. Nijardarson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **124**, 9825 (2002).
298. A. Furstner, F. Jeanjean, P. Razon, C. Wirtz, and P. Mynott, *Chem. Eur. J.*, 320 (2003).
299. S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed. Engl.*, **42**, 1900 (2003).
300. O. Brummer, A. Ruckert, and S. Blechert, *Chem. Eur. J.*, **3**, 441 (1997).

Triple bonds can also participate in the metathesis reaction. Intramolecular reactions give vinylcycloalkenes, whereas intermolecular reactions provide conjugated dienes.[301] The mechanism is similar to that for α, ω-diene metathesis, but in contrast to diene cyclization, no carbon atoms are lost.[302]

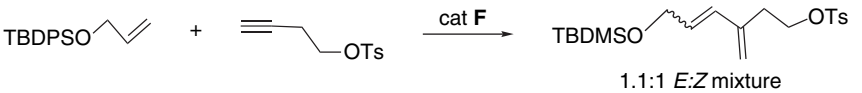


Intramolecular alkene-alkyne metathesis



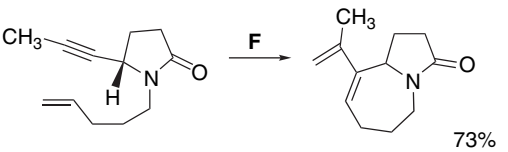
Intermolecular alkene-alkyne metathesis

The reaction has been applied in several synthetic contexts. The intermolecular reaction has been used to construct the conjugated diene side chain of mycothiazole, an antibiotic isolated from a sponge.



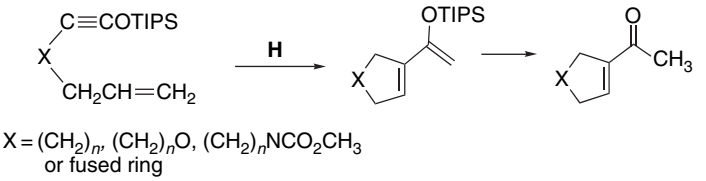
Ref. 303

The intermolecular version has been used in alkaloid synthesis.



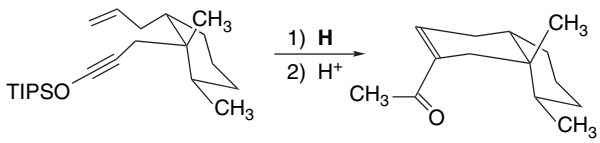
Ref. 304

When the intramolecular version is applied to silyloxyalkynes, the ultimate products are acetyl cycloalkenes.[305]

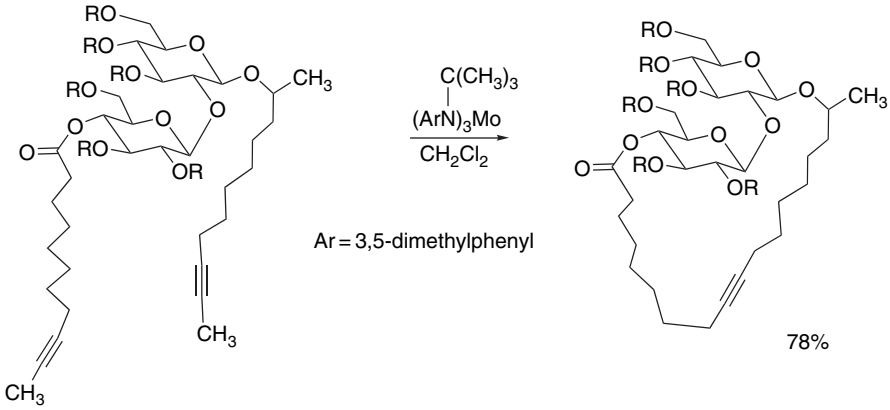


This reaction was used to prepare an intermediate suitable for synthesis of the sesquiterpenes α- and β-eremophilane and related structures.[306]

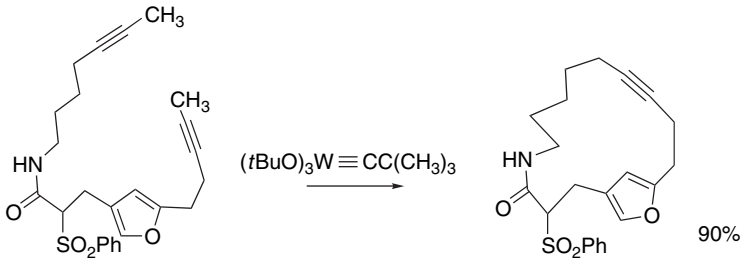
301. S. T. Diver and A. J. Giessert, *Synthesis*, 466 (2004).
302. R. Stragies, M. Schuster, and S. Blechert, *Angew. Chem. Int. Ed. Engl.*, **36**, 2518 (1997).
303. S. Rodriguez-Conesa, P. Candal, C. Jimenez, and J. Rodriguez, *Tetrahedron Lett.*, **42**, 6699 (2001).
304. A. Kinoshita and M. Mori, *J. Org. Chem.*, **61**, 8356 (1996).
305. M. P. Schramm, D. S. Reddy, and S. A. Kozmin, *Angew. Chem. Int. Ed. Engl.*, **40**, 4274 (2001).
306. D. S. Reddy and S. A. Kozmin, *J. Org. Chem.*, **69**, 4860 (2004).



Diynes can be employed in intramolecular ring-closing metathesis. Several catalysts involving Mo and W have been investigated. These cyclizations can be combined with semihydrogenation to give macrocycles with *Z*-double bonds.



Ref. 307



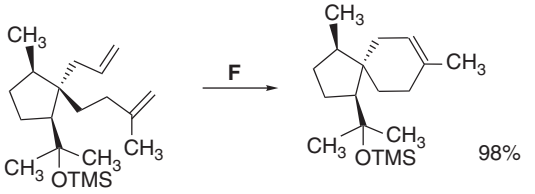
Ref. 308

Scheme 8.16 gives some examples of the synthetic application of the olefin metathesis reaction. Entry 1 is the synthesis of a structure related to a flour beetle aggregation pheromone. Entry 2 was used in the synthesis of a component of sandalwood oil. These two examples illustrate use of the ring-closing metathesis in the synthesis of common rings. Entry 3 forms an α,β-unsaturated lactone and was used in the synthesis of fostriecin, which has anticancer activity. Entry 4 forms a cyclohexenone. Generally, alkenes with EWG substituents have somewhat reduced reactivity and in this case a mild Lewis acid cocatalyst was required. Entry 5 illustrates the synthesis of a medium-sized ring. In this case, catalyst **G** showed a preference for the *E*-double bond but a catalyst similar to **H** formed the *Z*-isomer. This difference was attributed to more rapid reversibility and thermodynamic control in the latter case. Entry 6 also shows the formation of a medium-size ring. Entries 7 and 8 illustrate the application of the ring-closing metathesis to large rings, with Entry 8 being an example of the synthesis of epothilone by this method.

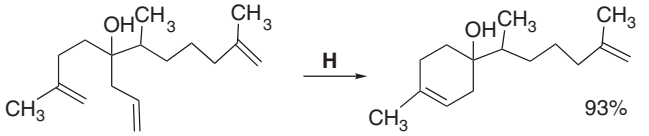
[307] A. Furstner, O. Guth, A. Rumbo, and S. Seidel, *J. Am. Chem. Soc.*, **121**, 11108 (1999).
[308] A. Furstner, K. Radkowski, J. Grabowski, C. Wirtz, and R. Mynott, *J. Org. Chem.*, **65**, 8758 (2000).

Scheme 8.16. Examples of the Ring-Closing Olefin Metathesis Reaction

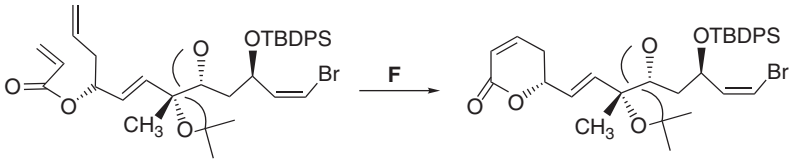
1[a]



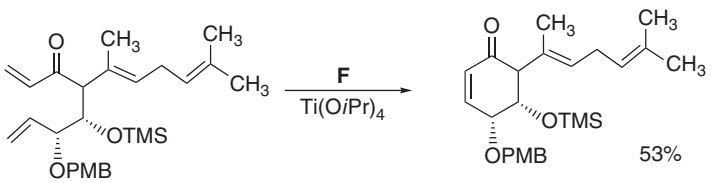
2[b]



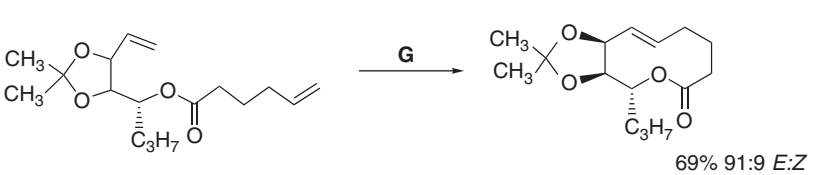
3[c]



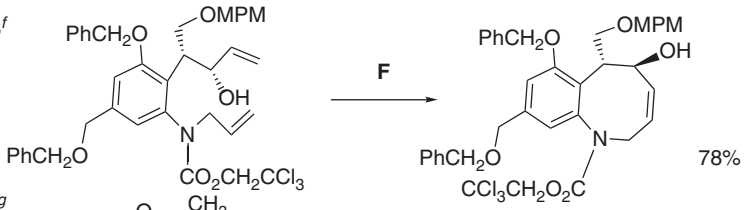
4[d]



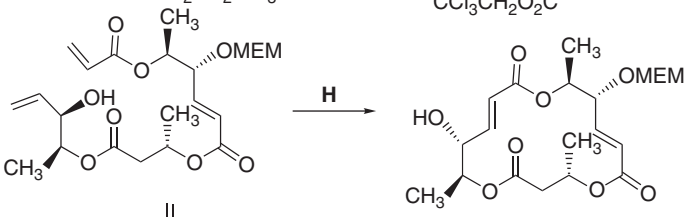
5[e]



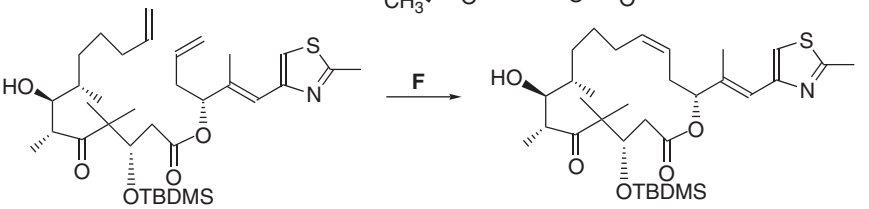
6[f]



7[g]



8[h]



(*Continued*)

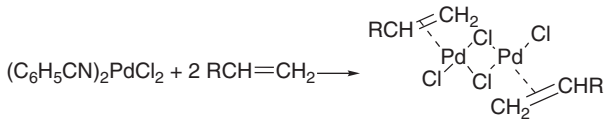
Scheme 8.16. (*Continued*)

a. S. Kurosawa, M. Bando, and K. Mori, *Eur. J. Org. Chem.*, 4395 (2001).
b. J. M. Mörgenthaler and D. Spitzner, *Tetrahedron Lett.*, **45**, 1171 (2004).
c. Y. K. Reddy and J. R. Falck, *Org. Lett.*, **4**, 969 (2002).
d. J.-G. Boiteau, P. Van de Weghe, and J. Eustache, *Org. Lett.*, **3**, 2737 (2001).
e. A. Furstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, and R. Mynott, *J. Am. Chem. Soc.*, **124**, 7061 (2002).
f. I. M. Fellows, D. E. Kaelin, Jr., and S. F. Martin, *J. Am. Chem. Soc.*, **122**, 10781 (2000).
g. Y. Matsuya, T. Kawaguchi, and H. Nemoto, *Org. Lett.*, **5**, 2939 (2003).
h. Z. Yang, Y. He, D. Vourloumis, H. Vallberg, and K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.*, **36**, 166 (1997).

8.5. Organometallic Compounds with π-Bonding

The organometallic reactions discussed in the previous sections in most cases involved intermediates carbon-metal with σ bonds, although examples of π bonding with alkenes and allyl groups were also encountered. The reactions emphasized in this section involve compounds in which organic groups are bound to the metal through delocalized π systems. Among the classes of organic compounds that can serve as π ligands are alkenes, allyl groups, dienes, the cyclopentadienide anion, and aromatic compounds. There are many such compounds, and we illustrate only a few examples. The bonding of polyenes in π complexes is the result of two major contributions. The filled π orbital acts as an electron donor to empty *d* orbitals of the metal ion. There is also a contribution to bonding, called "back bonding," from a filled metal orbital interacting with ligand π^* orbitals. These two types of bonding are illustrated in Figure 8.6. These same general bonding concepts apply to all the other π organometallics. The details of structure and reactivity of the individual compound depend on such factors as: (a) the number of electrons that can be accommodated by the metal; (b) the oxidation level of the metal; and (c) the electronic character of other ligands on the metal.

Alkene-metal complexes are usually prepared by a process by which some other ligand is dissociated from the metal. Both thermal and photochemical reactions are used.



Ref. 309

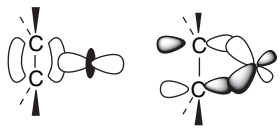
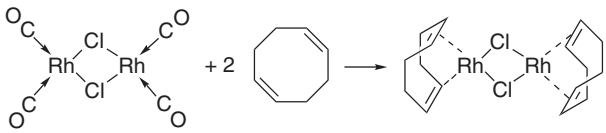


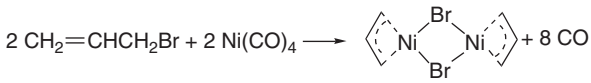
Fig. 8.6. Representation of π bonding in a alkene-metal cation complex.

309. M. S. Kharasch, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.*, **60**, 882 (1938).

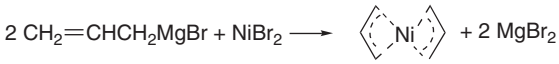


Ref. 310

π-Allyl complexes of palladium were described in Section 8.2.1. Similar π-allyl complexes of nickel can be prepared either by oxidative addition on Ni(0) or by transmetallation of a Ni(II) salt. Some reactions of these allyl nickel species are discussed in Section 8.3.1.



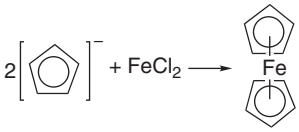
Ref. 311



Ref. 312

Organic ligands having a cyclic array of four carbon atoms have been of particular interest in connection with the chemistry of cyclobutadiene. Organometallic compounds containing cyclobutadiene as a ligand were first prepared in 1965.[313] The carbocyclic ring in the cyclobutadiene–iron tricarbonyl complex reacts as an aromatic ring and can undergo electrophilic substitutions.[314] Subsequent studies showed that oxidative decomposition of the complex can liberate cyclobutadiene, which is trapped by appropriate reactants.[315] Some examples of these reactions are given in Scheme 8.17.

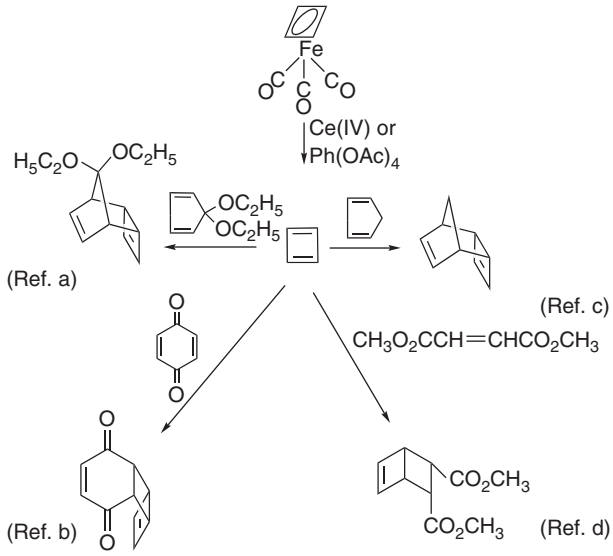
One of the most familiar of the π-organometallic compounds is ferrocene, a neutral compound that is readily prepared from cyclopentadienide anion and iron(II).[316]



Numerous chemical reactions have been carried out on ferrocene and its derivatives.[317] The molecule behaves as an electron-rich aromatic system, and electrophilic substitution reactions occur readily. Reagents that are relatively strong oxidizing agents, such as the halogens, effect oxidation at iron and destroy the compound.

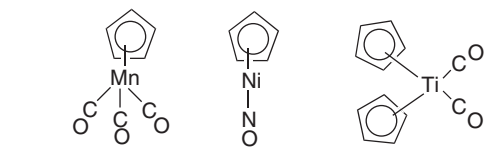
310. J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, 4735 (1957).
311. E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).
312. D. Walter and G. Wilke, *Angew. Chem. Int. Ed. Engl.*, **5**, 151 (1966).
313. G. F. Emerson, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 131 (1965); R. Pettit and J. Henery, *Org. Synth.*, **50**, 21 (1970).
314. J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3254 (1965).
315. R. H. Grubbs and R. A. Grey, *J. Am. Chem. Soc.*, **95**, 5765 (1973).
316. G. Wilkinson, *Org. Synth.*, **IV**, 473, 476 (1963).
317. A. Federman Neto, A. C. Pelegrino, and V. A. Darin, *Trends in Organometallic Chem.*, **4**, 147 (2002).

Scheme 8.17. Reactions of Cyclobutadiene



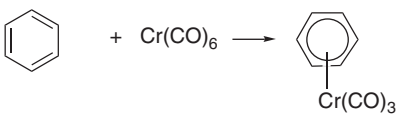
a. J. C. Barborak and R. Pettit, *J. Am. Chem. Soc.*, **89**, 3080 (1967).
b. J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966).
c. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 623 (1966).
d. P. Reeves, J. Henery, and R. Pettit, *J. Am. Chem. Soc.*, **91**, 3889 (1969).

Many other π-organometallic compounds have been prepared. In the most stable of these, the total number of electrons contributed by the ligands (e.g., four for allyl anions and six for cyclopentadiene anion) plus the valence electrons on the metal atom or ion is usually 18, to satisfy the *effective atomic number rule*.[318]



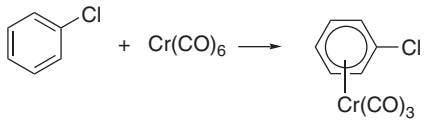
Metal	6	9	2
Ligands	12	9	16
Total	18	18	18

One of the most useful types of π complexes of aromatic compounds from the synthetic point of view are chromium tricarbonyl complexes obtained by heating benzene or other aromatics with $Cr(CO)_6$.



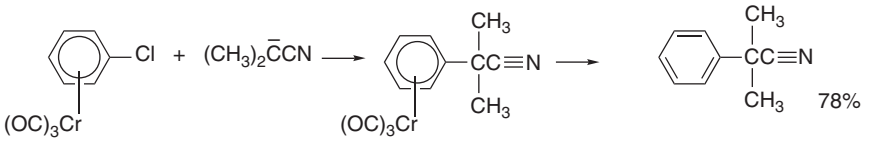
Ref. 319

318. M. Tsutsui, M. N. Levy, A. Nakamura, M. Ichikawa, and K. Mori, *Introduction to Metal π-Complex Chemistry*, Plenum Press, New York, 1970, pp. 44–45; J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, 1987, pp. 166–173.
319. W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1961).

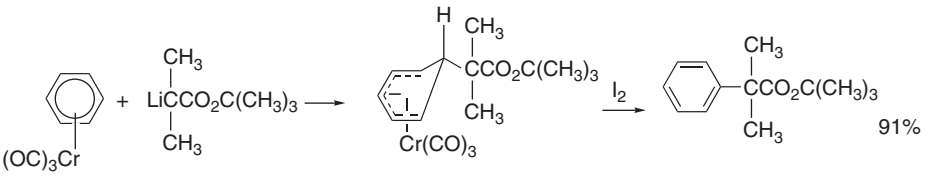


Ref. 320

The $Cr(CO)_3$ unit in these compounds is strongly electron withdrawing and activates the ring to nucleophilic attack. Reactions with certain carbanions results in arylation.[321]

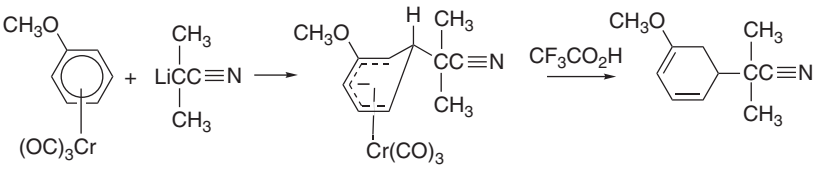


In compounds in which the aromatic ring does not have a leaving group, addition occurs. The intermediate can by oxidized by I_2.



Ref. 322

Existing substituent groups such as CH_3, OCH_3, and $^{+}N(CH_3)_3$ exert a directive effect, often resulting in a major amount of the *meta* substitution product.[323] The intermediate adducts can be converted to cyclohexadiene derivatives if the adduct is protonolyzed.[324]



Not all carbon nucleophiles will add to arene chromium tricarbonyl complexes. For example, alkyllithium reagents and simple ketone enolates do not give adducts.[325]

Organometallic chemistry is a very large and active field of research and new compounds, reactions, and useful catalysts are being discovered at a rapid rate. These developments have had a major impact on organic synthesis and future developments can be expected.

320. J. F. Bunnett and H. Hermann, *J. Org. Chem.*, **36**, 4081 (1971).
321. M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.*, **96**, 7091 (1974).
322. M. F. Semmelhack, H. T. Hall, M. Yoshifuji, and G. Clark, *J. Am. Chem. Soc.*, **97**, 1247 (1975); M. F. Semmelhack, H. T. Hall, Jr., R. Farina, M. Yoshifuji, G. Clark, T. Bargar, K. Hirotsu, and J. Clardy, *J. Am. Chem. Soc.*, **101**, 3535 (1979).
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E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, 1980.
M. Schlosser, ed., *Organometallics in Synthesis: A Manual*, Wiley, Chichester, 1994.

Organocopper Reactions

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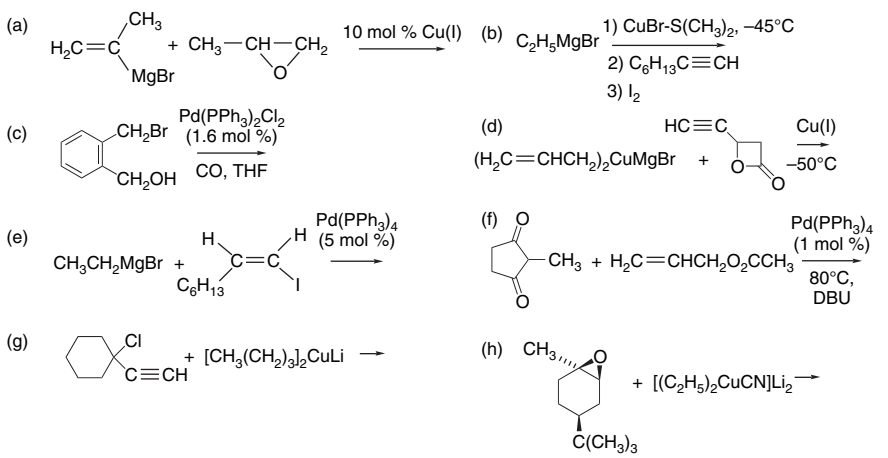
Organopalladium Reactions

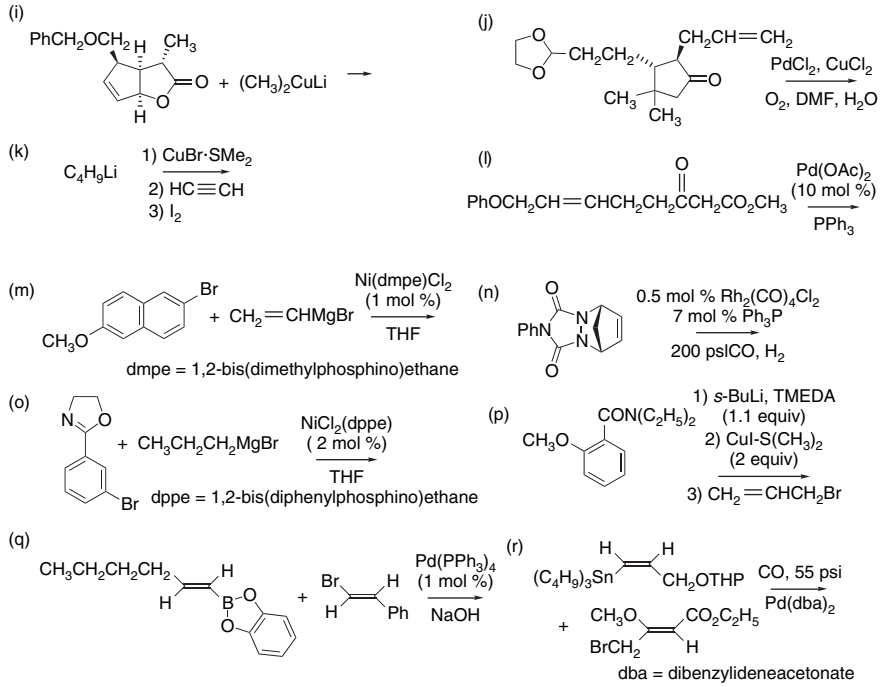
R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, Orlando, FL, 1985.
R. F. Heck, *Org. React.*, **27**, 345 (1982).
E. Negishi and A. de Mejeire, eds., *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1 and 2, Wiley-Interscience, New York, 2002.
J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, New York, 1996.

Problems

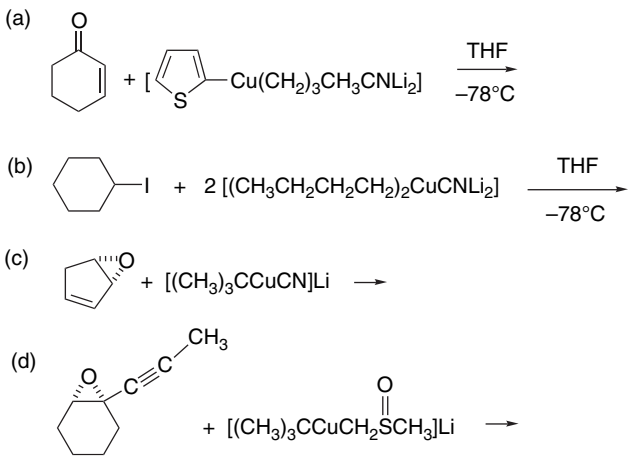
(*References for these problems will be found on page 1284.*)

8.1. Predict the product of the following reactions. Be sure to specify all elements of regiochemistry and stereochemistry.



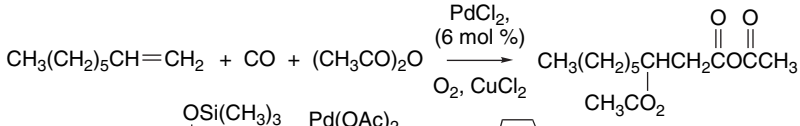


8.2. Give the products expected from each of the following reactions involving mixed cuprate reagents.

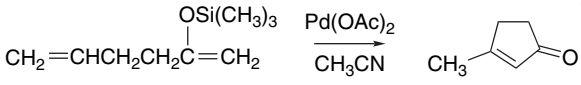


8.3. Write a mechanism for each of the following reactions that accounts for the observed product and is in accord with other information that is available concerning the reaction.

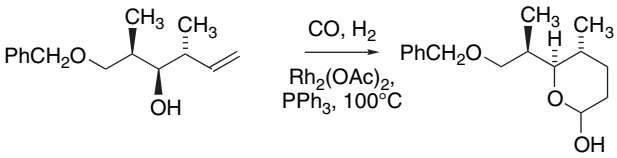
(a)



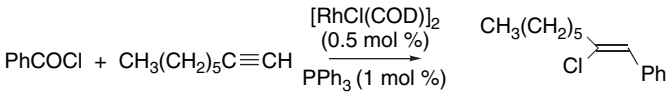
(b)



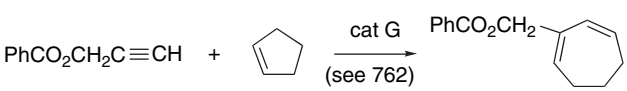
(c)



(d)

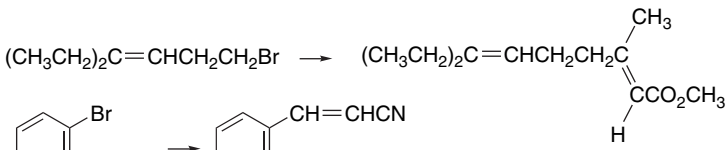


(e)



8.4. Indicate appropriate conditions and reagents for effecting the following transformations. Identify necessary co-reactants, reagents, and catalysts. One-pot processes are possible in all cases.

(a)



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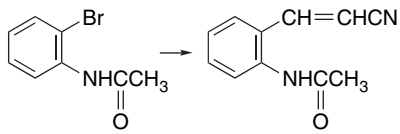

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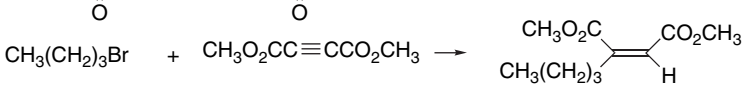

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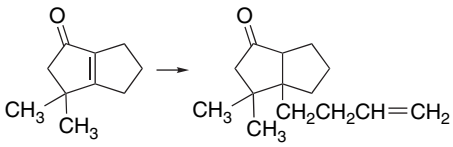

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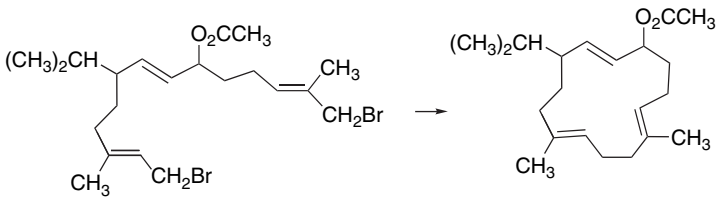

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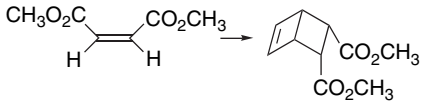
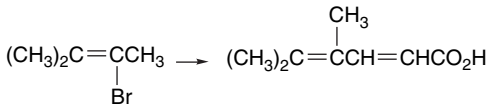


(g)



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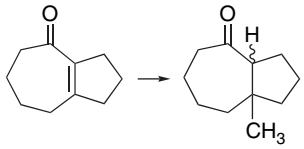
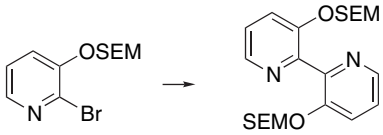


(i)



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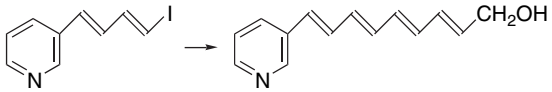

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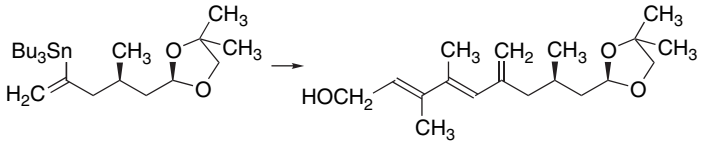

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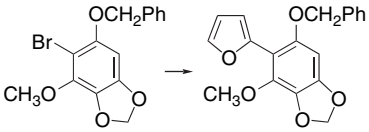

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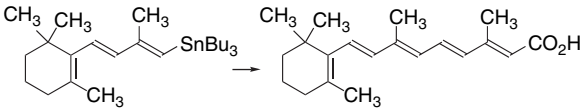

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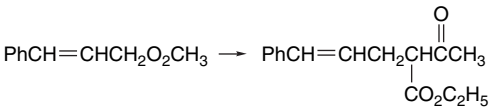
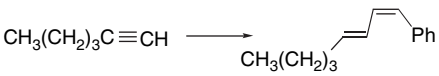


(o)



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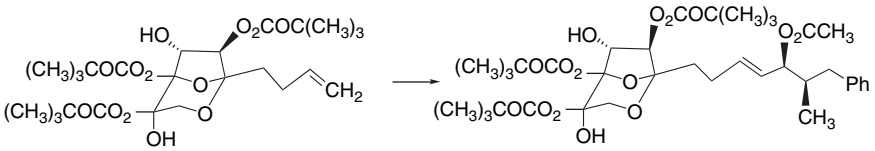
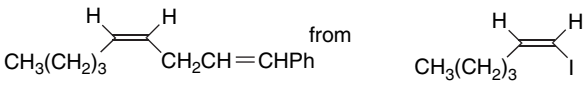
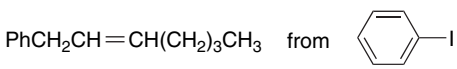
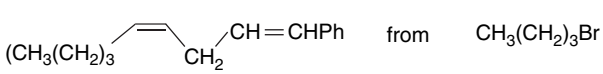


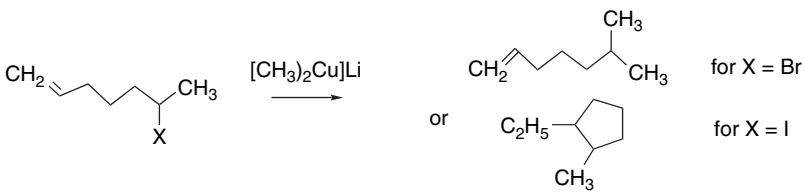
8.5. Vinyltriphenylphosphonium ion has been found to react with cuprate reagents by nucleophilic addition, generating an ylide that can react with aldehydes to give alkenes. In another version of the reaction, an intermediate formed by the reaction of the cuprate with acetylene adds to vinyltriphenylphosphonium ion to generate an ylide intermediate. Show how these reactions can be used to prepare the following products from the specified starting materials.

(a) 

(b) 

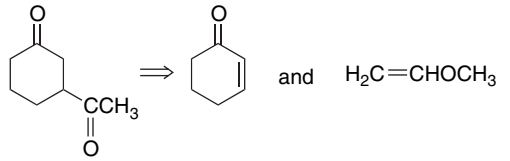
(c) 

8.6. It has been observed that the reaction of $[(C_2H_5)_2Cu]Li$ or $[(C_2H_5)_2CuCNLi_2]$ with 2-iodooctane proceeds with racemization in both cases. On the other hand, the corresponding bromide reacts with nearly complete inversion of configuration with both reagents. When 6-halo-2-heptenes are used in similar reactions with $[(CH_3)_2Cu]Li$, the iodide gives a cyclic product 1-ethyl-2-methylcyclopentane, whereas the bromide gives mainly 6-methyl-1-heptene. Propose a mechanism that accounts for the different behavior of the iodides as compared to the bromides.



8.7. Short synthetic sequences involving no more than three steps can be used to prepare the compound shown on the left from the potential starting materials on the right. Suggest an appropriate series of reactions involving one or more organometallic reagent for each transformation.

(a)



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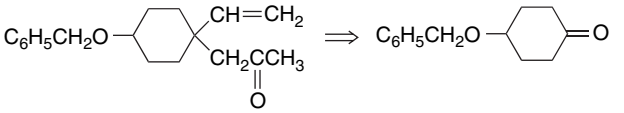

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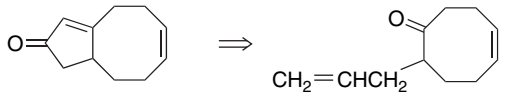

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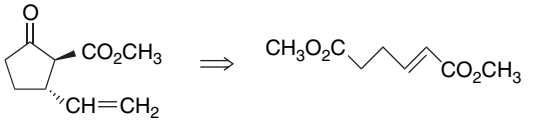

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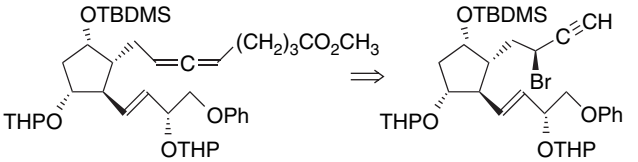

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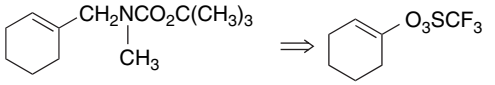
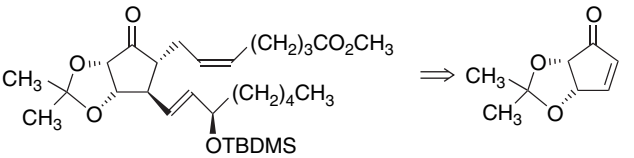


(g)



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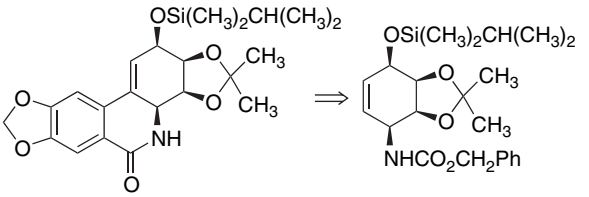
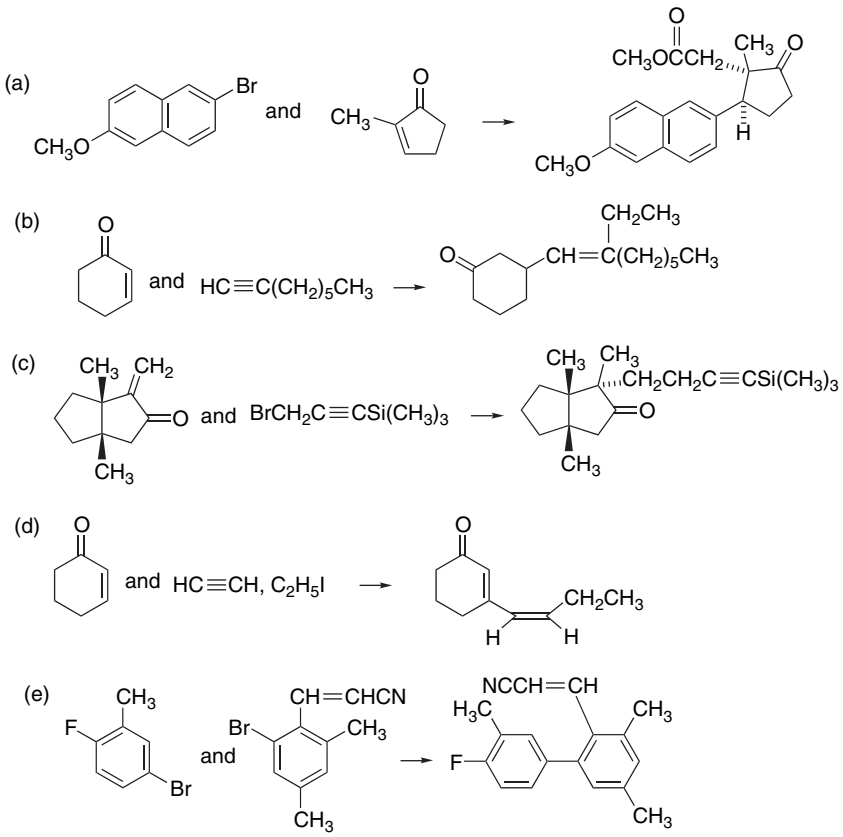
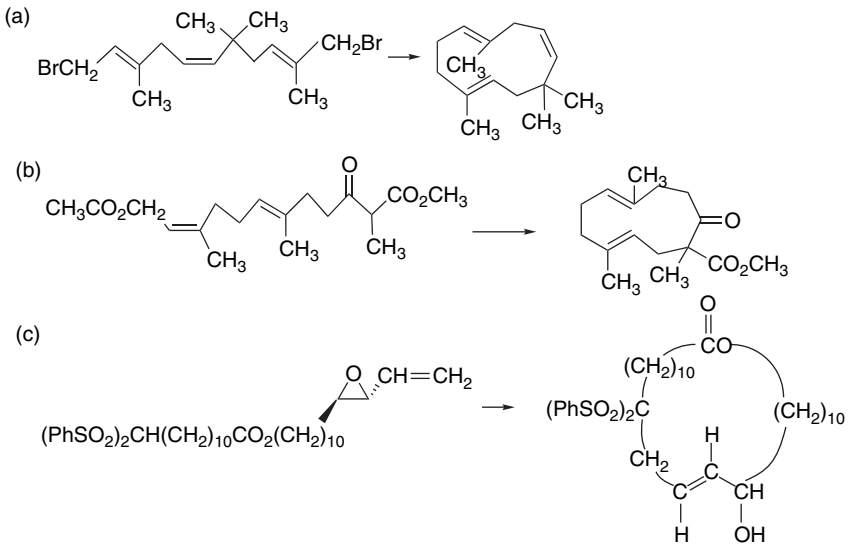


8.8. The conversions shown below can be carried out in multistep, but one-pot, reactions in which none of the intermediates needs to be isolated. Show how you would perform the transformations by suggesting a sequence of reagents and the approximate reaction conditions.



8.9. A number of syntheses of medium- and large-ring compounds that involve transition metal reagents or catalysts have been described. Suggest an organometallic reagent or catalyst that could bring about each of the following transformations.



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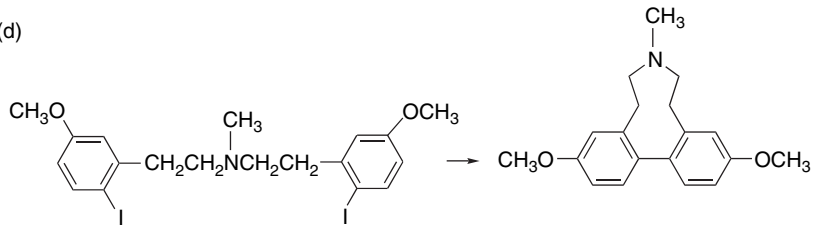

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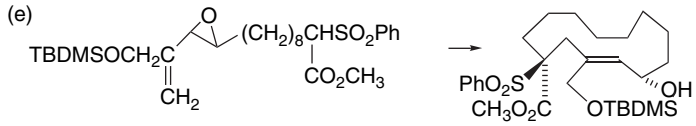

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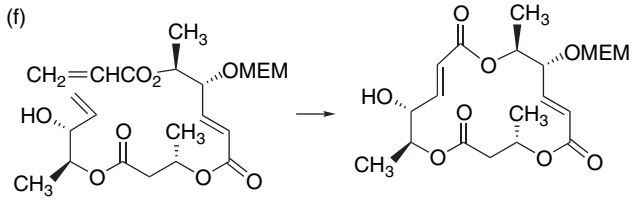
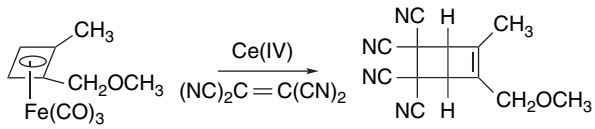
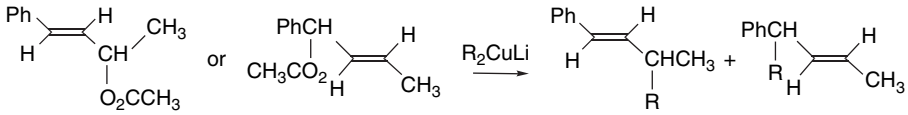


8.10. The cyclobutadiene complex **10-A** can be prepared in enantiomerically pure form. When the complex is decomposed by an oxidizing reagent in the presence of a potential trapping agent, the products are racemic. When the reaction is carried out only to partial completion, the unreacted complex remains enantiomerically pure. Discuss the relevance of these results to the following question: "In oxidative decomposition of cyclobutadiene–iron tricarbonyl complexes, is the cyclobutadiene released from the complex before or after it has reacted with the trapping reagent?"



10 – A

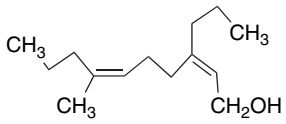
8.11. When the isomeric allylic acetates **11-A** and **11-B** react with dialkylcuprates, they give very similar product mixtures that contain mainly **11-C** with a small amount of **11-D**. Discuss the mechanistic implications of the formation of essentially the same product mixture from both reactants.



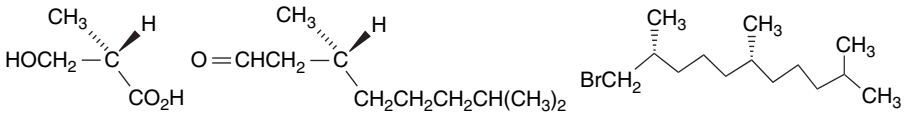
11-A **11-B** **11-C** **11-D**

8.12. The compound shown below is a constituent of the pheromone of the codling moth. It has been synthesized using *n*-propyl bromide, propyne, 1-pentyne,

ethylene oxide, and CO_2 as the source of the carbon atoms. Devise a route for such a synthesis. Hint: Extensive use of organocopper reagents is the basis for the synthesis.



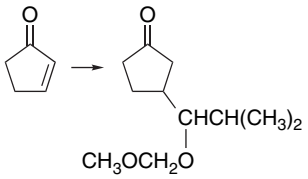
8.13. (*S*)-3-Hydroxy-2-methylpropanoic acid, **13-A**, can be obtained in enantiomerically pure form from isobutyric acid by a microbiological oxidation. The aldehyde **13-B** is available from a natural product, pulegone, also in enantiomerically pure form. Devise a synthesis of enantiomerically pure **13-C**, a compound of interest as a starting material for the synthesis of α-tocopherol (vitamin E).



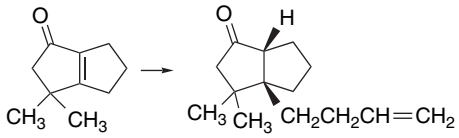
13-A **13-B** **13-C**

8.14. Each of the following conjugate additions can be carried out in good yield under optimized conditions. Consider the special factors in each case and suggest a reagent and reaction conditions that would be expected to give good yields.

(a)

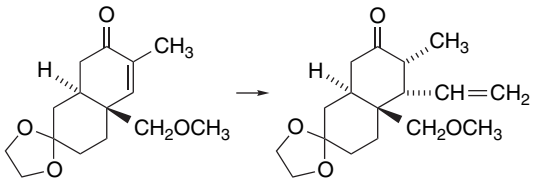


(b)



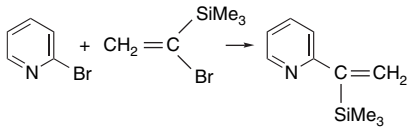
(c) $(CH_3)_2C{=}CHCO_2C_2H_5 \longrightarrow CH_3(CH_2)_3C(CH_3)_2CH_2CO_2C_2H_5$

(d)



8.15. Each of the following synthetic transformations can be accomplished by use of organometallic reagents and/or catalysts. Indicate a sequence of reactions that will permit each of the syntheses to be completed.

(a)



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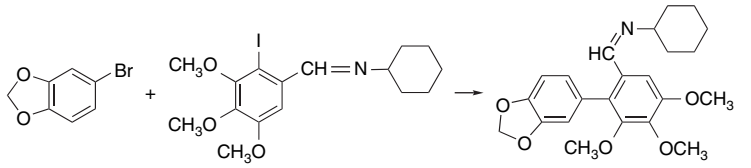

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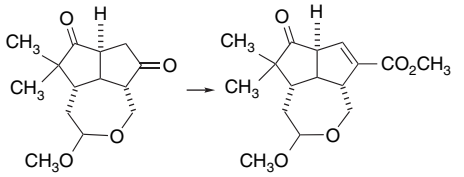

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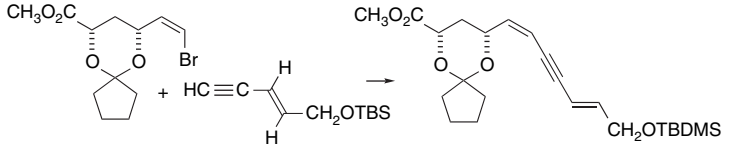

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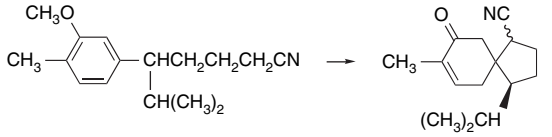

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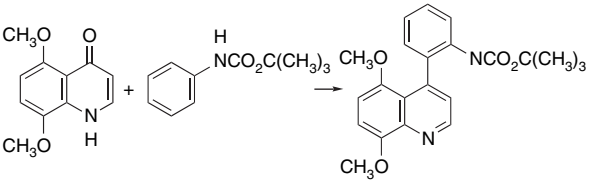
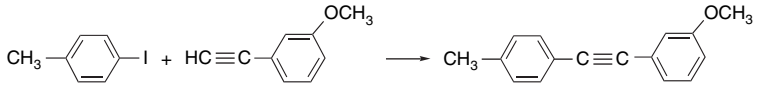


(g)



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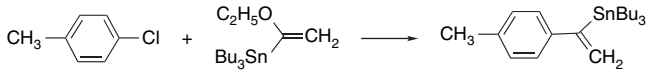
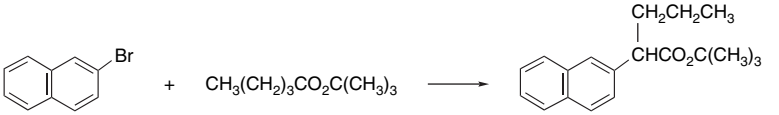


(i)



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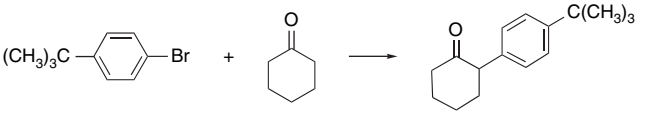

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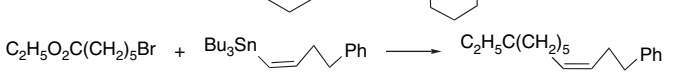

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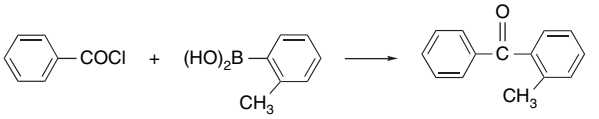
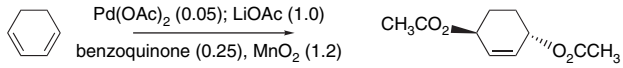


8.16. Each of the following reactions can be accomplished with a palladium reagent or catalyst. Write a detailed mechanism for each reaction. The number of equivalents of each reagent is given in parentheses. Specify the oxidation state of Pd in the intermediates. Be sure your mechanism accounts for the regeneration of catalytically active species in those reactions that are catalytic in palladium.

(a)



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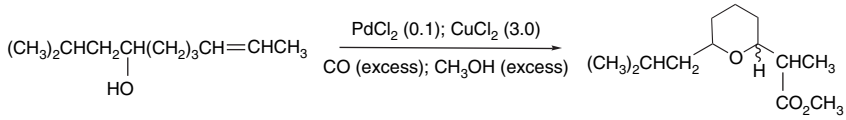

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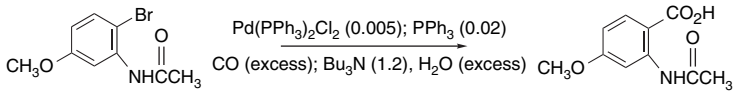

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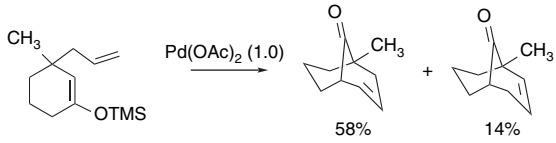
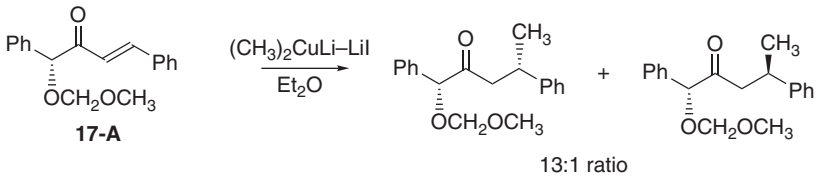
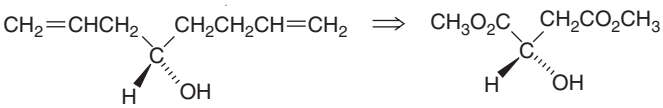


8.17. The reaction of lithium dimethylcuprate with **17-A** shows considerable 1,4-diastereoselectivity. Offer an explanation, including a transition structure.

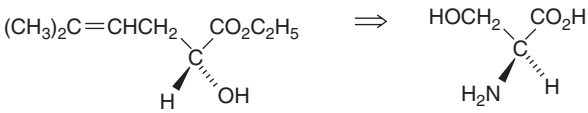


8.18. The following transformations have been carried out to yield a specific enantiomer using organometallic reagents. Devise a strategy by which organometallic reagents or catalysts can be used to prepare the desired compound from the specified starting material.

(a)



(b)



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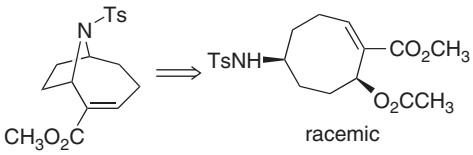
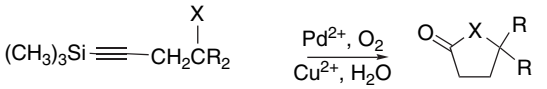
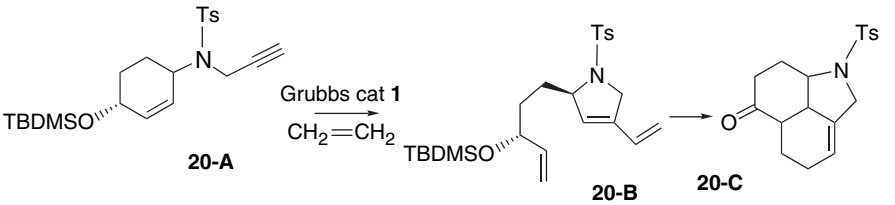


8.19. Under the conditions of the Wacker oxidation, 4-trimethylsilyl-3-alkyn-1-ols give γ -lactones. Similarly, *N*-carbamoyl or *N*-acetyl 4-trimethylsilyl-3-alkynamines cyclize to γ -lactams. Formulate a mechanism for these reactions. (Hint: In D_2O, the reaction gives 3,3-dideuterated products.)



X = OH, $HNCOCH_3$, $HNCO_2R$
R = H, alkyl

8.20. The tricyclic compound **20-C**, a potential intermediate for alkaloid synthesis, has been prepared by an intramolecular Diels-Alder reaction of the ketone obtained by deprotection and oxidation of **20-B**. Compound **20-B** was prepared from **20-A** using alkyne-ethene metathesis chemistry. Show the mechanistic steps involved in conversion of **20-A** to **20-B**.