Pergamon

Tetrahedron 56 (2000) 817–846

TETRAHEDRON

Tetrahedron Report Number 513

Nickel Catalyzed Reactions of Nucleophiles with Unactivated and Partially Activated Olefins and Acetylenes

Ioannis N. Houpis* and Jaemoon Lee†

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, USA

Received 2 August 1999

Contents

1. Introduction

For several decades nickel catalysis has been successfully applied in a number of industrial processes, particularly in the oligomerization of alkenes and alkynes, and carbonylation reactions.[1] Somewhat ironically this early success in polymer chemistry delayed the use of organonickel complexes by synthetic organic chemists who are by training averse to polymer-producing substances. Nonetheless early reports do describe the reaction of η^3-allyl-organonickel complexes with aldehydes to form allylic alcohols, while significant research has been devoted, in the last two decades, to the cross-coupling reaction of alkyl Grignards and organic halides. This early work has been described in several review articles.[2]

With the rapid expansion of the utility of organopalladium catalysts in organic synthesis, several research groups have been shifting their attention to nickel catalysis. As work in the area progressed, it became apparent that these catalysts offered certain advantages to the practicing synthetic organic chemist both in industry and academia. Organonickel catalysts are cheap, air stable (as the Ni^{II} salts) and are stable in the presence of hard organometallics. The reactivity of such catalysts is also unique

* Corresponding author. Fax: +1-732-594-6703; e-mail: ioannis_houpis@merck.com
† Fax: +1-732-594-1499; e-mail: jaemoon_lee@merck.com

PII: S0040-4020(99)00965-5

in that they also provide the possibility of a Ni^{I}/Ni^{III} pathway as well as the more common M^{0}/M^{II} (M=Ni or Pd) mechanistic pathway that Pd catalysts follow. The former would exhibit similar reactivity to radicals with the added advantage of the stability of the carbon–metal bond.

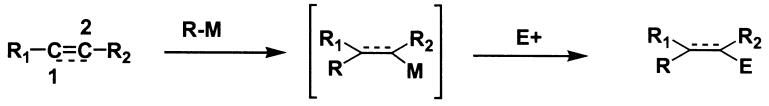
In this review, we will describe the addition of organonickel species to olefins and acetylenes to form a new C–C bond. The initial C–Ni moiety is generated in a number of ways from the appropriate organic precursor and Ni pre-catalyst. In most cases proper arrangement of multiple unsaturation in the same molecule allows for sequential additions to form complex carbocyclic and heterocyclic frameworks. We will not describe here sp^2–sp^2 couplings as they have been described adequately elsewhere.[3]

This work is also not meant to be an exhaustive review of the literature but rather give the reader a flavor of the various ways to use Ni catalysis to add to olefins and acetylenes, of the reaction conditions commonly used, and the mechanism of these reactions as well as reagent and functional group compatibility. We have also tried to concentrate our review in the literature descriptions of the last decade.[4]

2. Addition of C–Ni Species to Unactivated Olefins and Acetylenes

2.1. Reaction of olefins and acetylenes with external organometallics

The carbometallation of unactivated acetylenes and alkenes is a powerful synthetic transformation since the overall outcome is the formation of a new carbon–carbon bond at one end of the unsaturation (C-1) and a carbon–metal bond at the other end (C-2) which can be used for further functionalization (Scheme 1).[5]

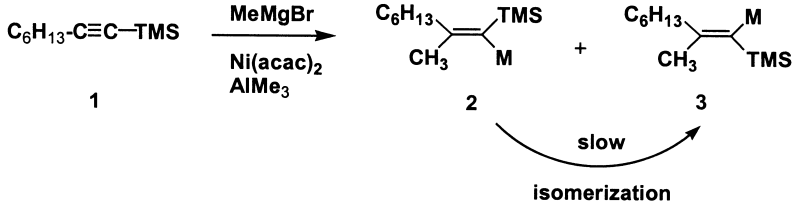


Scheme 1.

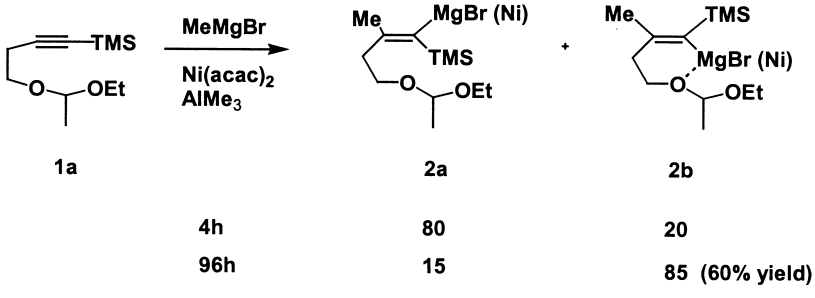
This transformation can be even more powerful if high regio- and stereoselectivity can be achieved. In the case of carbometallation of olefins, controlling the stereochemistry of the newly formed sp^3 centers is also important. In order to create an even more powerful methodology, the process should be able to tolerate functional groups in R_1, R_2 and R.

Nickel-catalysis provides some elegant solutions to the above considerations since Ni species are stable in the presence of a number of hard and soft nucleophiles, are able to function as one-electron donors and can be transmetallated by relatively unreactive organometallics.[6]

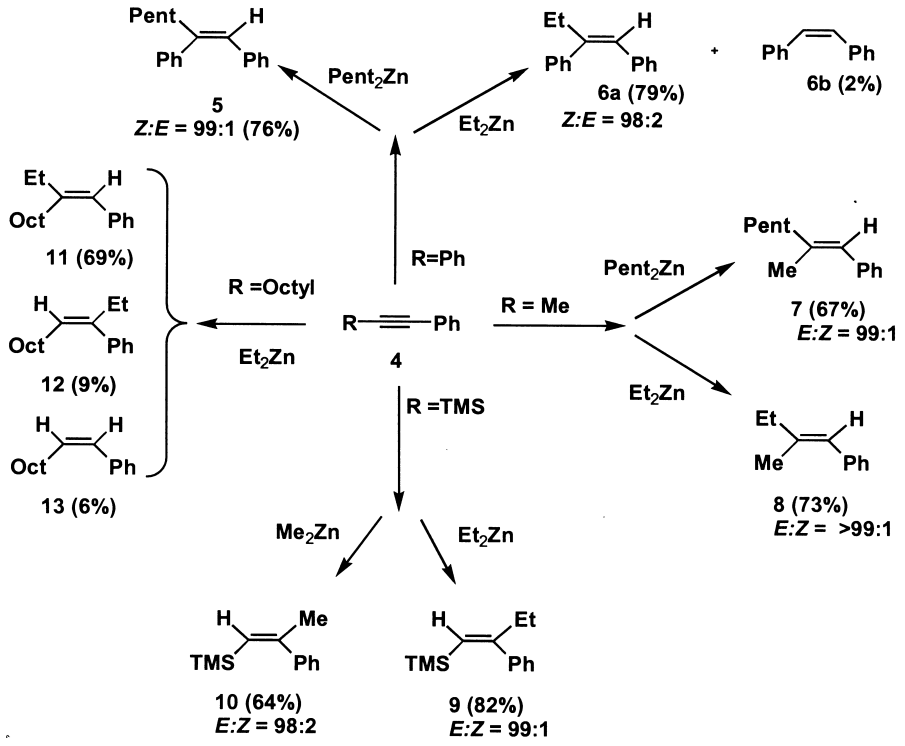
In early reports from the Snider group,[7] carbometallation of silyl acetylene **1** with ligand-less Ni^0 [generated in situ from $Ni(acac)_2$] proceeded successfully (Eq. (1)) to produce initially the *syn*-adduct **2** (M=H) in good yield (78% after workup). Upon standing, **2** slowly isomerizes to the *anti*-isomer **3** (**2**:**3**=9:1 over 24 h). The equilibrium of the reaction favors the *anti*-adduct especially if chelating groups are present (Eq. (2)).



(1)



(2)



Scheme 2.

More recently, the carbometallation of acetylenes was achieved with greatly improved regio- and stereocontrol by using organozinc reagents instead of the more reactive Grignards. This reaction (Scheme 2) provides an excellent alternative to the stoichiometric carbocupration or Zr-catalyzed carboalumination of acetylenes.[8]

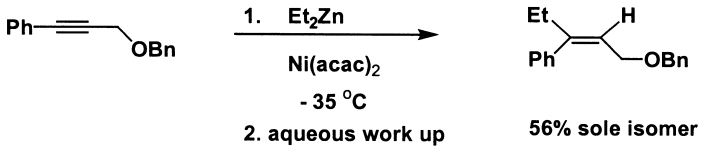
Specifically, addition of dialkylzinc reagents to internal, aryl acetylenes proceeds at −35°C in THF/NMP (1:3) in the presence of 25 mol% $Ni(acac)_2$ to afford in good yields the corresponding olefins (Scheme 2).

Reaction of **4** (R=Ph) with $(pentyl)_2Zn$ afforded a good yield (76%) and excellent *syn*-selectivity of the olefin **5**, while reaction with Et_2Zn afforded **6** (79%) along with small amounts of *cis* styrene (2%). The latter is thought to be the result of H–Ni addition to the acetylene, a species formed from β-hydride elimination of the more reactive Et–Ni intermediate.

High regio- and *syn*-selectivity is achieved with alkyl substituents that are less sterically demanding. So reaction of **4** (R=Me) with $(pentyl)_2Zn$ and Et_2Zn gives **7** and **8** in 67 and 73% yield, respectively, as the main products. However, when **4** (R=octyl) was reacted with Et_2Zn substantial amounts (9%) of the regioisomer **12** was produced along with the reduction product **13** (6%).

As seen in the results above, the regioselectivity of the reaction is controlled well with the newly formed C–C bond being directed away from the phenyl substituent (Scheme 2). The trimethylsilyl group reverses that trend (similar to Eq. (1)); so when **4** (R=$SiMe_3$) is reacted with Et_2Zn or Me_2Zn, **9** and **10** are produced in 82 and 64%, respectively, as the sole regioisomers.[9]

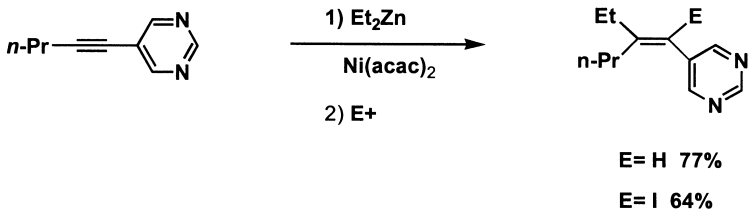
Phenyl substituted propargyl ethers also give olefins where the newly formed C–C bond is on the same carbon as the aryl substituent (Eq. (3)).



(3)

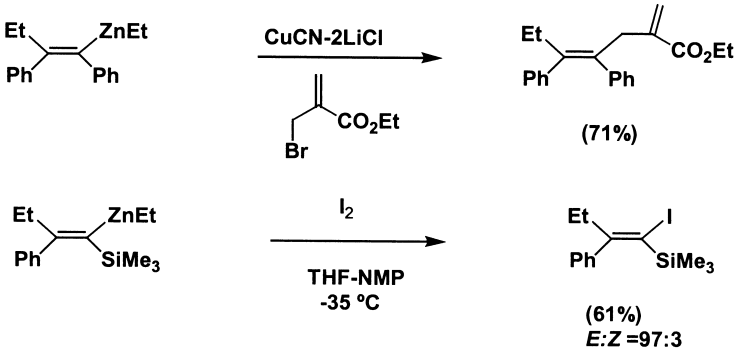
On the other hand, the electronic demands of alkyl substituted heteroaromatic acetylenes give the olefin with reverse

regiocontrol (Eq. (4)).



(4)

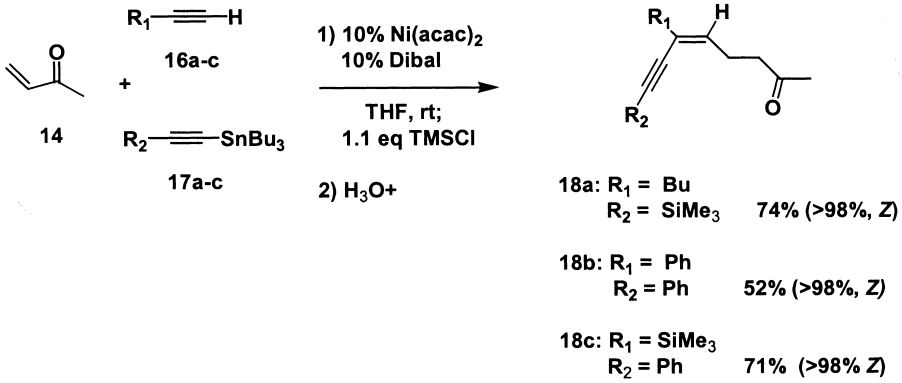
This powerful methodology can be expanded further by using the resulting carbozincation product to form, in a highly selective manner, diversely functionalized tetra-substituted olefins (Eq. (5)). The use of vinyl zinc reagents in the synthesis of functionalized olefins has been investigated thoroughly.[10]



(5)

2.2. Sequential additions of C–Ni species to olefins and acetylenes

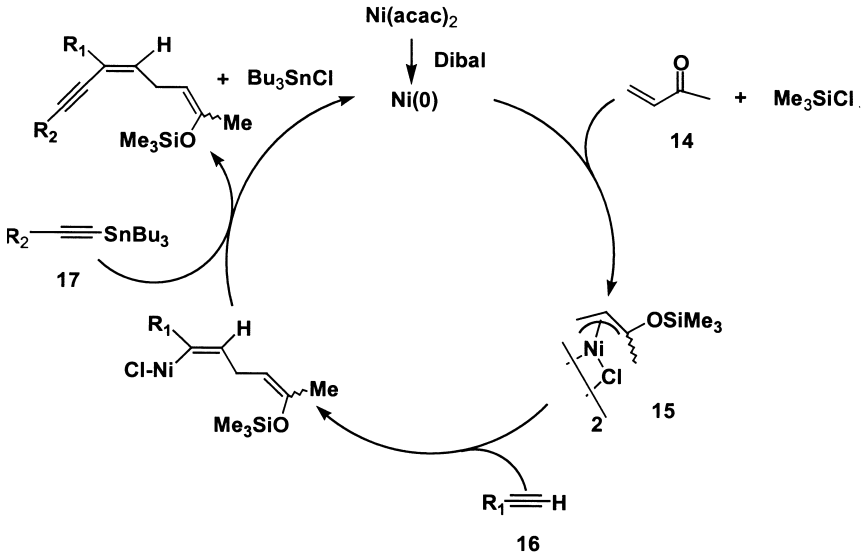
The nickel-catalyzed carbometallation reaction of acetylenes has been elegantly expanded by several research groups to induce, in a controlled manner, tandem additions to sp and sp^2 centers and thus to construct complex structural frameworks.



(6)

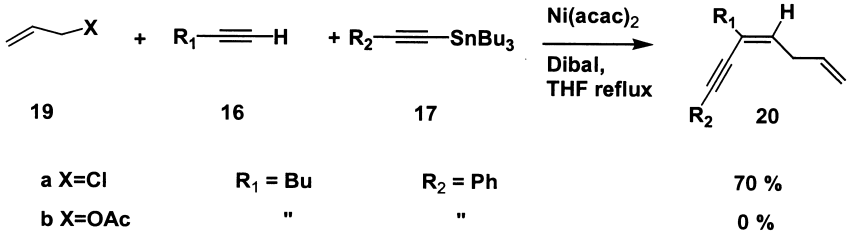
Ikeda and Sato discovered an elegant and controlled enyne synthesis (Eq. (6)),[11] inspired by the report by Mackenzie and co-workers that enones (e.g. **14**) react with Ni^0 complexes in the presence of trimethylsilyl chloride to produce the π-allyl oxo-Ni^{II} species **15** (Scheme 3). In their work, Ni^0, generated in-situ by reduction of $Ni(acac)_2$ with diisobutylaluminum hydride, was reacted with a terminal acetylene (**16**) and a stannyl acetylene (**17**) in the presence of 1.1 equiv. of trimethylsilyl chloride to produce the enynes **18** in good yield and excellent *Z*-selectivity. The reaction is thought to proceed via **15** (Scheme 3), carbometallating **16**, followed by Stille-type transmetallation of the resulting vinyl–Ni–Cl intermediate by **17** and, finally, reductive elimination. Hydrolysis of the silyl enol ether gives the desired product.

Subsequent work showed that simple π-allyl Ni complexes generated from allyl chloride **19a** (X=Cl) can also be used to give



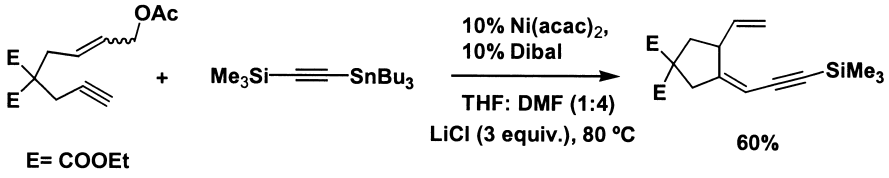
Scheme 3.

the enyne product **20** in 70% yield (Eq. (7)) and high *E*-selectivity.[12]



(7)

However, when the allyl acetate **19b** was used, none of the enyne **20** was produced. Addition of 1 equiv. of LiCl to the reaction mixture restores some of the reactivity affording ca. 30% of **20**. Interestingly, acetate is the leaving group of choice in the intramolecular variant of this reaction (Eq. (8)).

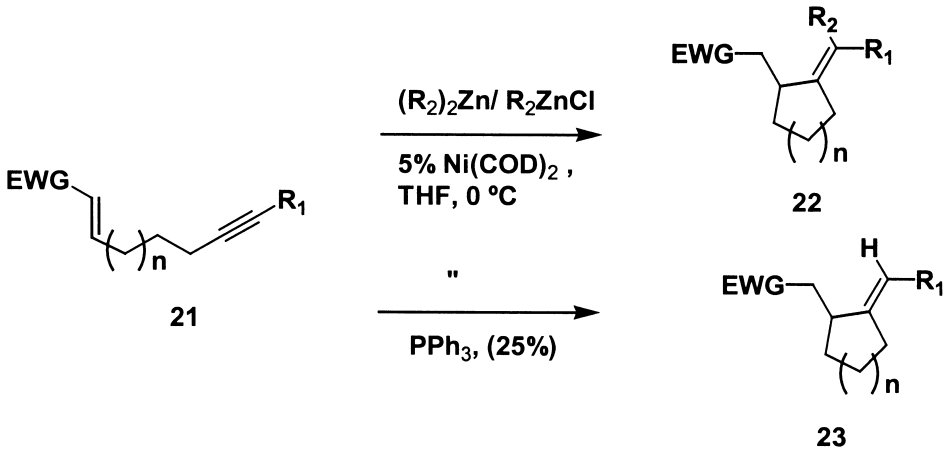


(8)

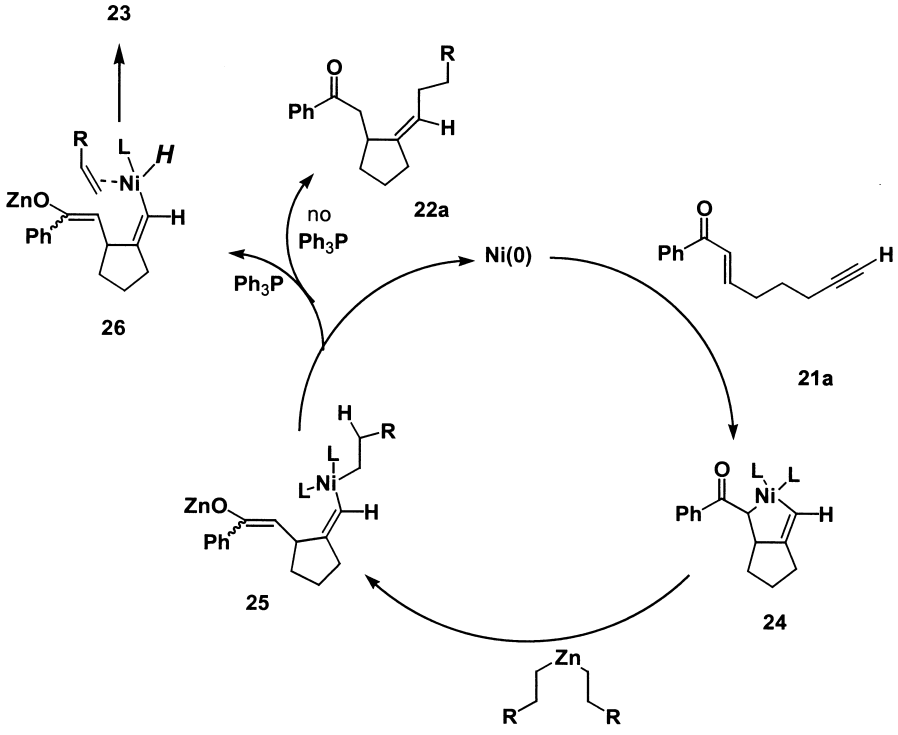
A similar, albeit mechanistically different, process has recently been discovered by the Montgomery group.[13] At its conception, following the mechanistic path of Scheme 3, the process involved: (a) the formation of an oxo-allyl Ni complex from an enone and a Lewis acid in the presence of a Ni^0 catalyst; (b) intramolecular trapping by a tethered acetylene; (c) transmetallation of the presumed vinyl Ni intermediate with a dialkylzinc reagent; and (d) reductive elimination to give the product. Later mechanistic studies (see Scheme 5) showed a somewhat different mechanistic pathway; nonetheless, synthetically the concept proved to be very useful as shown below. When enone **21** (Scheme 4) was treated with a mixture of $(R_2)_2Zn$ and R_2ZnCl (generated from R^2Li or R^2MgCl and $ZnCl_2$ mixed in the appropriate proportions) in the presence of $Ni(COD)_2$ in THF at 0°C a fast reaction ensued to give good yields and complete olefin stereocontrol of the *alkylative cyclization* product **22**. However, in the presence of 5 equiv. of PPh_3 (with respect to Ni) and dialkyl Zn reagent bearing β-hydrogens, the reaction followed a different pathway to give the *reductive cyclization product* **23**.

Detailed mechanistic studies led to an interesting mechanistic hypothesis (Scheme 5)[14] to account for the formation of **22** and **23** as well as other experimental results observed in this work.

The reaction of **21a** with Ni^0 is thought to produce the metallacycle **24** as the first step and not the π-oxoallyl Ni^{II} species (Scheme 3) involved in the Ikeda and Mackenzie work. Transmetallation with the dialkyl zinc reagent produces the σ-vinyl Ni complex **25** which can undergo reductive elimination to give **22a**. In the presence of β-hydrogens and PPh_3, β-hydride elimination is the predominant pathway to give **26** which then undergoes reductive elimination to give **23a**.



Scheme 4.

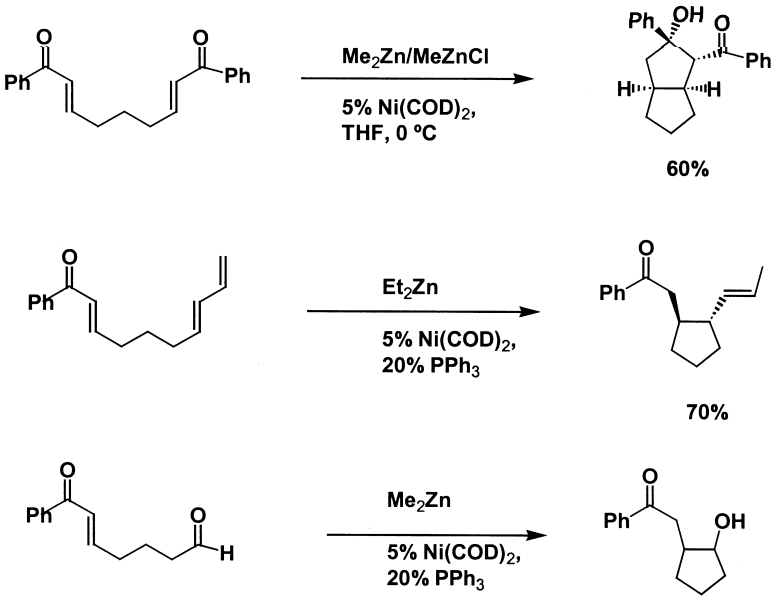


Scheme 5.

Table 1.

Entry EWG	*n*	R_1	R_2	PPh_3, equiv.	Yield **22** (%)	Yield **23** (%)
1 **21a** PhCO	1	H	Me	0	82	0
2 **21b** PhCO	1	Ph	Bu	0	68	8
3 **21c** PhCO	1	H	Vinyl	0	59	Trace
4 **21d** PhCO	1	H	Bu	0.25	0	92
5 **21e** $(CO_2Me)_2$	1	H	Me	0	74	
6 **21f** NO_2	1	H	Et	0	47	
7 **21g** CO_2Me	1	H	Me	0	15	
8 **21h** PCO	2	H	Me	0	54	
9 **21i** PhCO	3 or 4	H	Me	0	0[a]	

[a] Cyclic dimers and direct 1-4 addition products were produced in low yield.

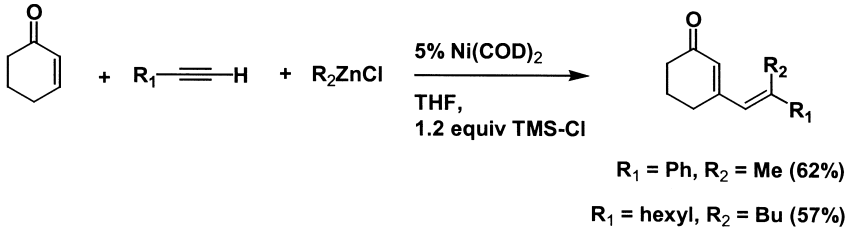


Scheme 6.

During the last several years, thorough investigation[15] of the parameters of this reaction have delineated the structural requirements of each of the components. The reaction requires an electron deficient alkene as the initiator (Entries 1–6, Table 1) although the ester function (entry 7, Table 1) gives only low yields of the cyclization product.[16] Both internal and terminal alkynes function as efficient terminators to give good yields of the alkylative cyclization product **22** (entry 2, Table 1) although small amounts of the reductive cyclization products **23** are also produced for those cases. Both five- and six-member rings (entry 8, Table 1) can be formed; however, longer tethers (entry 9) fail to give the seven or eight-member ring products.

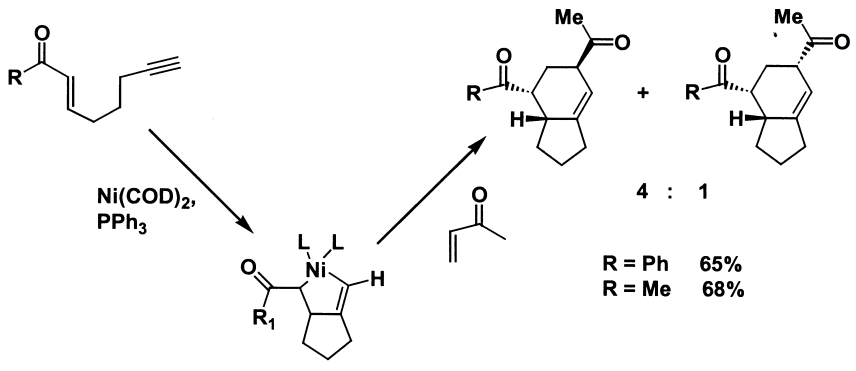
Although simple alkenes do not function as efficient terminating groups, enones, dienes and aldehydes all give the corresponding cyclization product (Scheme 6).

The intermolecular version of this reaction has also been explored[17] to give 5-disubstituted dienones in good yields and stereoselectivities (Eq. (9)).

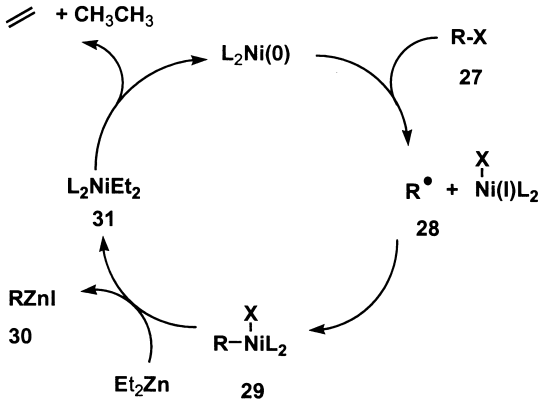


(9)

Finally, these workers[18] were able to exploit their mechanistic understanding of this reaction and the intermediate metallacycle **24** to effect an elegant 2+2+2 cycloaddition reaction (Eq. (10)).



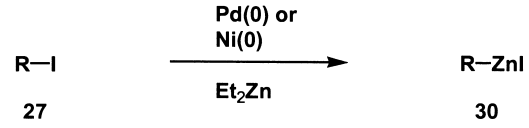
(10)



Scheme 7.

2.3. Ni-catalyzed Zn–halogen exchange of alkyl halides and addition to olefins and acetylenes

The utility of organozinc reagents in the Ni-catalyzed addition of carbon nucleophiles to olefins and acetylenes can be greatly expanded by the discovery that Ni and Pd catalyze the zinc-iodide exchange reaction to produce alkylzinc iodides (Eq. (11)).[10]

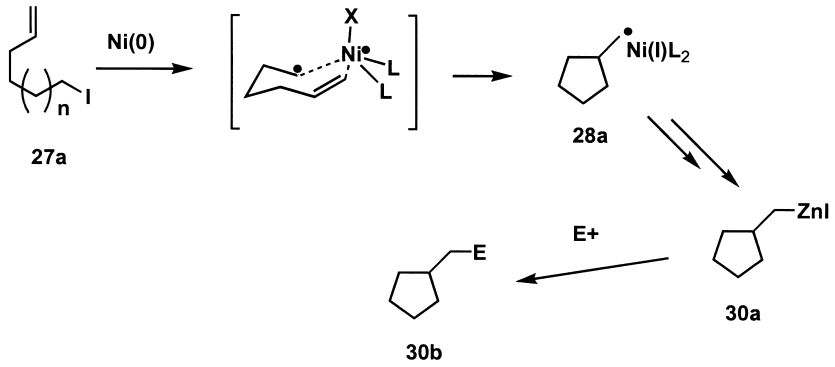


(11)

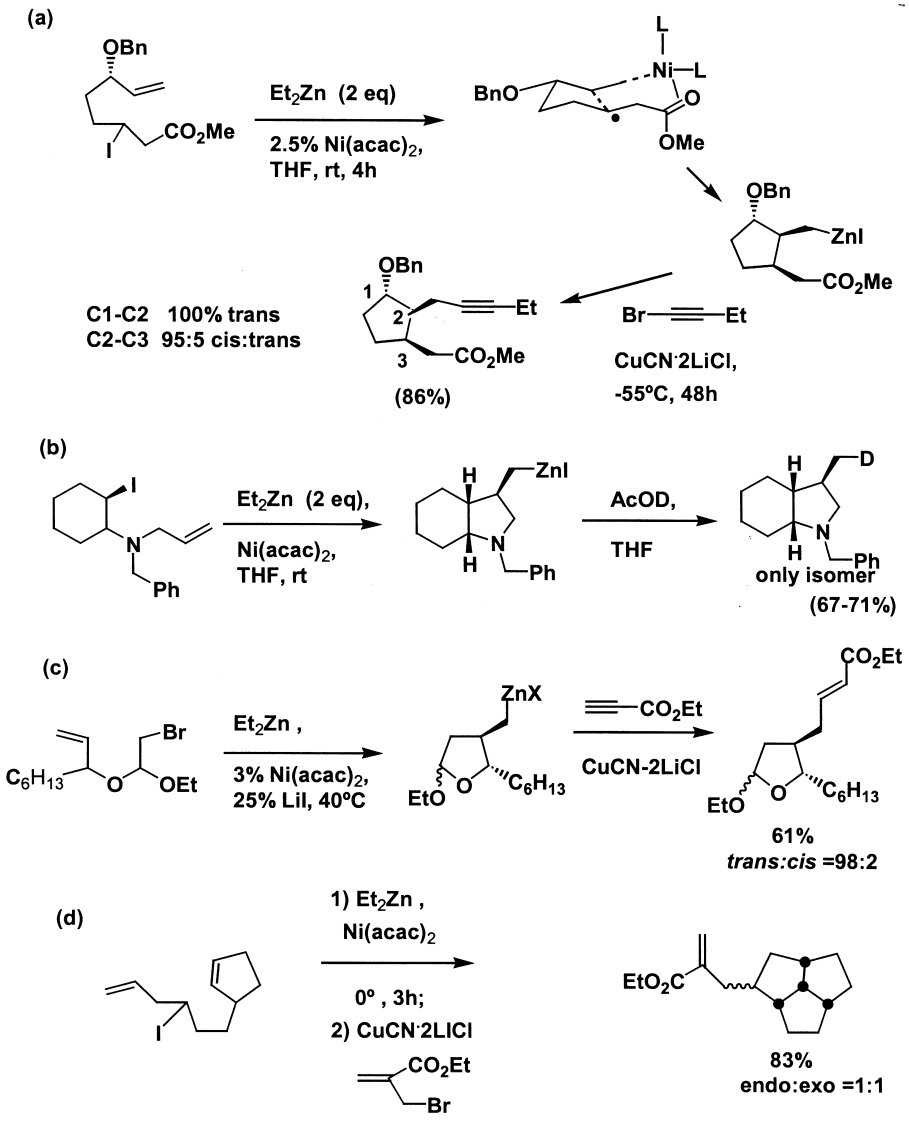
Mechanistic studies[19] have indicated that this reaction proceeds via a one-electron transfer from the Ni^0 complex (Scheme 7) onto the alkyl halide **27** to generate the alkyl radical **28** and $L_2Ni(I)X$. These two components could combine to give the Ni^{II} complex **29**. Transmetallation with diethylzinc produces **30** and diethyl–Ni complex **31** which, after β-hydride elimination and reductive elimination, regenerates the active catalyst Ni^0 along with ethane and ethylene.

This process becomes more useful if the alkyl moiety, R, in **28** (or **29**) contains an intramolecular radical trap such as a C=C (e.g. **27a**). In a such case, cyclization (Scheme 8) could ensue to produce the *cyclic*, functionalized organozinc reagent **30a** that could be further reacted via a number of protocols to give elaborated carbocyclic or heterocyclic compounds (**30b**).

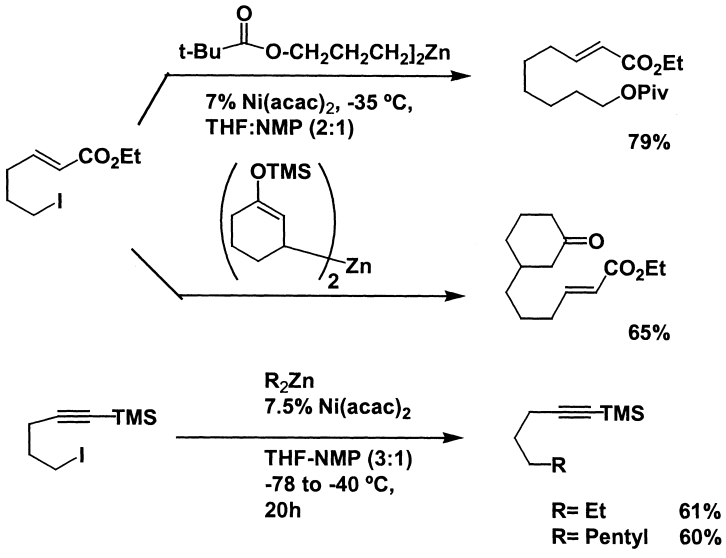
The above premise has been explored elegantly by the Knochel group[20] to prepare a multitude of complex structures as well as natural product skeletons. A small sample of representative examples is shown in Scheme 9, where it can be clearly seen that this process is highly stereo- and chemo-selective. The reaction is tolerant of functional groups such as esters, acetals and polar heteroatoms (N and O) and is governed by the high and predictable selectivity of radical cyclization reactions. The substantial



Scheme 8.



Scheme 9.

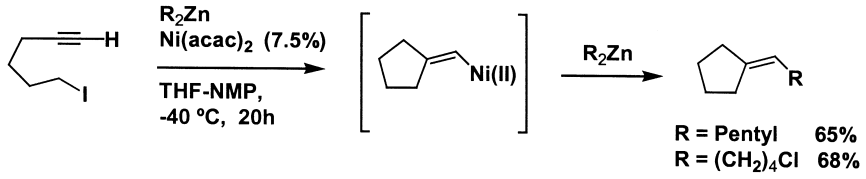


Scheme 10.

advantage of this method over classical radical cyclizations is that the intermediate **28a** is not a highly reactive primary radical, which reacts rapidly to give the reduced product, but rather it gets converted to a stable organozinc halide (**30a**), which reacts further under controllable reaction conditions (Scheme 9).

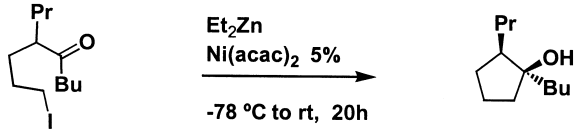
Primary iodides that possess a tethered olefin or acetylene that is electron deficient do not undergo cyclization in the presence of a Ni catalyst and organozinc reagents (Scheme 10).[21] Instead, a fairly general cross-coupling reaction takes place to give the Wurtz-type coupling product in good yield. The mildness of the reaction allows the use of functional groups (esters, silylenol ethers) that would have been incompatible with Grignard or sodium reagents more typically used for these couplings (Scheme 10).

It is noteworthy that terminal acetylenes do afford the cyclization-coupling product (Eq. (12)).[22]



(12)

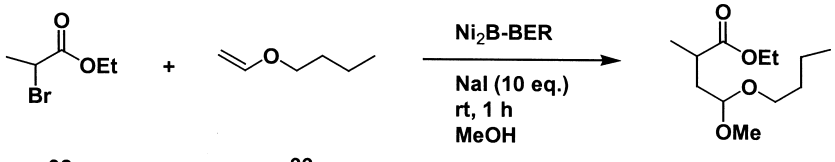
More recently, in the related topic of addition to the C=O moiety, this Ni-catalyzed Zn–halogen exchange[23] has been used for the cyclization of 5-haloketones thus providing a catalytic version to the SmI_2 or alkyl lithium induced cyclizations (Eq. (13)).[24]



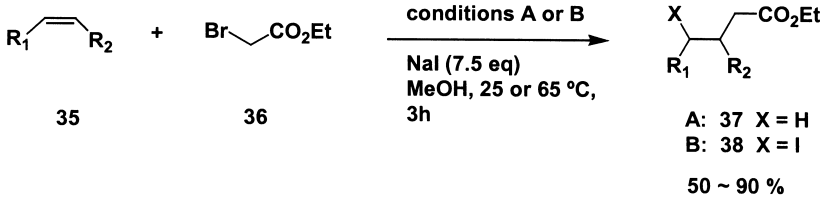
(13)

2.4. Addition to olefins and acetylenes of C–Ni species generated from chemical reduction of halides

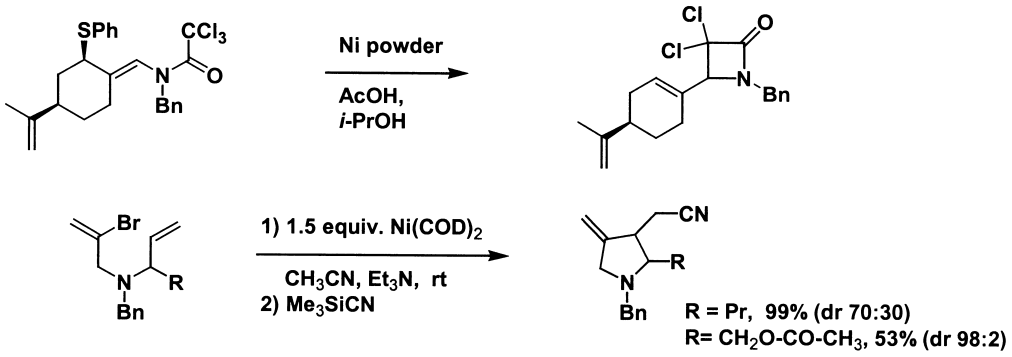
Chemical reductants, other than R_2Zn, have also been used successfully to effect reduction of alkyl halides and generation of species like **28** or **29** which could then add to sp^2 and sp centers inter- or intramolecularly. Resin bound Ni^0 catalysts generated from Borohydride Exchange Resin (BER) catalyze the reaction of bromopropionate **32** with enol ether **33** to give the adduct **34** in 95% yield (Eq. (14)).[25] Simple olefins (e.g. **35**) also react with bromoacetate **36** to give the reductive addition product **37** (Scheme 11) or the atom transfer adduct **38** depending on the catalyst load (conditions A and B, respectively).



(14)

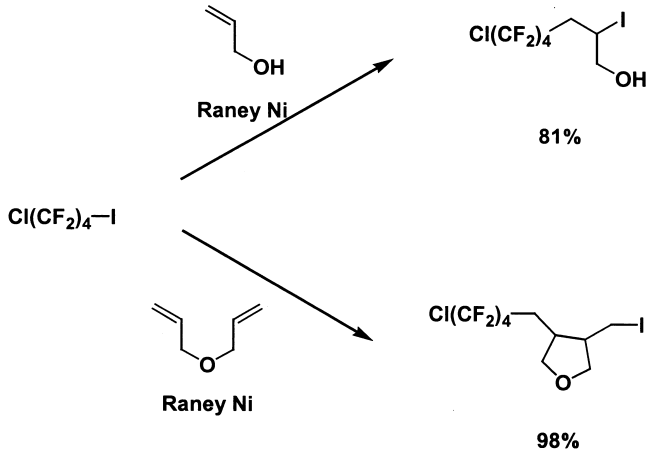


Scheme 11. R_1=C_5H_{11}, $C_6H_{11}CH_2$, $C_6H_5CH_2$, $C_6H_5C_2H_4$; R_2=H or Me. Conditions A=15% $Ni(OAc)_2$, 5 equiv. BER; Conditions B=7.5% $Ni(OAc)_2$, 2.5 equiv. BER.



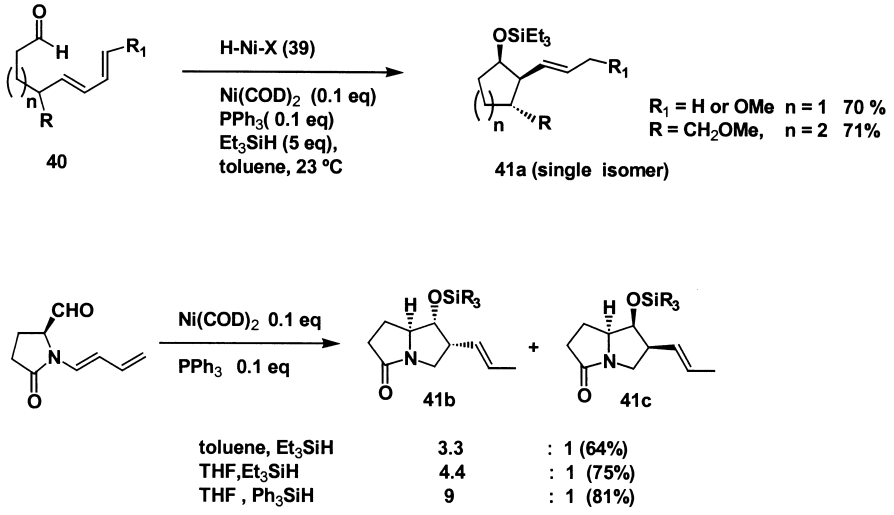
Scheme 12.

Atom transfer additions to C=C have also been obtained with perfluoro iodoalkanes in the presence of Raney-Ni (Eq. (15)).[26]

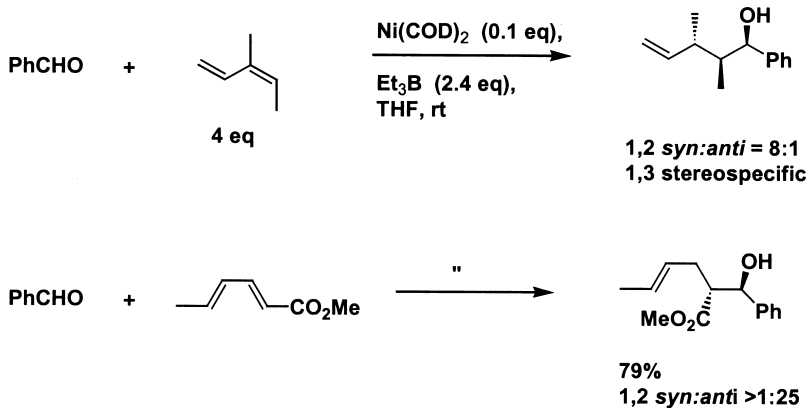


(15)

On the other hand, β-iodoenones in the presence of Ni–Phosphine complexes and Zn metal react with 1,3-dienes to afford the 1,4-homocoupling products (Eq. (16)).[27] Chemical reduction of organic halides to produce C–Ni bonds can also be achieved

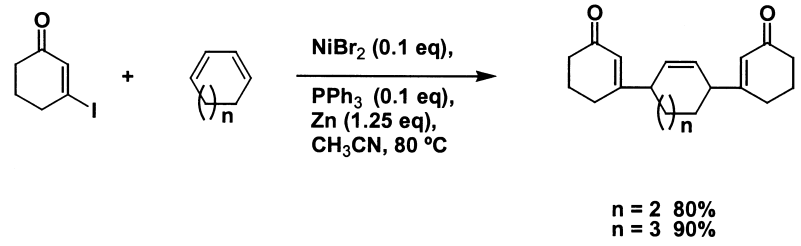


Scheme 13.

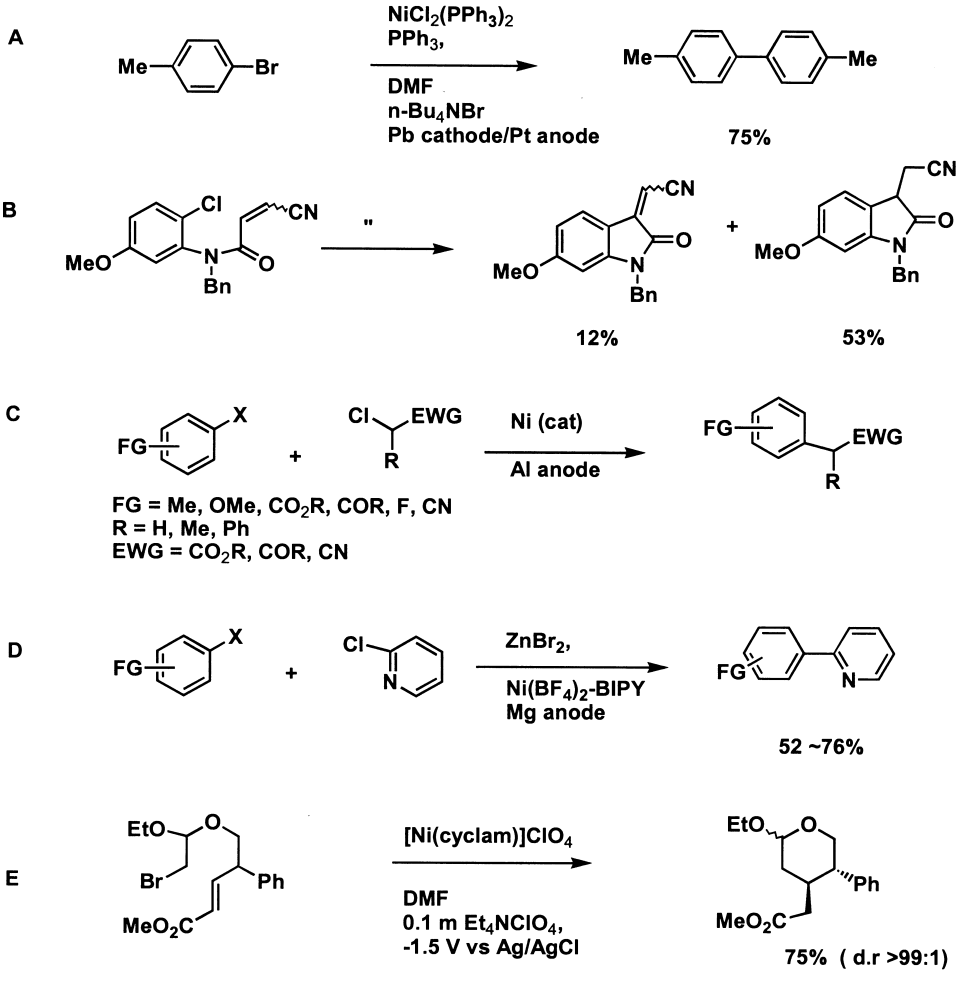


Scheme 14.

with stoichiometric Ni^0 metal.



(16)

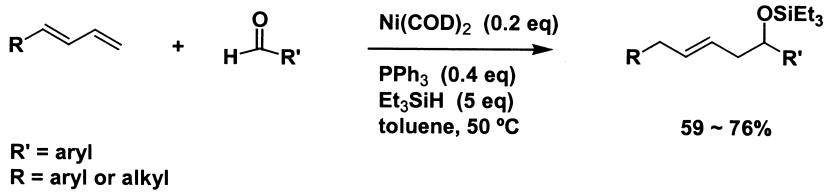


Scheme 15.

Normally this use of a transition metal would not be cost effective, however the low price of Ni-metal, and its derivatives, makes stoichiometric procedures feasible in the laboratory scale. Two examples are shown in Scheme 12.[28]

Finally, in an elegant series of papers, Mori and co-workers have been able to generate H–Ni–X catalyst **39** (from Ni^0 and Et_3SiH) which react with 1,3-dienes **40** to generate π-allyl-Ni complexes.[2c] When a tethered aldehyde is present (Scheme 13), this nucleophilic allyl Ni complex adds in a 1,2 fashion to produce carbocyclic (**41a**) and heterocyclic derivatives (**41b** and **41c**).[29]

Notably the intermolecular version of this reaction also gives high yield of the adducts (Eq. (17)).



(17)

Remarkable 1,2 and 1,3 selectivity can be obtained in this reaction when substituted dienes react with aromatic aldehydes in the presence of $Ni(acac)_2$ and Et_3B to give the monoallylation products shown in Scheme 14.[30]

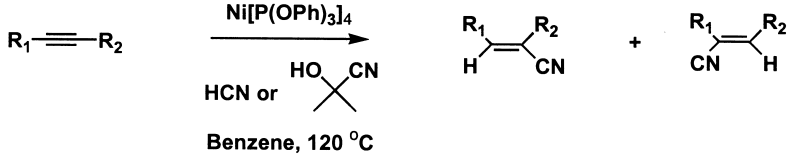
2.5. Addition to olefins and acetylenes of C–Ni species generated from electrochemical reduction of halides

An alternative method for the generation of intermediates such as **28** or **29** (Scheme 7)[31] is the electrochemical reduction of appropriately functionalized alkyl, alkenyl and aryl halides in the presence of Ni salts. A number of examples in the literature (Scheme 15) have demonstrated this method in the synthesis of biaryl derivatives (Scheme 15A), oxyindoles (Scheme 15B), α-aryl-ester, ketone, and nitrile derivatives (Scheme 15C) and bis-heteroaryl compounds (Scheme 15D). Alkyl halides have also been cyclized in this manner to give tetrahydropyran (Scheme 15E) and lactone derivatives in good yield and stereoselectivity.

3. Addition of HCN to Acetylenes and Olefins

3.1. Addition of HCN to acetylenes

The Ni-catalyzed addition of HCN to acetylenes is a useful transformation since it generates not only a new C–C bond but also an α,β unsaturated nitrile which can be used for further functionalization.[32] Early studies (Scheme 16) showed that Ni^0 phosphite complexes such as $Ni[P(OPh)_3]_4$ can successfully catalyze the addition of HCN, or its precursor acetone–cyanohydrin, across non-polar acetylenes. The yield and stereoselectivity of the reaction depends largely on the metal ligands [$(PPh_3)_4Ni$ is not a good catalyst for this reaction] and the steric and electronic properties of the acetylene. The reaction works well with alkyl or aryl, internal and terminal acetylenes. However, electron-withdrawing substituents diminish the yield



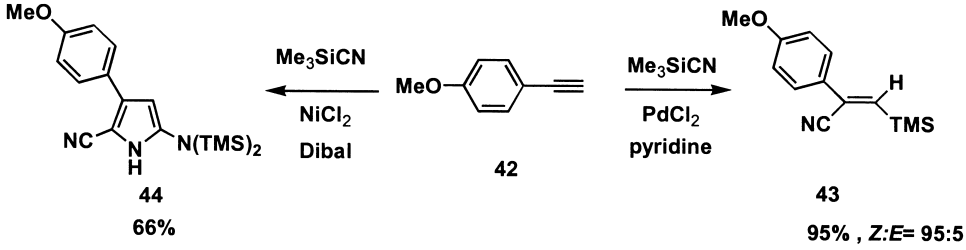
Scheme 16.

Table 2.

Entry	Substituents	Yield (%)	Ratio
1	R_1=R_2=Ph	93	
2	R_1=R_2=CO_2Me	27	
3	R_1=*t*-Bu; R_2=Me	78	90:10
4	R_1=*n*-Bu; R_2=H	73	14:86
5	R_1=Ph; R_2=H	45	90:10

substantially (entry 2, Table 2). Internal acetylenes favor formation of the new C–C bond at the least substituted site (entry 3, Table 2) while terminal acetylenes exhibit opposite selectivity (entry 4, Table 2). However, the electronics of the phenyl ring reverse the latter regioselectivity (entry 5, Table 2).

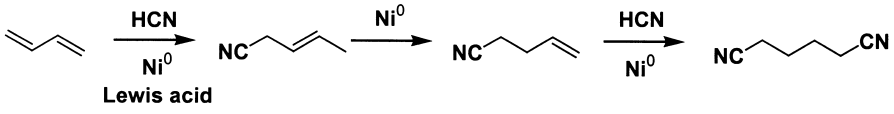
Remarkably, Ni and Pd show dramatically different reactivity when Me_3SiCN is used as the cyanation reagent (Eq. (18)).[33] Namely, acetylene **42** in the presence of $PdCl_2$ reacts with $Me_3Si–CN$ to give excellent yield and regioselectivity of the expected vinyl nitrile **43**. Conversely good yield of the functionalized pyrrole derivative **44** was obtained when a Ni^0 catalyst was employed.



(18)

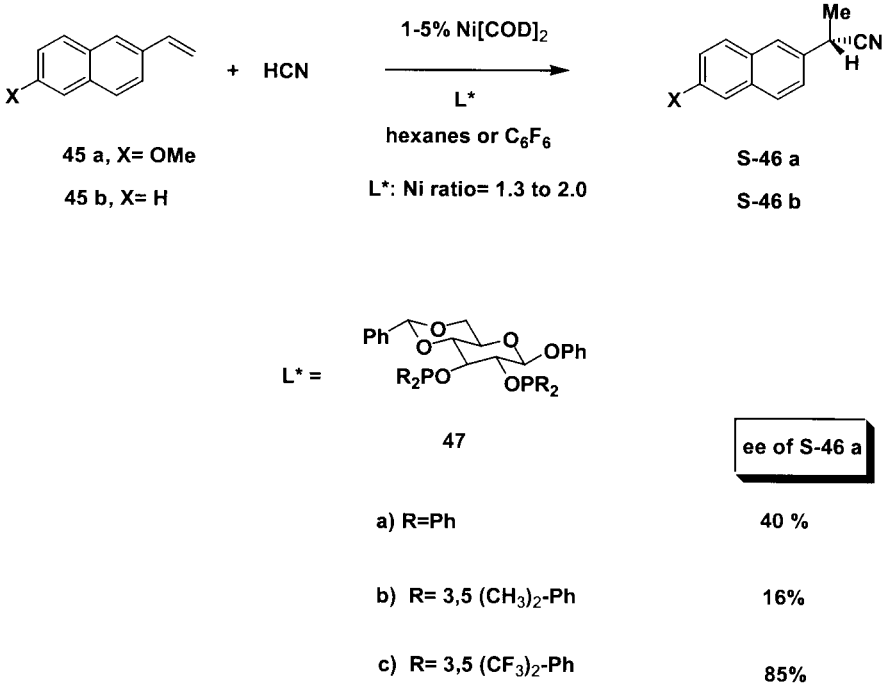
3.2. Ni-catalyzed addition of HCN to olefins

The addition of HCN to olefins is admittedly "…one of the important success stories in the industrial application of homogeneous catalysis".[34] Indeed the addition of HCN to butadiene is responsible for about 75% of the total production of adiponitrile (Eq. (19)) and is used exclusively by DuPont to prepare starting materials for nylon as well as other amine and nitrile products. The reaction proceeds through three discreet steps and is successful only when $(PhO)_3P$ or $P(O\text{-}p\text{-tolyl})_3$ are used as ligands.[35] The latter ligand gives rapid reaction at 25°C while the addition of Lewis acids afforded longer catalyst life and product distribution favoring linear products.



(19)

Interestingly, phosphines are not useful ligands for this reaction, and lead to catalyst deactivation. Further work at DuPont has



Scheme 17.

produced a remarkable example of an enantioselective addition of HCN to vinyl arenes under Ni-catalysis.[36] This study, originally aimed at the synthesis of Naproxen and its derivatives, has recently been expanded into other areas (e.g. hydrovinylation) and uses, quite elegantly, *electronic* as well as steric tuning to effect the desired selectivity. So the reaction of **45a** or **45b**, with a toluene solution of HCN in a non-polar solvent in the presence of $Ni(COD)_2$ and phosphinite ligand **47** afforded the naproxen precursor **46a** or **46b** (Scheme 17).

High yield, enantioselectivity and catalyst turnover were found to depend on the following parameters: (a) phosphinite ligands (such as **47**) of a 1,2 diol are required, while phosphines are not useful ligands for this reaction; (b) the 1,2 diol must be of the gluco-configuration as phosphonite derivatives of BINOL or (*S*,*S*)1,2-cyclohexanediol give poor selectivity; (c) the phosphonite phosphorous substituents must be electron withdrawing. This latter parameter turned out to be the most important factor in dictating the enantioselectivity of this reaction. So **47a** (R=Ph) gives modest enantiomeric excess of **46a** (40% ee) while introduction of the two electron donating methyl groups (**47b**) reduces the selectivity further (16% ee). Great success was achieved when the electron withdrawing bistrifluoromethylphenyl derivative **47c** is used. It is noteworthy that the ligand affording the highest selectivity also gives the highest catalytic activity. About 552 turnovers/h were possible at 25°C with loads as low as 0.13 mol% of **47c** or 0.1 mol% of $Ni(COD)_2$. Interestingly, the reaction rate and selectivity is not affected by the Ni/substrate ratio, the Ni/ligand ratio or the percent conversion of the reaction.

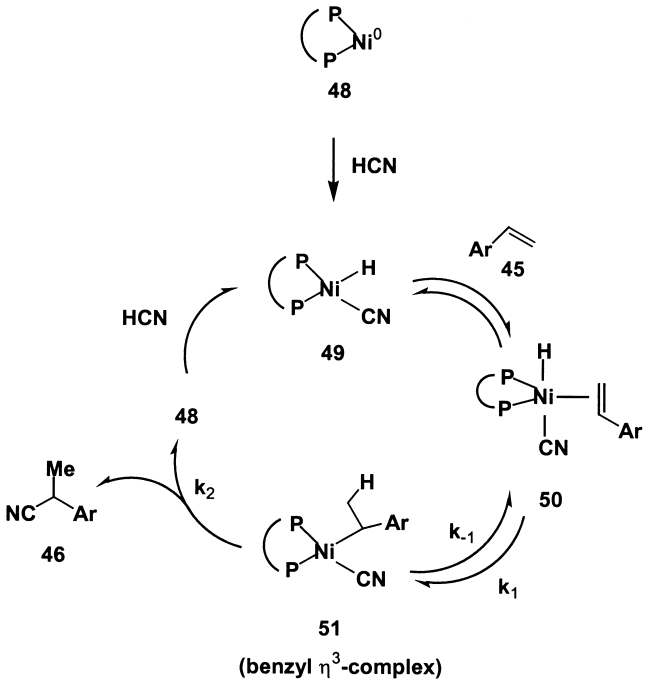
A careful mechanistic study has given some insight as to why electron-withdrawing substituents afford higher enantiomeric excess (Scheme 18).

Detailed kinetic work[37] supports the supposition that the chiral induction does not come from a face selective coordination event that forms **50**, but rather from the migratory insertion and/or reductive elimination steps that form **51** and **46**, respectively. Based on the above mechanism, it is thought that the electronics of the ligand affect the enantiomeric excess in the following two ways: First, for ligand **47a** (R=Ph), k_2 and k_{-1} are similar leading to rapid equilibration between **50** and **51** while for **47c** (R=3,5-difluoromethyl-phenyl) $k_2 \gg k_{-1}$ leading to rapid formation of **46** and regenerating the active catalyst **48**. Second, it is then speculated that as the electron density on the Ni is decreased, the reductive elimination of *S*-**51** must be considerably faster than the *R* isomer (perhaps due to steric compression) leading to high selectivity for *S*-**46** (Scheme 17).

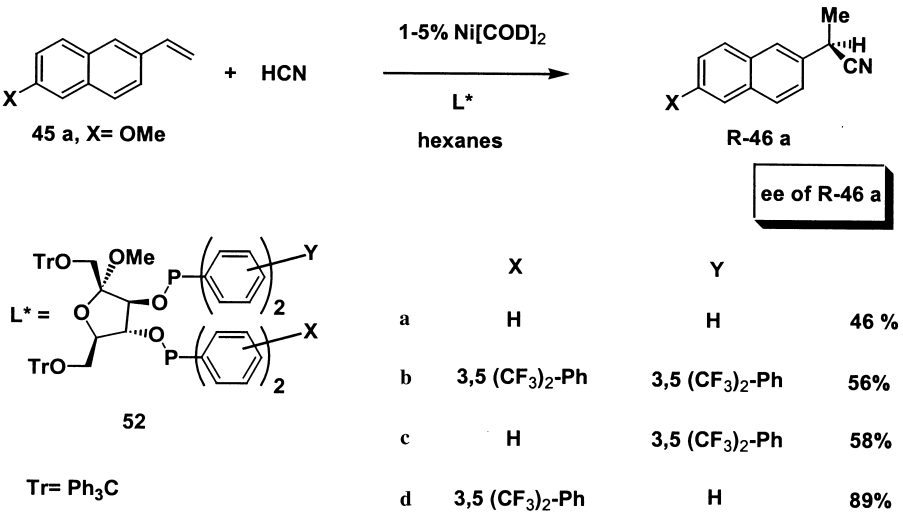
Synthesis of the *R*-**46** isomer required the design of a new ligand that possessed electronic asymmetry (Scheme 19).[38] Remarkable selectivity was observed when the fructofuranoside system **52a**–**d** was employed. The highest ee of *R*-**46** was obtained when only one of the phosphinite phosphorous is substituted with electron withdrawing groups (**52d**).

3.3. Ni-catalyzed asymmetric hydrovinylation reaction

Similarly to the hydro-cyanation reaction,[39] vinyl arenes, such as **45a**, undergo a hydrovinylation reaction under Ni catalysis to

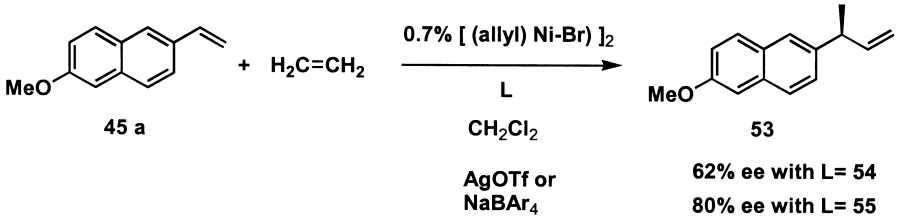


Scheme 18.



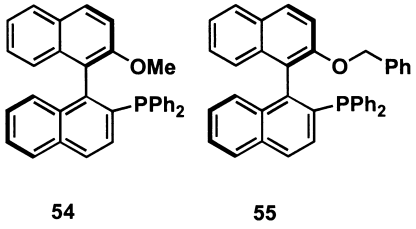
Scheme 19.

give the chiral olefin **53** (Eq. (20)).

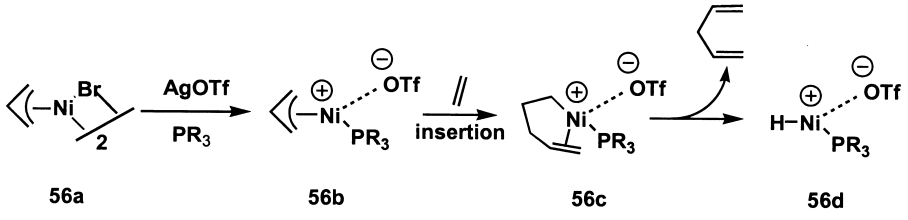


(20)

Incorporation of a chiral monophosphine ligand containing a second weakly coordinating group (**54** and **55**) leads to substantial amount of chiral induction.

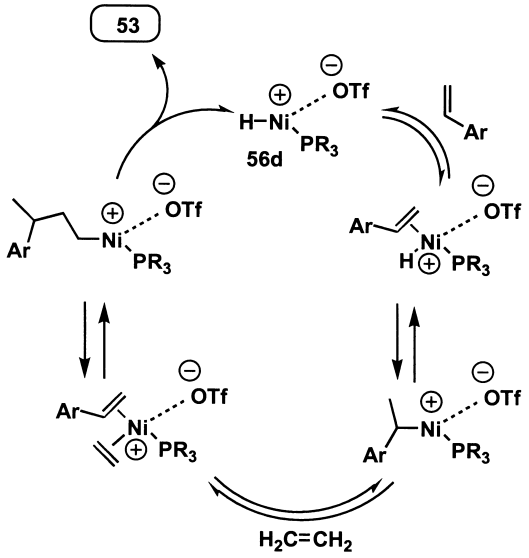


The success of this reaction depends on the in situ generation of more reactive Ni-species by replacing the halide from the stable allyl-Ni–Br dimer (**56a**) with a weakly coordinating $^{-}$OTf (or in some cases Ar_4B^{-}) counterion (Eq. (21)).



(21)

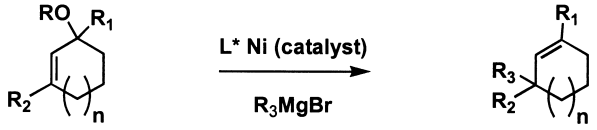
The catalyst precursor **56a** is activated by reaction with AgOTf to form the allyl Ni complex **56b**. Coordination of the ethylene of insertion gives **56c** which after β-hydride elimination gives 1,4-pentadiene and the catalytically active species **56d**. The latter affords the product **53** as shown in Scheme 20.



Scheme 20.

4. Substitution of Allylic Systems by Organometallics

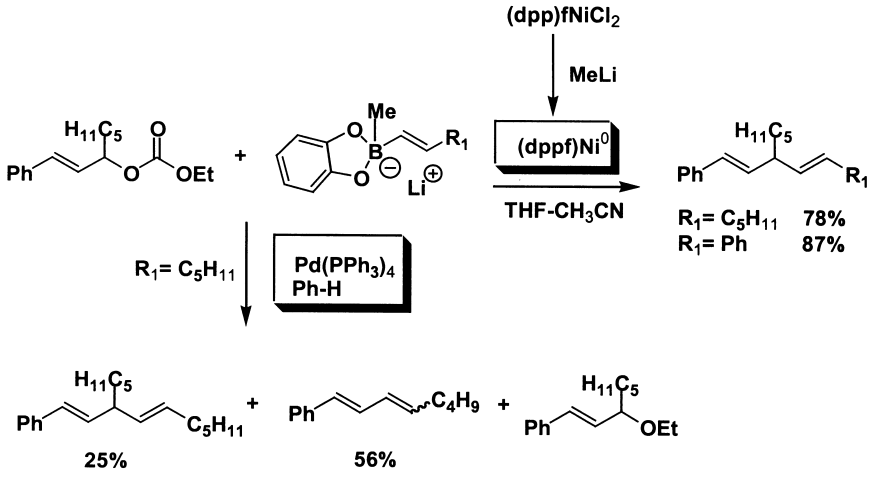
Ni-catalyzed allylic alkylation reactions of allyl ethers, halides, carbonates and alcohols with hard nucleophiles have provided an excellent method to form new C–C bonds.[40] Manipulation of the ligands on the metal and the reaction conditions has allowed control of the stereochemical and regiochemical outcome of these reactions and in some cases the absolute configuration of the newly formed sp^3 center. As a consequence, several research groups have explored this reaction and their work has been thoroughly reviewed (Eq. (22)).



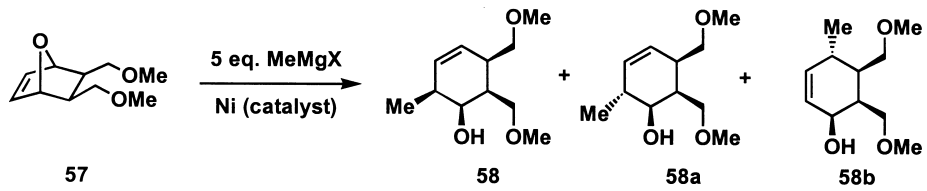
(22)

4.1. Substitution of allyl ethers, carbonates and amines

More recently, borates[41] have been used in place of commonly utilized alkali and alkaline earth organometallics to achieve coupling products with excellent chemo- and regio-control (Eq. (23)). It is worth noting that Pd catalysis gives a mixture of regiomeric products. By exploiting the unique reactivity and stereochemical properties of oxabicyclic compounds (e.g. **57**),[42] stereoselective addition of Grignard reagents to the C=C of these systems can be achieved, under Ni-catalysis, to give diversely functionalized six- and seven-member rings. Reaction of **57** with MeMgX in the presence of a catalytic amount of $Ni(COD)_2$ in THF gives preferentially the *syn* product **58** in 70% yield (Eq. (24)).



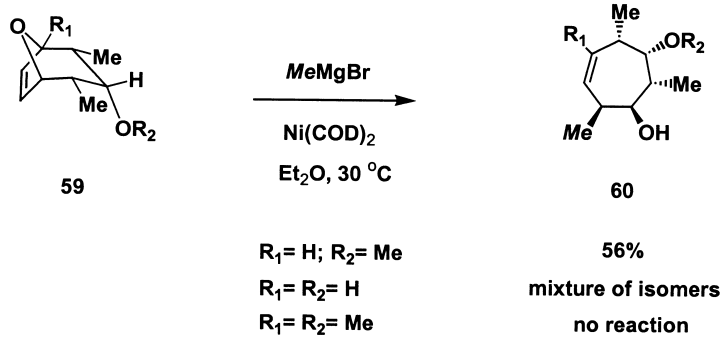
(23)



(24)

The choice of solvent had little impact on the product distribution with $Ni(COD)_2$, although the yield fell dramatically when Et_2O (48%) or Et_2O–HMPA (30%) were used instead of THF. Other catalyst precursors showed much greater solvent dependence. Thus, $(PPh_3)_2NiCl_2$ in THF gave **58** in 64% yield while the *anti* isomers **58a** and **58b** were obtained exclusively in Et_2O–HMPA in 95% yield.

The less strained [3.2.1] oxabicyclic compound **59** reacts with MeMgX to give modest yields of the seven-member ring **60**. This reaction (Eq. (25)) is more sensitive to the substituents (R_1 and R_2) and the reaction conditions than the reaction of the [2.2.1] counterpart.

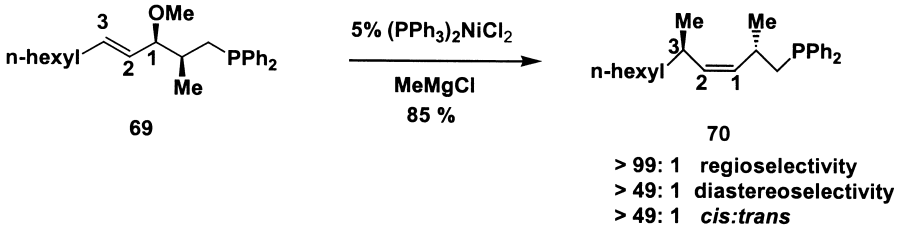


(25)

Reductive ring opening of diversely functionalized [2.2.1] and [3.2.1] oxabicyclic systems has also been achieved, using diisobutylaluminum hydride as the reducing agent. Moreover, the use of chiral nickel phosphine complexes can successfully induce de-symmetrization of *meso* compounds (Scheme 21).[43]

So reaction of **61** with Dibal in the presence of $Ni(COD)_2$ (7 mol%) and BINAP (14 mol%) in THF at room temperature gives the tertiary alcohol **62** in good yield and enantiomeric excess. This reaction is successful even in the presence of acid sensitive functionality especially when THF is used as the solvent (**63**⇔**64**). The reductive opening of larger sized ring (**67**⇔**68**) requires higher reaction temperature (80°C), toluene as the solvent, and slow addition of Dibal. Indeed when Dibal was added in one portion to a solution of **67** in toluene at ambient temperature, **68** was produced in only 20% yield and 56% ee.

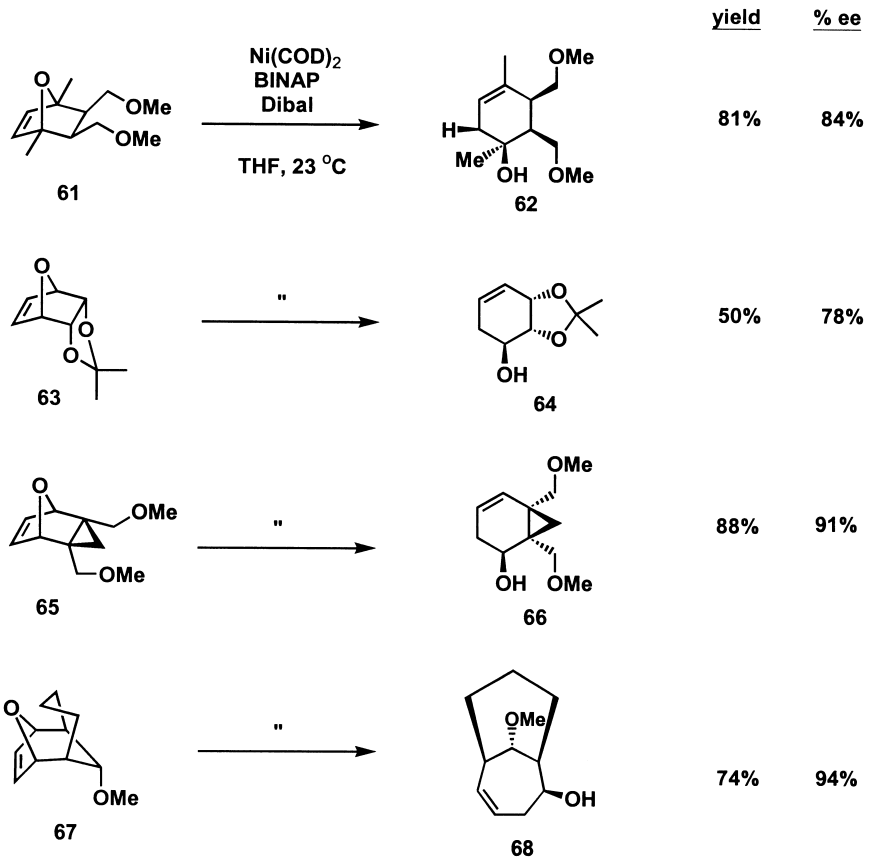
Linear allyl ethers can also undergo Ni-catalyzed allylic alkylation that exhibits excellent regio- and stereochemical control.[44] To achieve high levels of selectivity, a coordinating ligand must be part of the molecular framework at the appropriate distance to the reaction center (Eq. (26)).



(26)

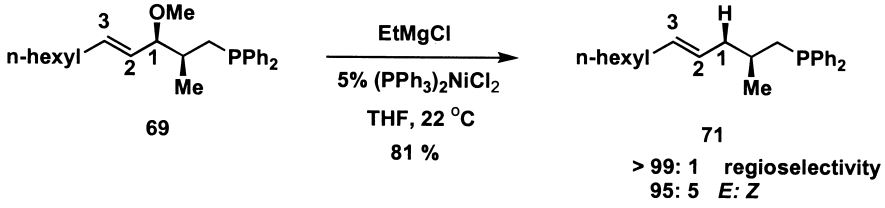
The allyl ether **69**, containing a distal PPh_2 tether, reacts with MeMgCl under $(PPh_3)_2NiCl_2$ catalysis to give high yields of the *cis* olefin **70**, where the new C–C bond has formed exclusively at the C-3 position of the allylic system.

Interestingly, the above selectivity changed dramatically when a hydride (generated from EtMgCl via β-hydride elimination) is delivered (Eq. (27)). The divergent outcome for the reactions in Eqs. (26) and (27) can be explained by postulating that **70** and **71** are formed from the η^3 complexes **72** and **73**, respectively. These two complexes are assumed to be the most favored

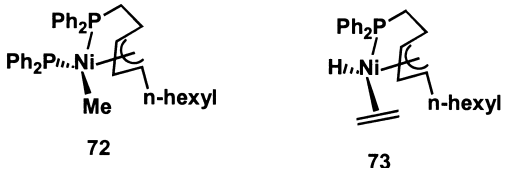


Scheme 21.

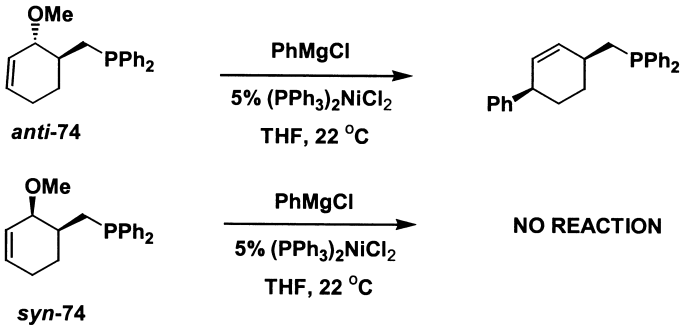
species formed in each case as non-bonded steric interactions are minimized.



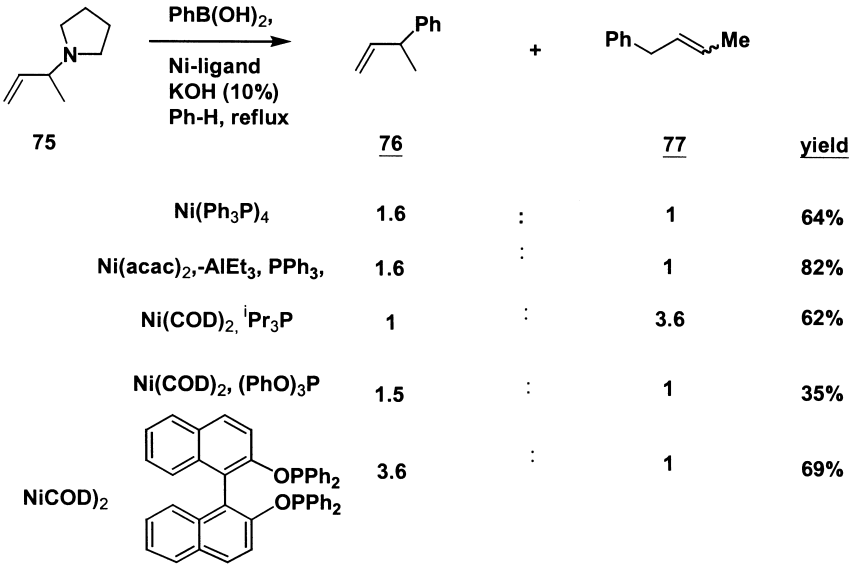
(27)



As expected, in cyclic systems the relative stereochemistry of the leaving group and phosphine tether determine the success of the reaction (Eq. (28)).



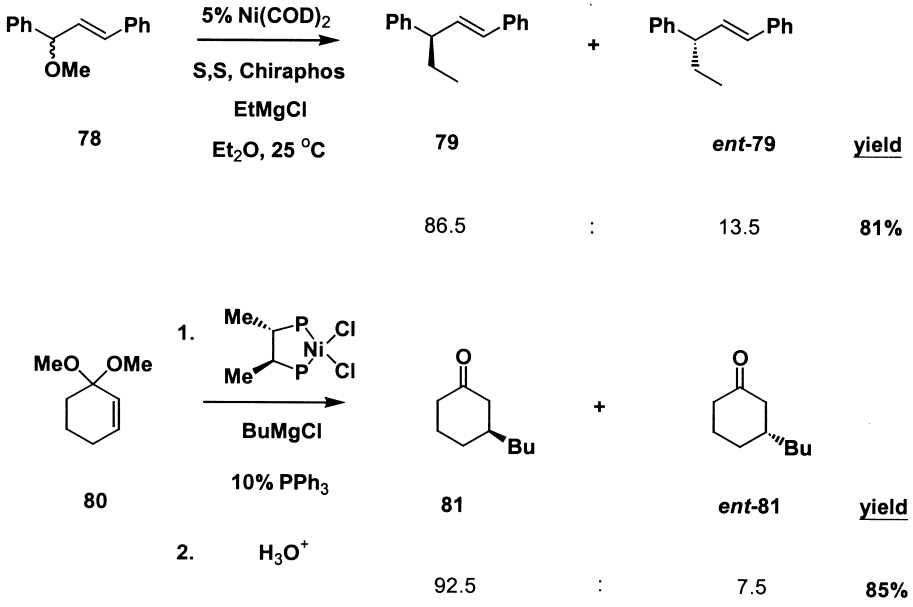
(28)



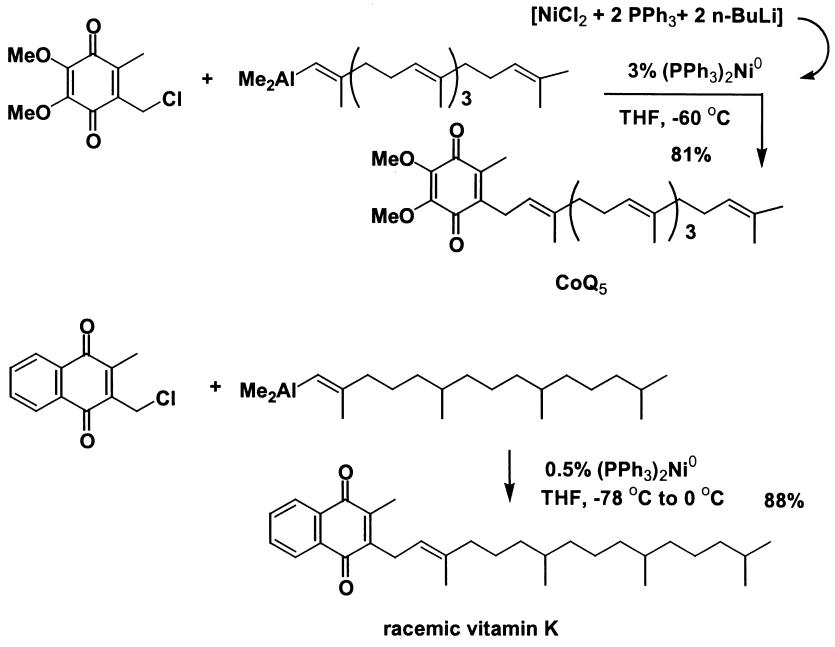
Scheme 22.

Yet another way to control the allylic alkylation reaction is the judicious choice of the leaving group and nucleophile. So the propensity of amines to coordinate boronic acids affords an excellent opportunity to effect selective C–C bond formation in the reaction of allylic amines and boronic acids under Ni catalysis.[45] As usual, the ligands, catalyst precursor, and additives have a profound effect on the selectivity. Hence, $Ni(PPh_3)_4$ catalyzes the reaction of allyl amine **75** and phenyl boronic acid (Scheme 22) in the presence of KOH (10 mol%) to give a mixture of the internal adduct **76** and the terminal addition product **77** (1.6:1, respectively). A significant shift in the selectivity can be achieved by changing the ligands and generating the catalyst in situ from $Ni(acac)_2$ and Et_3Al. Thus, *i*-Pr_3P favors formation of **77** while a bulky bidentate phoshinite ligand (BINAPO) induces preferential formation of **76**.

As mentioned before (Eq. (22)) the absolute stereochemistry of the alkylation has been controlled by the use of chiral ligands. Some more recent applications of this principle have been published (Scheme 23). In these examples, allyl ethers (**78**)[46] and allylic ketals (**80**)[47] afford, respectively, the optically enriched olefin **79** and conjugate addition product **81** when reacted with alkyl Grignards in the presence of a chiral Ni complex.



Scheme 23.



Scheme 24.

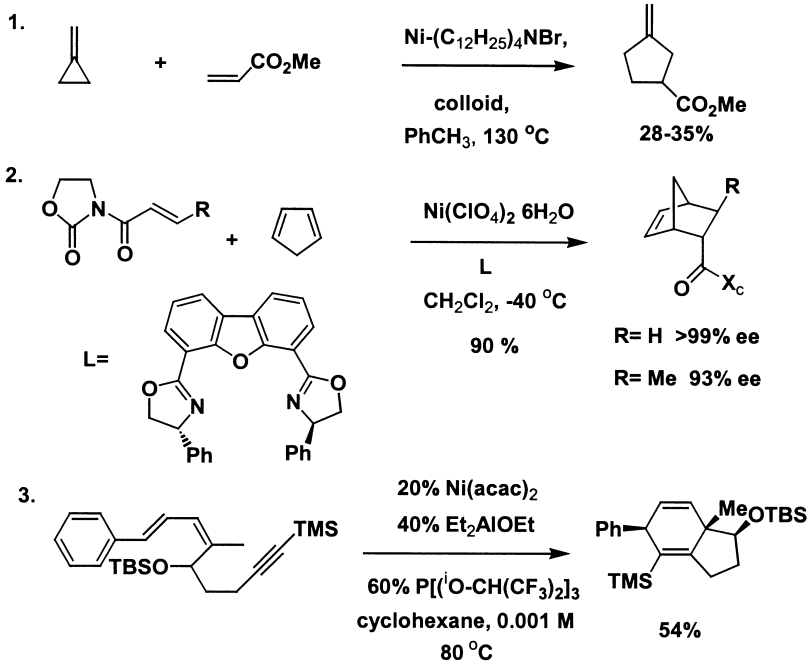
4.2. Substitution of allyl halides

The cross-coupling reaction of allylic halides with hard or soft organometallics in the presence of Ni or Pd catalysis is well known and extensively reviewed.

A more recent example[48] of Ni-catalyzed coupling of vinyl alanes with *p*-quinone chloromethyl derivatives is of particular importance since it provides general methodology for the synthesis of co-enzyme Q and vitamins K_1 and K_2 (Scheme 24). This work demonstrates an extremely mild and fast coupling, in which the reaction is usually done in minutes at low temperatures.

5. [*n*+*m*] Cycloadditions

Ni-catalyzed cycloaddition reactions have been used extensively to produce three- to seven-membered rings with remarkable



Scheme 25.

selectivity. The process has been used by several research groups to synthesize a large variety of carbocyclic and heterocyclic systems as well as a number of natural products. As a consequence this subject has been the topic of recent reviews and will not be reiterated here.[49]

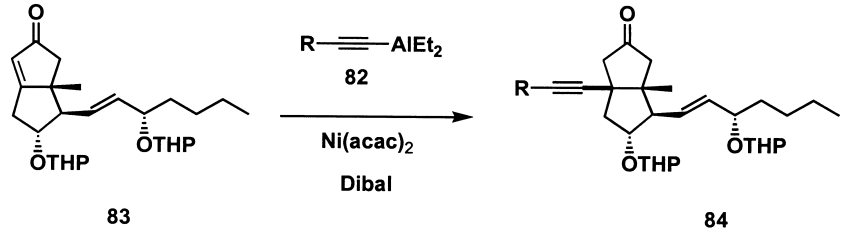
Some more recent papers in the field describe studies on: the nature of the catalysts involved in the cyclotrimerization of acetylenes to form substituted aromatics,[50] electrochemically generated Ni-clusters that catalyze 3+2 cycloaddition reactions (Scheme 25-1),[51] synthesis of aqua–Ni complexes that catalyze enantioselective Diels–Alder reactions (Scheme 25-2),[52] the discovery that *E*, *Z* dienes can be used to incorporate angular alkyl groups in the 4+2 cycloaddition with acetylenes (Scheme 25-3).[53]

6. Ni-Catalyzed Conjugate Addition Reactions

6.1. Alkyl organo-nickel additions to enones

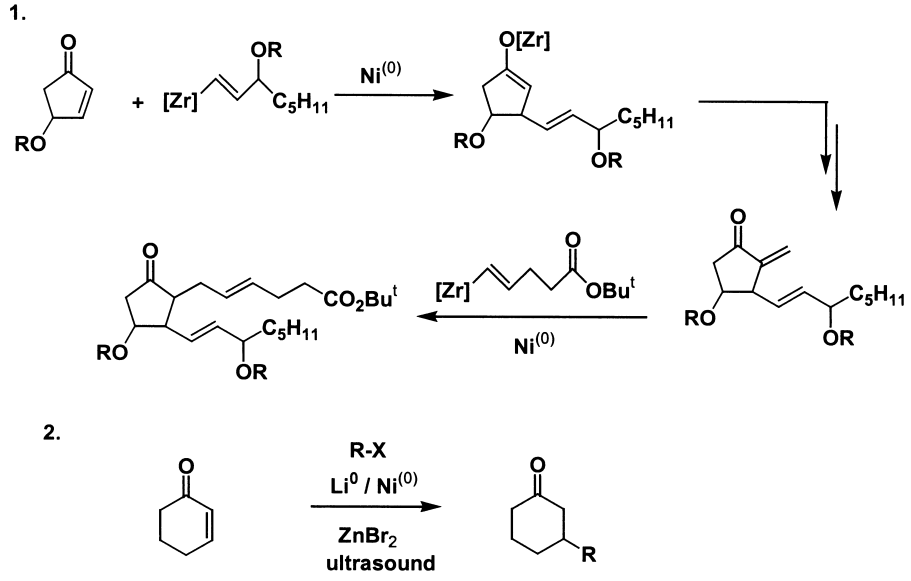
In the last 20 years, Ni-catalysis has been used successfully in the conjugate addition of unreactive organometallic reagents to α,β unsaturated carbonyl derivatives. These organometallics include alkyl, alkenyl and alkynyl aluminum and alkenyl zirconium compounds, pioneered by Schwartz (Scheme 26), as well as dialkyl or diaryl zinc reagents. The latter can be formed in situ under ultrasonic irradiation from the corresponding halides, Li metal and $ZnBr_2$, the Luche protocol. Several other examples have also been reported in the literature (Scheme 26).[54] These reactions have several advantages: (a) the less reactive organoaluminum, zirconium or zinc species are compatible with an array of functional groups; (b) these organometallic reagents need not be derived from metallation of a carbon–halogen bond or a deprotonation to form an enolate, but can be generated via hydro-zirconation, carboalumination, etc.; (c) Ni is used as catalyst avoiding the use of stoichiometric copper and its accompanying environmental problems; and (d) chiral ligand on the Ni can be used to effect an enantioselective conjugate addition.

One example of the application of the Schwartz protocol in total synthesis, involves the stereoselective addition of an alkynyl aluminum reagent **82** (derived from the Li-acetylide and $EtAlCl_2$) to **83** to give a good yield of the 1-4 adduct **84** (Eq. (29)).[55] It is noteworthy that cuprates would not allow the transfer of an acetylene function so this method nicely complements traditional copper-induced conjugate additions.

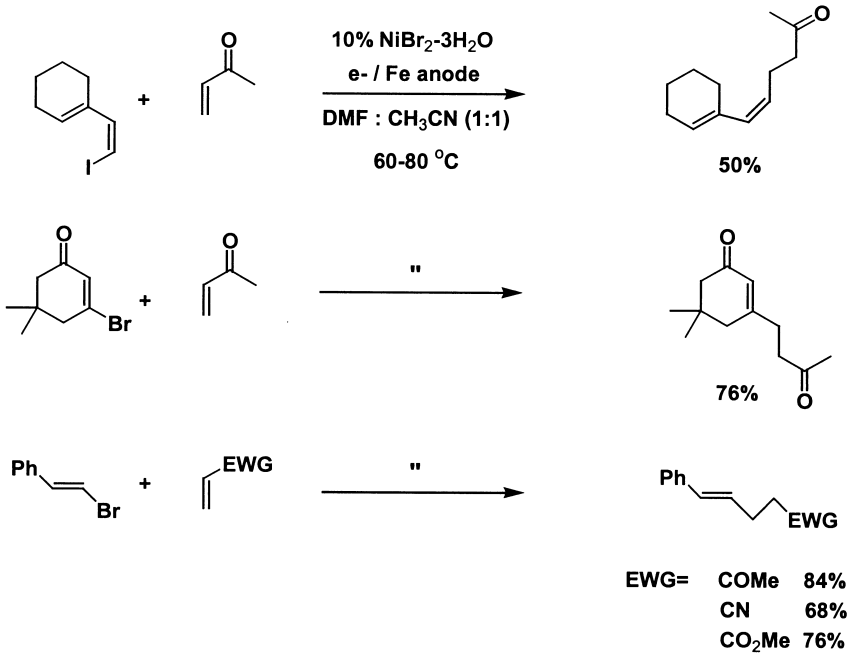


(29)

The Luche conditions have also proven useful in the preparation of **86**, an advanced intermediate towards the total synthesis of

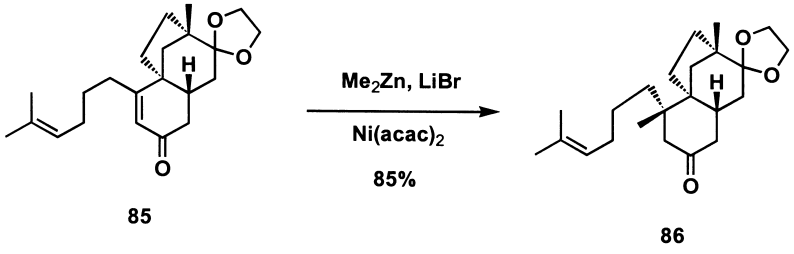


Scheme 26.



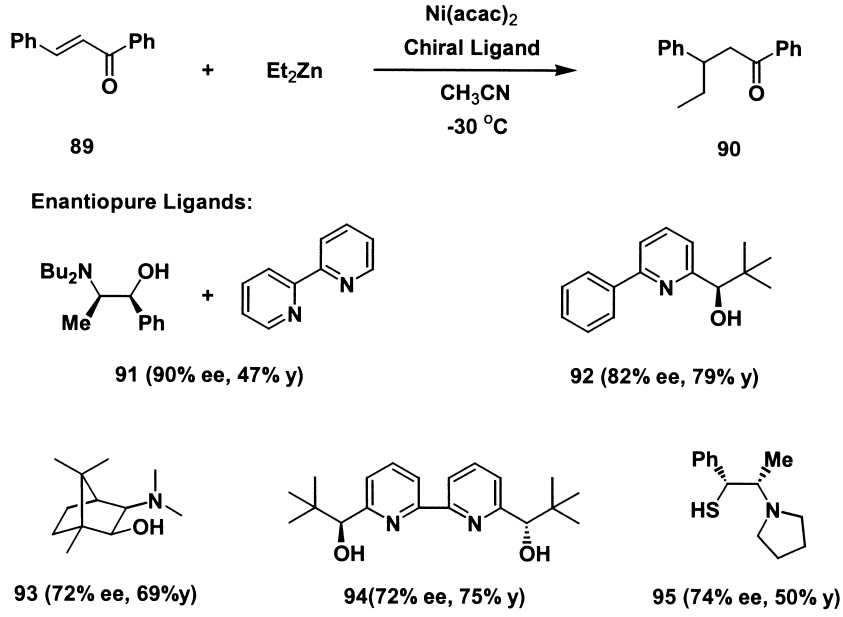
Scheme 27.

Scopadulic acids A and B (Eq. (30)).[56]

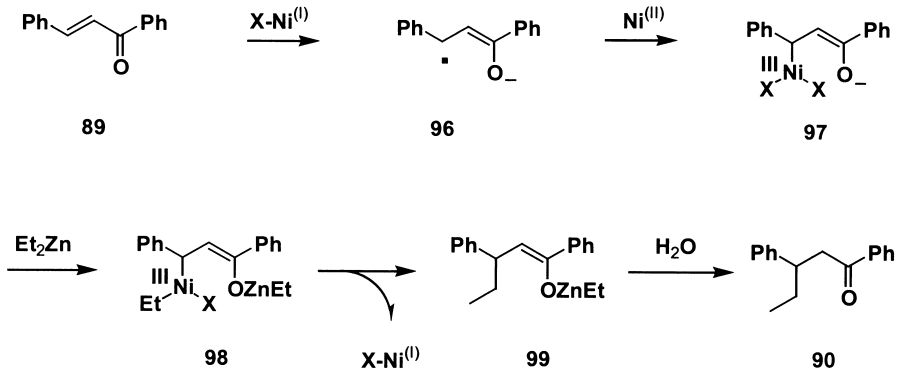


(30)

A Ni-Heck type procedure was employed to effect a remarkable double cyclization (Eq. (31)) in the synthesis of a key

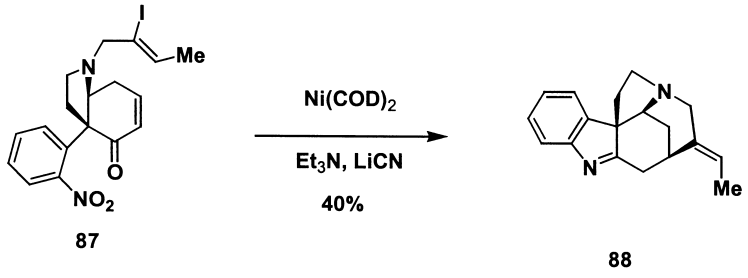


Scheme 28.



Scheme 29.

intermediate (**88**) in the synthesis of strychnos alkaloids akuammicine and norfluorocurarine.[57]

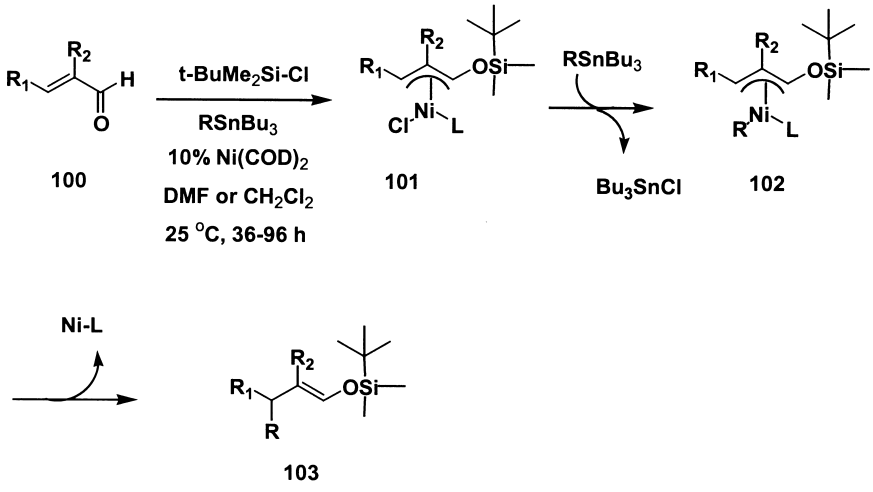


(31)

Electroreductive conjugate addition of *E*- or *Z*-alkenyl halides (I, Br as well as Cl) proceeds efficiently to give γ,δ unsaturated ketones, esters or nitriles in good yields while maintaining the stereochemistry of the C=C double bond (Scheme 27).

Considerable research effort has been devoted to the enantioselective addition of dialkylzinc reagent to chalcone using chirally modified Ni catalysts (Scheme 28).[59] A typical procedure involves heating $Ni(acac)_2$ and the aminoalcohol ligand in CH_3CN to preform the active catalyst followed by addition of chalcone (**89**) and Et_2Zn at low temperature to give the product **90** in good yield and enantiomeric excess. The reaction proceeds best in CH_3CN while other solvents (DMF, THF, toluene) gave substantially lower ee's. The ligand to Ni ratio also proved critical as did the addition of chiral additives such as bipyridine.

Mechanistically, these reactions are presumed to involve a Ni^{I} active species, generated from reduction of Ni^{II} by the organometallic reagent (Scheme 29).[58] Reaction with **89** gives the radical anion **96** or perhaps directly the Ni^{III} species **97**. Reaction with Et_2Zn gives the dialkyl Ni^{III} compound **98** which after reductive elimination regenerates the active catalyst and the product **90**.



Scheme 30.

Table 3.

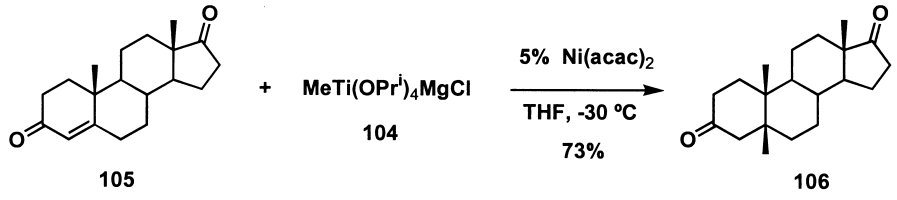
Entry	R	R_1	R_2	Time (h)	*E*:*Z*	Yield (%)
A	CH_2=CH	H	H	44	>19:1	75
B	CH_2=CH	Me	Me	71	>19:1	56
C	PhCH=CH	*n*-Pr	H	66	ca. 20:1	48
D	$CH_3C(O)$	H	Me	36	6:1	52
E	$CH_3C(O)$	Me	H	48	5:1	50

As mentioned above the Ni-catalyzed version of these additions work at low temperature (ca. −30°C, 12 h), however the uncatalyzed reaction also proceeds to completion albeit at a much lower rate.

A different mechanistic paradigm is used to explain the conjugate addition of alkenylstannane to α,β unsaturated aldehydes (**100a**–**e**). Initial formation of the Ni^{II} π-allyl complex **101** is facilitated by *t*-$BuMe_2SiCl$, followed by transmetallation to give **102** and reductive elimination to the adduct **103** (Scheme 30 and Table 3).[60]

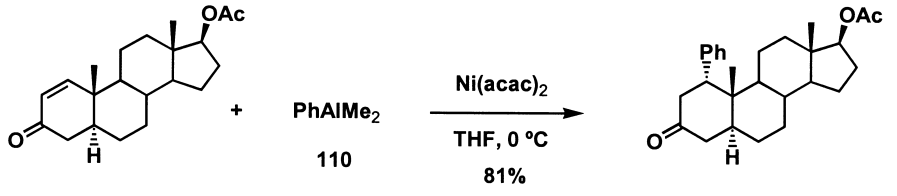
6.2. Ni-catalyzed additions to enones by -ate complexes

Recently, Ni-catalyzed additions with metal-ate complexes have allowed C–C bond formation of less activated or hindered conjugated systems. Titanate complex **104**, derived from MeMgCl and $Ti(OPr^i)_4$ (Eq. (32))[61] adds readily to the sterically hindered ketone **105** with high chemoselectivity even in the presence of a second ketone functionality. A similar yield of **106** was obtained when **104** was replaced with Me_3Al, however, *ethyl acetate had to be used instead of THF*.



(32)

Aluminate, titanate and aluminum reagents also react with dienones (e.g. **107**)[62] to give mixtures of **108** and **109**. The product ratio depends substantially on the counterion of the -ate complex (Table 4, entries 1–5) and the catalyst (Ni vs. Cu) used. Indeed Ni and Cu show useful complementarity in this reaction (Scheme 31) (compare entries 1 and 6 in Table 4).



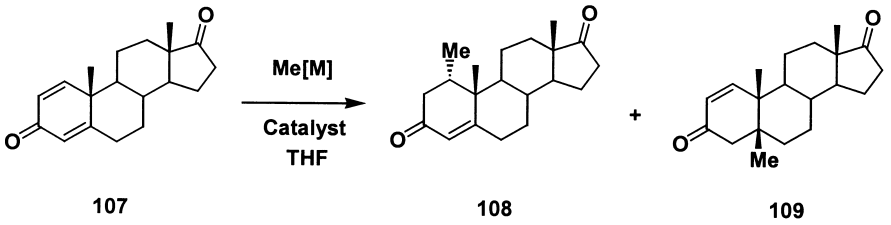
(33)

A limitation of the titanate complex is its inability to effect the addition of aryl derivatives. This problem was elegantly solved by using the mixed aluminum reagent **110** (Eq. (33)).[63]

The use of zincate reagents[64] under Ni catalysis promotes the addition of alkyl and aryl groups to less activated conjugated systems. Addition of zincate reagents to the vinyl sulfoxide **111**, occurs smoothly under $Ni(acac)_2$ catalysis at −25°C (Eq. (34) and Table 5) to afford the adduct **112** in high yield and diastereoselectivity. After desulfurization, the medicinally important triaryl ethyl derivatives **113** are produced in good yield and optical purity. Both alkyl and aryl groups add efficiently across the double bond, but vinyl and acetylene zincates fail to effect the desired transformation. However, it is not clear at present, if the latter zincates were indeed formed under the conditions used to form their alkyl or aryl counterparts. Only $Ni(acac)_2$ or Ni^{II} carboxylate complexes are useful catalysts for this reaction and addition of phosphine, or pyridine ligands inhibits the catalyst. The selectivity of this reaction depends largely on the electronics of the aryl group of **111** (entries 4 and 6, Table 5) as well as

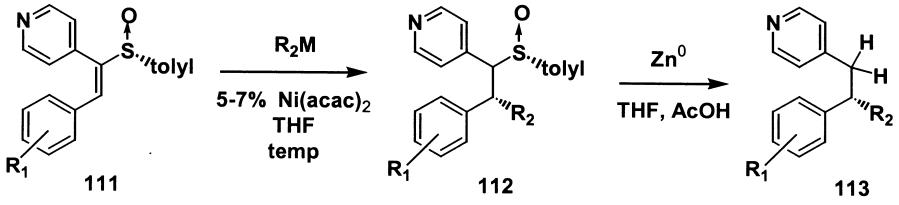
Table 4.

Entry	Me[M]	Catalyst	Ratio **108**:**109**	Yield (%)
1	Me_4AlLi	$Ni(acac)_2$	38:62	90
2	$Me_3Al(OAr)MgBr$	”	33:67	89
3	$Me_3Al(OAr)Li$	”	15:85	90
4	$MeTi(OPr^i)_4MgCl$	”	34:66	85
5	$MeTi(OPr^i)_4Li$	”	11:89	87
6	Me_4AlLi	CuCN	92:8	73



Scheme 31.

the counter ion of the zincate (Entries 1 and 2, Table 5). Interestingly, the reaction rate does not substantially change in any of the reactions in Table 5.



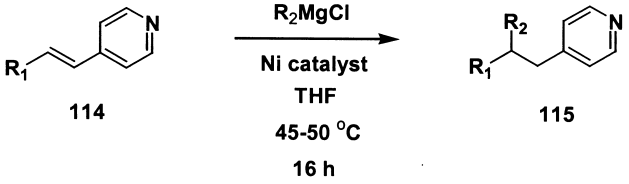
(34)

Table 5.

Entry	Organometallic	R_1[a]	R_2	Temp (°C)	Yield (%)	% ee
1	Ph_3ZnLi	*p*-OMe; *m*-OCp	Ph	−25	>90	82
2	$Ph_3ZnMgBr$	*p*-OMe; *m*-OCp	Ph	−25	>90	92
3	$Et_3ZnMgCl$	*p*-OMe; *m*-OCp	Et	−25	60	88
4	$Ph_3ZnMgCl$	CF_3	Ph	−25	62	71
5	$Ph_3ZnMgCl$	Cl	Ph	−25	80	89
6	$Et_3ZnMgCl$	Cl	Et	−25	75	64
7	Bu_3ZnLi	*p*-OMe; *m*-OCp	Bu	−25	87	75–80
8	Me_3ZnLi	*p*-OMe; *m*-OCp	Me	23	80	65

[a] Cp=cyclopentyl.

Even a less activated olefin such as vinyl pyridine **114** undergoes conjugate-type addition reactions; however in this case more drastic reaction conditions are needed (Eq. (35) and Table 6).[65] So **114a**–**e** react with a variety of aryl, vinyl and alkyl Grignard reagents at 45–50°C in the presence of a Ni catalyst to give adducts **115a**–**h** in good yield. In this case alkyl Grignards with β-hydrogens only give the C=C reduction product corresponding to **114**, due to competing β-hydride elimination.



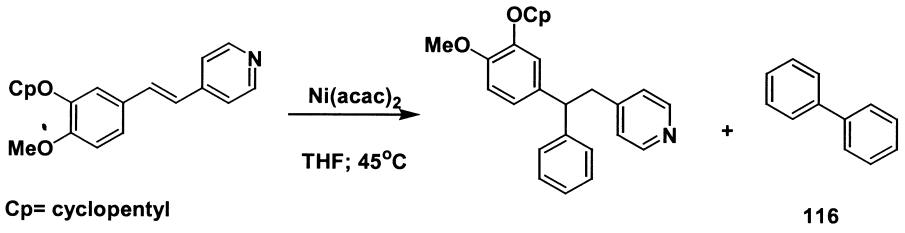
(35)

Table 6.

Entry	R_1	R_2	Product	Catalyst	Yield (%)
1	*p*-MeO-, *m*-CpO-Ph **114a**	Ph	**115a**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	93
2	*p*-MeO-, *m*-CpO-Ph **114a**	Ph	**115a**	$Ni(acac)_2$	95
3	Cyclopropyl **114b**	Ph	**115b**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	95
4	*p*-MeO-Ph **114c**	Ph	**115c**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	90
5	*p*-MeO-, *m*-CpO-Ph **114a**		**115d**	$Cl_2Ni(PPh_3)_2$	53
6	Naphthyl **114d**	Ph	**115e**	$Cl_2Ni(PPh_3)_2$	82
7	Propyl **114e**	Ph	**115f**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	74
8	*p*-MeO-, *m*-CpO-Ph **114a**	*o*-Ph-$N(SiMe_3)_2$	**115g**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	79
9	*p*-MeO-Ph **114c**	$PhCH_2$	**115h**	$Cl_2Ni[Ph_2P(CH_2)_3PPh_2]$	70

Functionalized triaryl zincates can also be used in this reaction (Eq. (36)). However, the formation of biaryl (e.g. **116** in Eq. (36)) can be a disadvantage if expensive aryl groups must be transferred. The problem was solved by using the mixed zincate reagent $PhZnMe_2MgCl$. As in the case of $PhAlMe_2$ (Eq. (36)) only the phenyl group is transferred and the formation of

biphenyl is minimized.



(36)

2 eq $Ph_3ZnMgCl$	93%	50%
2 eq Ph_3ZnLi	67%	50%
1.2 eq $PhZnMe_2MgCl$	65%	3%

7. Conclusion

As shown in the discussion above, Ni-catalyzed addition to olefins and acetylenes provide a mild method for formation of carbon–carbon bonds with high stereo- and chemoselectivity. In the cases where new chiral centers are generated, enantiomerically pure chiral ligands on the metal allow good control of absolute stereochemistry at the newly formed center. Interestingly, synthesis of complex and diversely functionalized compounds can also be accomplished with Ni-catalysis.

Even though the use of organonickel catalyst in synthesis is still in its early stages compared to the widespread utility of Pd-catalysts, we are confident that future work from various research groups will greatly expand the use of this chemistry.

Acknowledgements

We would like to thank Dr Mark Huffman and Professors Eric Jacobsen and Bruce Lipshutz for their editorial comments. Special thanks to Judith Baron for her expert assistance in the preparation of this document.

References

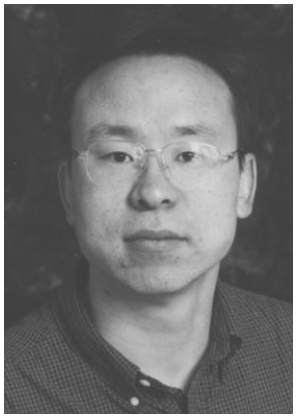
1. (a) Jolly, P. W.; Willie, G. *The Organic Chemistry of Nickel;* Academic Press: New York, 1974; Vols. I and II, p 1975. (b) Jolly, P. W. In *Comprehensive Organometallic Chemistry;* Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, p 613.
2. (a) Hegedus, L. S.; *J. Organomet. Chem. Library* **1976**, *96*, 3250. (b) Corey, E. J., Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2735. (c) Semmelhack, M. F. *Org. React.* **1972**, *19*, 115. (d) Billington, D. C. *Chem. Soc. Rev.* **1985**, *14*, 93. (e) Baker, R. *Chem. Rev.* **1973**, *73*, 487.
3. (a) Knight, D. W. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds. (Pattenden, G., Vol. Ed.); Pergamon: Oxford, 1991; Vol. 3, p 481. (b) Klunder, J. M.; Posner, G. H. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds. (Pattenden, G., Vol. Ed.); Pergamon: Oxford, 1991; Vol. 3, p 207.
4. For excellent earlier comprehensive reviews see Ref 6 and Hayashi, T. In *Catalytic Asymmetric Synthesis;* Ojima, I., Ed.; VCH: Hamburg, 1993; p 325.
5. Knochel, P. In *Comprehensive Organic Synthesis*, Trost, B. M. Ed.; Pergamon: New York, 1990; Vol. 4, p 865.
6. Tamao, K.; Kumada, M. In *The Chemistry of the Metal*, Hartley, F. R. Ed.; , 1987; Vol. 4, p 819.
7. (a) Snider, B. B.; Conn, R. S. E.; Karras, M. *Tetrahedron Lett.* **1979**, 1679. (b) Conn, R. S. E.; Karras, M.; Snider, B. B. *Israel J. Chem*., **1984**, *24*, 108. (c) for Cu and Pd catalysis: Wakamatsu, K.; Nonaka, T.; Okuda, Y.; Tueckmantel, W.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1986**, *42*, 4427.
8. Stuedemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299.
9. See Ref. 7 and Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978** *100* 4624.
10. (a) Knochel, P. *Synlett* **1995**, 393. (b) Also see Ref. 5, p 879. (c) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117.
11. Sato, Y.; Ikeda, S. *J. Am. Chem. Soc.* **1994**, *116*, 5975.
12. Cui, D.-M.; Tsuzuki, T.; Miyake, K.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, *54*, 1063.
13. (a) Montgomery, J.; Sauchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. (b) Sauchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562. (c) Montgomery, J.; Oblinger, E. *J. Org. Chem.* **1997**, *119*, 9065. (d) Chevliakov, M. V.; Montgomery, J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3144.
14. Montgomery, J.; Seo, J. *Tetrahedron* **1998**, *54*, 1131.
15. Montgomery, J.; Oblinger, E.; Sauchenko, A. *J. Am. Chem. Soc.* **1997**, *119*, 4911.
16. See Ref. 13d for use of α,β-unsaturated oxazolidinone derivatives instead of esters for this reaction.
17. Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839.
18. Seo, J.; Chui, J. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.
19. Stadtmueller, H.; Vaupel, A.; Tucker, C. E.; Stuedeman, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204.

20. (a) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 8349. (b) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231. (c) Stadtmueller, H.; Knochel, P. *Synlett* **1995**, 463. (d) Devasagayaraj, A.; Stuedeman, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723. (e) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743. (f) Stuedeman, T.; Gupta, V.; Engman, L.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 1005.
21. See Ref. 20d.
22. Stuedeman, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.
23. Stuedeman, T.; Ibrahim-Ouali, M.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 143.
24. Other methods for generating zinc reagents with or without Ni catalysis involve hydrozincation and B-Zn exchange reactions, see (a) Vettel, S.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 1023. (b) Klement, I.; Luetjens, H.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 3161. (c) Devasagayaraj, A.; Schwink, L.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 3311. (d) VeHel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473. (e) Oxidation of these Alkyl Zn reagents, Klement, I.; Knochel, P. *Synlett* **1995**, 1113.
25. (a) Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755. Other methods are: (b) Cancho, Y.; Martin, J. M.; Martinez, M.; Llebaria, A.; Moreto, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221. (c) Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895. (d) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, 1803. (e) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, 1807. (f) Mori, M.; Kudo, S.; Ban, Y. *J. Chem. Soc., Perkin Trans. 1* **1979** 771.
26. (a) Chen, Q.-Y.; Yang, Z.-Y. *J. Chem. Soc., Chem. Commun.* **1986**, 498. (b) von Werner, K. J., *Fluorine Chem.* **1985**, *28*, 229.
27. Jou, D.-C.; Hsiao, T.-Y.; Wu, M.-Y.; Kong, K.-C.; Cheng, C.-H. *Tetrahedron* **1998**, *54*, 1041.
28. Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029.
29. (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 1996. (c) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron Lett.* **1997**, *38*, 3931. (d) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (e) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *Tetrahedron Lett.* **1998**, *39* 5579. (f) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. (g) A Ni–H double bond migration of allylic ethers to enol ethers has been described, Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305.
30. Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033.
31. (a) Mori, M.; Hashimoto, Y.; Ban, Y. *Tetrahedron Lett.* **1980**, 631. (b) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677. (c) Gosmini, C.; Lasry, S.; Nedelec, J.-Y.; Perichon, J. *Tetrahedron* **1998**, *54*, 1280.
32. (a) Jackson, W. R.; Lovel, C. G. *Aust. J. Chem.* **1983**, *36*, 1975. (b) Jackson, W. R.; Lovel, C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1231.
33. Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539.
34. Keim, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 235.
35. (a) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (b) Baeckvall, J. E.; Andell, O. S. *Organometallics* **1986**, *5*, 2350.
36. (a) Rajan Babu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265. (b) Rajan Babu, T. V.; Casalnuovo, A. L. *Pure Appl. Chem.* **1994**, *66*, 1535.
37. Casalnuovo, A. L.; Rajan Babu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869.
38. Rajan Babu, T. V.; Caslnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325.
39. (a) Nomura, N.; Jin, J.; Park, H.; Rajan Babu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459. (b) Radetich, B.; Rajan Babu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007.
40. Ref. 6 and general allylic alkylation reviews, see: Godleski, S. A. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 585. For Ni catalyzed amination of allylic alcohols see: Bricout, H.; Carpentier, J. -F.; Mortreux, A. *Tetrahedron* **1998**, *54*, 1073.
41. Kobayashi, Y.; Mizojiri, R.; Ikeda, E. *Synlett* **1995**, 571.
42. Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246 (and references therein).
43. (a) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246. (b) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11 090. (c) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107.
44. (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 3613. (b) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1998**, *54*, 1117.
45. Trost, B. M.; Spagnal, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083.
46. Nomura, N.; Rajan Babu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713.
47. Gomez-Benjoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649.
48. (a) Lipshutz, B. H.; Kim, S.-K.; Mollard, P.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 1241. (b) Lipshutz, B. H.; Bulow, G.; Loew, R. F.; Stevens, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 5512.
49. Reviews: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*,
49. Papers: (a) Ikeda, S.-I.; Mori, M.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Pecosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908. (c) Lautens, M.; Edwards, L. G.; Tam, W.; Laugh, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10 276. (d) Sato, Y.; Nishimata, T.; Mori, M. *Hetrocycles* **1997**, *44*, 443. (e) Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133. (f) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231. (g) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268. (h) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824. (i) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. (j) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. (k) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (l) Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. (m) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (n) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (o) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771.
50. Eisch, J. J.; Aradi, A. A.; Lucarelli, M. A.; Qian, Y. *Tetrahedron* **1998**, *54*, 1169.
51. Reetz, M. T.; Breinbauer, R.; Wedemann, P.; Binger, P. *Tetrahedron* **1998**, *54*, 1233.

52. Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S. I.; Yamamoto, H.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 3074.
53. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255.
54. For reviews see Ref. 6, p 873. Also see (a) Tueckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (b) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 5761. (c) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931. (d) Petrier, C.; Luche, J.-L., Dupuy, C. *Tetrahedron Lett.* **1984**, *25*, 3463. (e) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466. (f) Schwartz, J.; Loots, J. M.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. (g) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3796. (h) Schwartz, J.; Carr. D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (i) Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 821. (j) Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 817. More recent examples include: Ikeda, S.-i., Cui, D.-M., Sata, Y. *J. Am. Chem. Soc.* **1992**, *121*, 4712; Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675.
55. Aristoff, P. A.; Johson, P. D.; Harrison, A. W. *J. Org. Chem.* **1983**, *48*, 5341.
56. Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.
57. Solé, D.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 4194.
58. Condon-Gueugnot, S.; Dupré, D.; Nédélec, J.-Y.; Périchon, J. *Synthesis* **1997**, 1457.
59. (a) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. (b) Boln, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011. (c) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95. (d) Boln, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205. (e) Jansen, J. F. G. A.; Feringa, b. L. *Tetrahedron: Asymmetry* **1992**, *3*, 581. (f) deVries, A. J. M.; Janse, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479. (g) Kang, J.; Kim, J.; Lee, J. H.; Kim, H. J.; Byun, Y. H. *Bull. Korean Chem. Soc.* **1998**, *19*, 601.
60. Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.
61. Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron Lett.* **1994**, *35*, 6075.
62. Westermann, J.; Neh, H.; Nickisch, K. *Chem. Ber.* **1996**, *129*, 963.
63. Westermann, J.; Imbery, U.; Nguyen, A. T.; Nickisch, K.; Eur *J. Inorg. Chem.* **1998**, 295.
64. Houpis, I. N.; Molina, A.; Dorziotis, I.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 7131.
65. Houpis, I. N.; Lee, J.; Dorziotis, I.; Molina, A.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1998**, *54*, 1185.

Biographical Sketch

Ioannis Houpis was born in Athens, Greece. He received his B.S. degree from Washington State University (1985) working under Prof. Manning P. Cooke Jr. He then moved to Harvard University where he obtained his Ph.D. (1990), working under the direction of Prof. E. J. Corey, by completing the synthesis of Glycinoeclepin A. In 1990 he moved to the Process Research department at Merck & Co. where he currently is a Senior Research Fellow.



Jaemoon Lee was born in Kyungpook, Korea. He received his B.S. degree from Kyungpook National University (1981) and his M.S. degree from Seoul National University (1983) working with Prof. Kyongtae Kim. After a year of research at Korea Advanced Institute of Science and Technology, he came to the United States and studied under the direction of Prof. Alan P. Kozikowski at the University of Pittsburgh where he obtained his Ph.D in 1990. He then undertook a research position with Prof. E. J. Corey at Harvard University as a Postdoctoral Research Fellow (1990–1993) and Research Associate (1993–1994). Currently, he is working at the Process Research Department in Merck & Co. where he is responsible for design and development of chemical processes for the synthesis of pharmaceutical candidates.