

Transition Metal-Catalyzed Activation of Aliphatic C–X Bonds in Carbon–Carbon Bond Formation

Tien-Yau Luh,* Man-kit Leung, and Ken-Tsung Wong

Department of Chemistry, National Taiwan University, Taipei, Taiwan 106

Received December 9, 1999

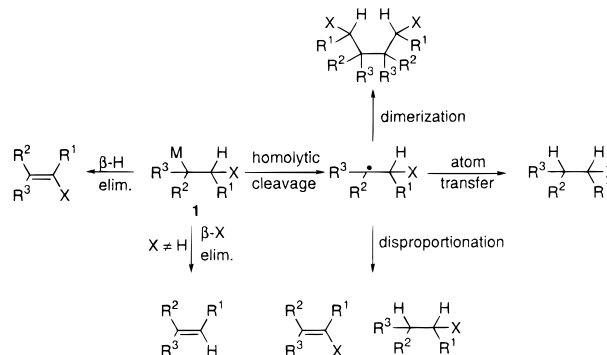
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I. Introduction

The activation of a C–X bond with a transition metal leading to the C–C bond formation has furnished an enormous variety of fascinating transformations in organic synthesis.^{1–6} The vast majority of the reactions, however, requires substrates having sp or sp² carbons at or immediately adjacent to an electrophilic center. In the absence of a strong activating group, the leaving group attached to an sp² carbon atom cannot be readily displaced by a

Scheme 1



nucleophile without the assistance of a transition metal catalyst. Remarkable selectivity has been observed in the transition metal-catalyzed reactions of allylic, propargylic, and benzylic substrates. Methyl iodide has been widely used as a precursor, leading to C–C bond formation in a number of industrially important homogeneous catalytic processes.^{4–6} However, the corresponding reactions with higher homologous aliphatic substrates have received more attention recently. Relatively speaking, the reactivity of the aliphatic C–X bond toward the oxidative addition with a transition metal is somewhat low.⁷ This argument is particularly true when the oxidative addition occurs via an initial S_N2 mechanism. Indeed, the order of the reactivity of alkyl halides and tosylates with the Collman reagent is consistent with such mechanism.⁸

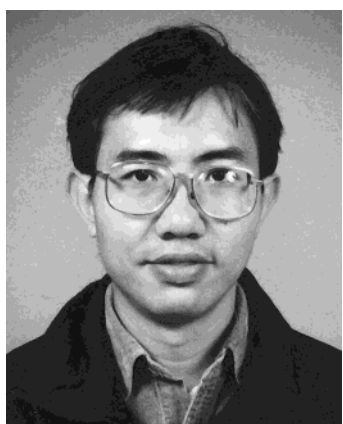
σ -Alkyl organometallic species **1** is the key intermediate in the coupling or insertion reaction leading to C–C bond formation. However, side reactions may readily occur from this σ -alkyl complex **1** (Scheme 1).^{4–6} β -Hydride or heteroatom elimination from a σ -alkyl organometallic complex are two of the most commonly observed side reactions. Alternatively, homolytic cleavage of the carbon–metal bond may take place, and the radical intermediate thus formed can undergo an atom-transfer process, dimerization, or disproportionation. It is important to note that certain alkylmetal intermediates formed by other means are known to undergo insertion reaction with an olefin moiety or CO or proceed to coupling with a nucleophile leading to C–C bond formation.^{1–4} In other words, as long as the rate of the desired reaction of such an alkyl organometallic intermediate



Tien-Yau Luh obtained his Ph.D. degree from the University of Chicago (L. M. Stock) in 1974 and did his postdoctoral research with P. G. Gassman at the University of Minnesota. He started his academic career at the Chinese University of Hong Kong in 1976 and moved back in 1988 to his alma mater, National Taiwan University, where he is Professor of Chemistry. He received numerous awards in Taiwan including a recent National Chair Award. His research interests include new synthetic methodology and chemistry of materials. He is also the Chairman for the IUPAC 11th International Symposium on Organometallic Chemistry Directed toward Organic Synthesis (OMCOS-11) to be held in Taipei in 2001.



Ken-Tsung Wong was born in 1966. In 1989 he received a B.Sc. Degree from Fu-Jen Catholic University and a Ph.D. degree from National Taiwan University in 1993. After spending one year at the University of Illinois at Urbana—Champaign and two years at the Université Louis Pasteur as a postdoctoral associate, he joined the National Taiwan University as an Assistant Professor of Chemistry from 1998. He is a recipient of the TR100 sponsored by the Technology Review of MIT. His research interests include the development of new synthetic methods using organometallic reagents, asymmetric synthesis, and synthesis of conjugated oligomers for optoelectronic materials.



Man-kit Leung was born in Hong Kong in 1961. After finishing his B.Sc. and M.Sc. from the Chinese University of Hong Kong, he joined Professor W. S. Trahanovsky's research group to work on the dimerization mechanisms of orthoquinodimethanes and received his Ph.D. from Iowa State University in 1991. He spent two years as a postdoctoral associate with Professor J. M. J. Fréchet at Cornell University. In 1993, he joined the Chinese University of Hong Kong as the Lecturer in Chemistry and initiated a research program on biphenylene-based materials. In 1994, he moved to the National Taiwan University where he is now Professor of Chemistry. His current interests are optoelectronic materials, organopalladium chemistry, and supramolecular chemistry.

is faster than those of the sequential side reactions mentioned in Scheme 1, the use of the transition metal-catalyzed activation of aliphatic C–X bonds in organic synthesis will be feasible. Various conditions have been developed to enhance the reactivity of the aliphatic C–X bonds and/or to stabilize the organometallic intermediate so that the desired coupling or other related reactions can be achieved. The purpose of this review is to summarize the recent progress on the use of transition metal catalysts for the activation of aliphatic C–X bonds (other than methyl) in organic synthesis. Reactions involving activated C–X bonds such as benzylic, allylic, propargylic, and related substrates will not be included in this review.

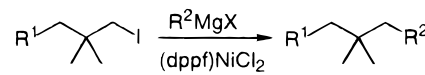
II. Reactions Involving Simple Aliphatic Substrates

A. Cross-Coupling Reactions

Transition metal-catalyzed cross-coupling reactions between R–X and an organometallic nucleophile leading to C–C bond formation has been shown to be particularly useful in organic synthesis.^{1–6} This kind of transformation involves a series of fundamental processes at the transition metal center. Each of these steps (e.g. oxidative addition, transmetalation, association of the nucleophile, reductive elimination, etc.) demonstrates a compromise of the relative reactivity of the organometallic intermediates which lead eventually to the corresponding cross-coupling products.

In general, most of the cross-coupling reactions require a good leaving group which is directly attached at or immediately adjacent to a carbon atom with sp^2 (allylic or benzylic) or sp (propargylic) hybridization. Presumably, coordination at these unsaturated centers may facilitate the cleavage of the corresponding C–X bond. Also, either the conjugative stabilization of the π -allyl or π -propargylic organometallic products or the interaction of the π -electrons of the σ -vinylic or alkynyl ligands with d-orbitals of the metal may account for the facile formation of these organometallic complexes.

As to the unstabilized σ -alkyl complexes, due to their kinetic instability, formation of side products as shown in Scheme 1 occasionally becomes the major impediment in the cross-coupling reactions of such aliphatic substrates. Several approaches have been employed to solve this problem. A change of the nucleophilicity at the metal center by modification of the ligands will facilitate the first oxidative addition step across the C–X bond. Variation of electronic or steric features at the catalytic center will minimize

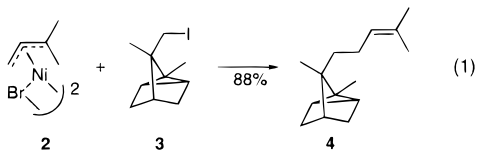
Table 1. (dppf)NiCl₂-Catalyzed Reaction of Neopentyl Iodides with Grignard Reagents^a


R ¹	R ²	X	conditions ^b	% yield
Ph	Me	Cl	A	77
		Cl	B	93
		Br	B	92
	Ph(CH ₂) ₃	Br	A	57
		Et	Br	A
	Ph	Br	A	71
		Cl	B	90
	2-MeC ₆ H ₄	Br	A	71
		Cl	B	83
	4-F ₃ CC ₆ H ₄	Br	B	86
		4-MeOC ₆ H ₄	Br	A
	2,4-(MeO) ₂ C ₆ H ₄	Br	B	80
2-thienyl		Br	A	59
1-naphthyl	Br	A	57	
	Br	B	88	
H	Ph	Br	A	86
		Br	B	72
	2-MeC ₆ H ₄	Cl	B	73
	4-F ₃ CC ₆ H ₄	Br	A	80
	4-MeOC ₆ H ₄	Br	B	84

^a References 11–14. ^b A: no ZnCl₂ added. B: 1.5 eq ZnCl₂ added.

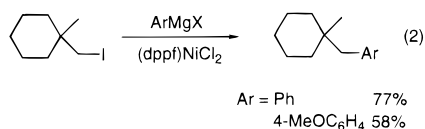
β -hydride elimination and favor reductive elimination, yielding the corresponding cross-coupling products.

The reaction of the π -allyl organonickel **2** with an aliphatic iodide **3** leading to **4** was first reported in 1967 (eq 1).⁹ Although the mechanism of the reaction remains unclear, this transformation was the first example of the use of a transition metal complex reacting with an aliphatic C–I bond.

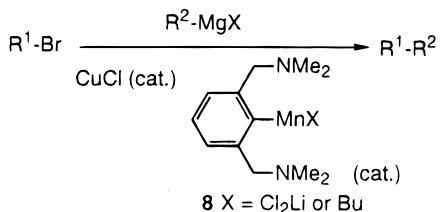


1. Kumada–Corriu Reaction

The first cross-coupling reactions of simple aliphatic iodides with a variety of Grignard reagents in the presence of an in situ generated (dppf)Pd(0) (dppf = 1,1'-bis-(diphenylphosphino)ferrocene) catalyst was reported in 1986.¹⁰ However, a mixture of alkane and alkene is occasionally obtained under these conditions.^{11–13} A more detailed study indicated that neopentyl iodides are the only substrates which give the corresponding coupling products in satisfactory yields (Table 1). The best results are obtained when aromatic Grignard reagents are employed and (dppf)NiCl₂ is used as the catalyst (Table 1 and eq 2).^{11–13} Even so, homocoupled dimers are sporadically



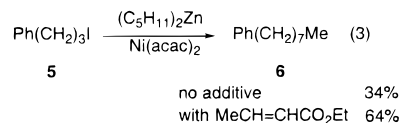
obtained as side products. Vinyl Grignard reagents do not couple under these conditions. Use of alkyl

Table 2. Manganese-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Bromides^a


R ¹	R ²	% yield
C ₈ H ₁₇	Bu	83
	<i>i</i> -Pr	75
	<i>t</i> -Bu	84
	<i>s</i> -Bu	92
BuCHMe	Et	94
	Bu	91
EtO ₂ C(CH ₂) ₂	Bu	89
CH ₂ =CH(CH ₂) ₂	C ₁₄ H ₂₉	91
Me ₃ SiC≡C(CH ₂) ₂	C ₁₄ H ₂₉	89

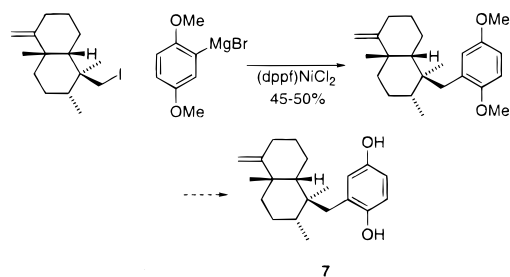
^a References 18 and 19.

Grignard reagents leads predominantly to reduction of the C–I bond. Accordingly, primary alkyl halides are reduced by EtMgBr using (dppf)PdCl₂ as the catalyst.¹² More recently, diorganozinc reagents formed in situ from aryl or methyl Grignard reagents and ZnCl₂-dioxane has been shown to enhance for the coupling of neopentyl iodides;¹⁴ the yields are, in general, 10–30% higher than those in the absence of ZnCl₂ (Table 1). An electron deficient alkene can serve as an additive to facilitate an efficient cross-coupling reaction between the simple alkyl iodide **5** and dipentylzinc in the presence of a catalytic amount of Ni(acac)₂ (eq 3).¹⁵ Some of the recent coupling reactions of aliphatic iodides have been highlighted.¹⁶



This cross-coupling reaction has been used as the key step in the synthesis of the marine natural product arenarol **7** (Scheme 2).¹⁷

Scheme 2



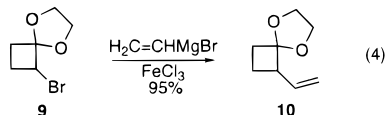
The manganese complex **8** with a nontransferable ligand which can be prepared in situ has been shown to be a powerful catalyst in the cross-coupling reaction of alkyl bromides with various Grignard reagents in the presence of CuCl as a cocatalyst (Table 2).^{18,19} It is highly chemoselective, and functional groups such as ketone and ester remain intact under the reaction conditions.

Table 3. Suzuki-Coupling Reaction of Alkyl Iodides with Organoboranes^a

$R^1I \xrightarrow[\text{(PPh}_3)_4\text{Pd}]{R^2\text{-9-BBN}} R^1\text{-}R^2$		
R ¹	R ²	% yield
Me	MeO ₂ C(CH ₂) ₁₀	71
C ₆ H ₁₃	C ₈ H ₁₇	64 ^b
<i>t</i> -Bu	MeO ₂ C(CH ₂) ₁₀	45
C ₆ H ₁₃	BnOCH ₂ CH ₂ CHMe	58 ^b
	MeO ₂ C(CH ₂) ₁₀	54 ^b
NC(CH ₂) ₃	Me ₂ C=CH(CH ₂) ₂ CHMe(CH ₂) ₃	61
MeO ₂ C(CH ₂) ₃		57 ^b
$R^1I \xrightarrow[\text{(PPh}_3)_4\text{Pd}]{R^2\text{-9-BBN}} R^1\text{-}R^2$		
C ₁₀ H ₂₁	Me(CH ₂) ₃ CH=CH	64 ^b
	Ph	55 ^b

^a Reference 21. ^b GLC yields.

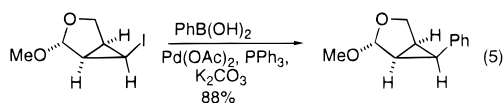
Reaction of an α -bromoketal **9** with vinylmagnesium bromide in the presence of a catalytic amount of FeCl₃ affords the corresponding cross-coupling product **10** (eq 4).²⁰



2. Suzuki Reaction

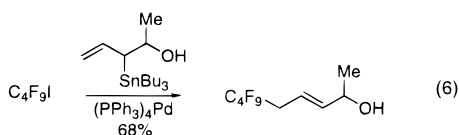
The Suzuki reaction turns out to be another successful cross-coupling reaction involving aliphatic iodides.^{21–24} Thus, a series of reactions between alkyl-9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane) and primary alkyl iodides have been carried out in the presence of (PPh₃)₄Pd to give the corresponding coupling products in good yields (Table 3).²¹ Functional groups such as esters, ketals, and cyanide are stable under these reaction conditions.

This approach has been extended to couple iodocyclopropanes with various boronic acids or esters (Table 4 and eq 5).^{22–24}



3. Stille Reaction

Alkyl halides can also react with organostannanes using Pd(0) as the catalyst (Table 5 and eq 6).^{25–28} The presence of a hydroxy group is well-tolerated under these conditions. Similar to that of the nickel-catalyzed cross-coupling reactions described above, electron-deficient alkenes such as fumaronitrile will retard β -hydride elimination and hence promote the Stille coupling of α -phenylethyl bromide with tetramethylstannane.²⁸

**Table 4. Suzuki Coupling Reaction of Cyclopropyl Iodides with Organoborates and Boronic Acids^a**

$R^1\text{-cyclopropyl-I} \xrightarrow[\text{Pd(OAc)}_2, \text{PPh}_3, \text{base}]{R^2\text{-B(OR}^3)_2} R^1\text{-cyclopropyl-R}^2$		
R ¹	R ²	% yield
BnOCH ₂ (<i>trans</i>)	Ph-cyclopropyl-CH=CH	84
	BnOCH ₂ CH=CH	64
	TBDMSOCH ₂ CH=CH	35
	C ₆ H ₁₃ CH=CH	86
	Ph	80
	4-MeOC ₆ H ₄	85
	4-ClC ₆ H ₄	83
	2-MeC ₆ H ₄	80
	2-thienyl	70
	3-thienyl	78
	Ph-cyclopropyl-CH=CH	60
	BnO-cyclopropyl	71
HOCH ₂ (<i>trans</i>)	Ph-cyclopropyl-CH=CH	81
	Bu-cyclopropyl	64
BnOCH ₂ (<i>cis</i>)	Ph-cyclopropyl-CH=CH	82
	Ph	78

^a References 22 and 23.

Table 5. Stille-Coupling Reaction of Alkyl Iodides with Organostannanes^a

$R^1I \xrightarrow[\text{M}]{R^2\text{SnBu}_3} R^1\text{-}R^2$		
R ¹	R ²	% yield
C ₈ F ₁₇ (CH ₂) ₂	allyl	57
	allyl	51
	PhC≡C	97
	(<i>E</i>)-PhCH=CH	83
	(<i>E</i>)-PhCH=CH	97
	Ph	68
CF ₃ (CH ₂) ₂	PhC≡C	61
C ₆ F ₁₃ (CH ₂) ₂	PhC≡C	79
C ₃ F ₇ CH ₂ CHBu	PhC≡C	41
C ₈ F ₁₇ CH ₂ CH(<i>c</i> -C ₆ H ₁₁)	PhC≡C	53
C ₄ F ₉	(<i>E</i>)-PhCH=CH	70
	(<i>Z</i>)-PhCH=CH	70
	CH ₂ =CH(HOCH ₂)CH	52
	CH ₂ =CH(HOCH[Me])CH	68
	THPO(CH ₂) ₄ C≡C	60
CF ₃ CH ₂	(<i>E</i>)-PhCH=CH	38
	(<i>Z</i>)-PhCH=CH	35
CF ₃	(<i>E</i>)-PhCH=CH	11
	allyl	24
C ₆ F ₁₃	PhC≡C	27
	C ₆ H ₁₃ C≡C	55

^a References 25–27.

B. Carbonylation

Carbonylation of organic halides or related substrates with CO is an important synthetic route to aldehydes, ketones, esters, and amides. Among numerous methods, transition metal-mediated carbon-

Table 6. Formation of Carboxylic Acids, Esters, and Amides from Carbonylation of Alkyl Halides or Sulfonates



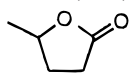
		$\text{RX} \xrightarrow[\text{cat}]{\text{CO, MY}} \text{R}(\text{CO})_n\text{Y}$					
		$n = 1 \text{ or } 2$					
RX	HY or MY	catalyst	T (°C)	CO (atm)	product (% yield)		
(EtO)SO ₂	MeOH/DCHEA	NaCo(CO) ₄ ^a	50	1	EtCO ₂ Me (20)		
C ₅ H ₁₁ I	EtOH/DCHEA	NaCo(CO) ₄ ^a	50	1	C ₅ H ₁₁ CO ₂ Et (33)		
C ₈ H ₁₇ Cl	MeOH/DCHEA	NaCo(CO) ₄ ^a	100	70	C ₈ H ₁₇ CO ₂ Me (28) ^m		
n	MeOH/DCHEA	NaCo(CO) ₄ ^a	50	1	C ₆ H ₁₃ CHMeCO ₂ Me (6) ^m		
C ₆ H ₁₃ CHMeI	MeOH/MeONa	NaCo(CO) ₄ ^a	25	1	C ₆ H ₁₃ CO ₂ Me (56) ^m		
C ₆ H ₁₃ CHMeI	MeOH/MeONa	Na ₂ Fe(CO) ₄ ^a	25	1	C ₆ H ₁₃ CHMeCO ₂ Me (41) ^m		
C ₈ H ₁₇ Br	Ti(OBu) ₄	(PPh ₃) ₄ Pd ^b	150	1	C ₆ H ₁₃ CHMeCO ₂ Me (43) ^m		
Ph(CH ₂) ₂ Br	B(OBu) ₃	(PPh ₃) ₄ Pd	150	1	C ₈ H ₁₇ CO ₂ Bu (63)		
C ₈ H ₁₇ Br	B(OBu) ₃	[1,5-HDRhCl] ₂ ^c	150	1	Ph(CH ₂) ₂ CO ₂ Bu (42)		
C ₁₂ H ₂₅ Br	B(OBu) ₃	(PPh ₃) ₄ Pd	150	1	C ₈ H ₁₇ CO ₂ Bu (57)		
Br(CH ₂) ₆ Br	B(OBu) ₃	[1,5-HDRhCl] ₂ ^c	150	1	C ₁₂ H ₂₅ CO ₂ Bu (88)		
C ₁₀ H ₂₁ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	BuO ₂ C(CH ₂) ₆ CO ₂ Bu (76)		
Ph(CH ₂) ₂ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	C ₁₀ H ₂₁ CO ₂ Me (68) ^m		
<i>c</i> -C ₆ H ₁₁ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	Ph(CH ₂) ₂ CO ₂ Me (56) ^m		
C ₆ H ₁₃ CHMeI	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	<i>c</i> -C ₆ H ₁₁ CO ₂ Me (74)		
(<i>E</i>)-EtCH=CH(CH ₂) ₂ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	C ₆ H ₁₃ CHMeCO ₂ Me (76)		
(<i>Z</i>)-EtCH=CH(CH ₂) ₂ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	(<i>E</i>)-EtCH=CH(CH ₂) ₂ CO ₂ Me (65) ^m		
C ₆ H ₁₃ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	EtCH=CH(CH ₂) ₂ CO ₂ Me		
C ₆ H ₁₃ I	<i>s</i> -BuOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ ^d	120	70	<i>Z</i> : <i>E</i> = 4:1 (66)		
C ₆ H ₁₃ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ PtCl ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (71) ^m		
C ₆ H ₁₃ I	MeOH/K ₂ CO ₃	(<i>P</i> -Pr) ₃ PtCl ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ (<i>s</i> -Bu) (62) ^m		
C ₆ H ₁₃ I	MeOH/K ₂ CO ₃	(AsPh ₃) ₂ PtCl ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (41) ^m		
C ₆ H ₁₃ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (48) ^m		
C ₁₀ H ₂₁ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (55) ^m		
<i>c</i> -C ₆ H ₁₁ I	MeOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (52)		
C ₆ H ₁₃ CHMeI	MeOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ Me (76) ^m		
<i>t</i> -BuI	MeOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	<i>c</i> -C ₆ H ₁₁ CO ₂ Me (62) ^m		
C ₆ H ₁₃ I	<i>i</i> -PrOH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CHMeCO ₂ Me (46)		
C ₆ H ₁₃ I	CF ₃ CH ₂ OH/K ₂ CO ₃	(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	<i>t</i> -BuCO ₂ Me (63) ^m		
<i>c</i> -C ₆ H ₁₁ I		(PPh ₃) ₂ Pt(CO) ₂ /hν ^e	rt	1	C ₆ H ₁₃ CO ₂ <i>i</i> -Pr (87) ^m		
					 (75)		
C ₈ F ₁₇ CH ₂ CHBuI	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₈ F ₁₇ CH ₂ CHBuCO ₂ Et (73)		
C ₈ F ₁₇ CH ₂ CHBuI	EtOH/Et ₃ N	(dppf) ₂ PdCl ₂ ^f	80	30	C ₈ F ₁₇ CH ₂ CHBuCO ₂ Et (83)		
C ₈ F ₁₇ CH ₂ CHBuI	EtOH/Et ₃ N	(PPh ₃) ₃ RhCl ^f	80	30	C ₈ F ₁₇ CH ₂ CHBuCO ₂ Et (48)		
C ₈ F ₁₇ CH ₂ CHBuI	MeOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₈ F ₁₇ CH ₂ CHBuCO ₂ Et (68)		
C ₈ F ₁₇ CH ₂ CHBuI	BuOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₈ F ₁₇ CH ₂ CHBuCO ₂ Bu (53)		
C ₈ F ₁₇ (CH ₂) ₂ I	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ Et (74)		
C ₈ F ₁₇ (CH ₂) ₂ I	EtOH/Et ₃ N	Co ₂ (CO) ₈ ^f	100	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ Et (85)		
C ₈ F ₁₇ (CH ₂) ₂ I	EtOH/Et ₃ N	Rh ₆ (CO) ₁₆ ^f	100	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ Et (66)		
C ₈ F ₁₇ (CH ₂) ₂ I	EtOH/Et ₃ N	(PPh ₃) ₂ PtCl ₂ ^f	100	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ Et (10)		
C ₈ F ₁₇ CH ₂ CHMeI	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	100	50	C ₈ F ₁₇ CH ₂ CHMeCO ₂ Et (88)		
C ₈ F ₁₇ CH ₂ CHMeI	EtOH/Et ₃ N	Co ₂ (CO) ₈ ^f	100	50	C ₈ F ₁₇ CH ₂ CHMeCO ₂ Et (83)		
C ₈ F ₁₇ CH ₂ CHMeI	EtOH/Et ₃ N	Rh ₆ (CO) ₁₆ ^f	100	50	C ₈ F ₁₇ CH ₂ CHMeCO ₂ Et (70)		
C ₆ F ₁₁ (CH ₂) ₂ I	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	100	30	C ₆ F ₁₃ (CH ₂) ₂ CO ₂ Et (57)		
C ₄ F ₉ (CH ₂) ₂ I	BuOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₄ F ₉ (CH ₂) ₂ CO ₂ Bu (44)		
C ₄ F ₉ CH ₂ CH(Hex)I	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	C ₄ F ₉ CH ₂ CH(Hex)CO ₂ Et (54)		
CF ₃ (CH ₂) ₂ I	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^f	80	30	CF ₃ (CH ₂) ₂ CO ₂ Et (93)		
CF ₃ (CH ₂) ₂ I	EtOH/Et ₃ N	Co ₂ (CO) ₈ ^f	100	50	CF ₃ (CH ₂) ₂ CO ₂ Et (65)		
(CF ₂ (CH ₂) ₂ I) ₂	EtOH/Et ₃ N	Co ₂ (CO) ₈ ^g	100	50	(CF ₂ (CH ₂) ₂ CO ₂ Et) ₂ (86)		
((CF ₂) ₂ (CH ₂) ₂ I) ₂	EtOH/KF	(PPh ₃) ₂ PdCl ₂ ^g	100	50	((CF ₂) ₂ (CH ₂) ₂ CO ₂ Et) ₂ (64)		
((CF ₂) ₂ CH ₂ CHMeI) ₂	EtOH/KF	(PPh ₃) ₂ PdCl ₂ ^g	100	50	((CF ₂) ₂ CH ₂ CHMeCO ₂ Et) ₂ (81)		
((CF ₂) ₃ (CH ₂) ₂ I) ₂	EtOH/Et ₃ N	(PPh ₃) ₂ PdCl ₂ ^g	100	50	((CF ₂) ₃ (CH ₂) ₂ CO ₂ Et) ₂ (67)		
((CF ₂) ₂ CH ₂ CHMeI) ₂	EtOH/KF	(PPh ₃) ₂ PdCl ₂ ^g	100	50	((CF ₂) ₂ CH ₂ CHMeCO ₂ Et) ₂ (77)		
C ₈ F ₁₇ (CH ₂) ₂ I	H ₂ O/Et ₃ N	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ H (58)		
C ₈ F ₁₇ (CH ₂) ₂ I	H ₂ O/KF	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ H (85)		
C ₈ F ₁₇ (CH ₂) ₂ I	H ₂ O/Ca(OH) ₂	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ H (42)		
C ₈ F ₁₇ (CH ₂) ₂ I					C ₈ F ₁₇ (CH ₂) ₂ COCO ₂ H (16)		
C ₈ F ₁₇ (CH ₂) ₂ I	H ₂ O/Ca(OH) ₂	Rh ₆ (CO) ₁₆ ^f	120	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ H (60)		
C ₈ F ₁₇ (CH ₂) ₂ I	H ₂ O/KF	(PPh ₃) ₂ PdCl ₂ ^f	80	50	C ₈ F ₁₇ (CH ₂) ₂ CO ₂ H (89)		
C ₈ F ₁₇ CH ₂ CHBuI	H ₂ O/Et ₃ N	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ CH ₂ CHBuCO ₂ H (63)		
					C ₈ F ₁₇ (CH ₂) ₆ CO ₂ H (10)		

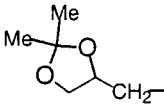
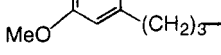
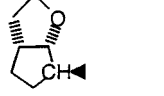
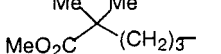
Table 6 (Continued)

RX	HY or MY	catalyst	T (°C)	CO (atm)	product (% yield)
C ₈ F ₁₇ CH ₂ CHBuI	H ₂ O/KF	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ CH ₂ CHBuCO ₂ H (84)
C ₈ F ₁₇ CH ₂ CHBuI	H ₂ O/Ca(OH) ₂	Co ₂ (CO) ₈ ^f	120	50	C ₈ F ₁₇ (CH ₂) ₆ CO ₂ H (2)
CF ₃ (CH ₂) ₂ I	H ₂ O/Et ₃ N	Co ₂ (CO) ₈ ^f	80	50	C ₈ F ₁₇ CH ₂ CHBuCO ₂ H (46)
(CF ₂ (CH ₂) ₂ I) ₂	H ₂ O/KF	Co ₂ (CO) ₈ ^g	80	50	C ₈ F ₁₇ (CH ₂) ₆ CO ₂ H (22)
((CF ₂) ₂ (CH ₂) ₂ I) ₂	H ₂ O/KF	(PPh ₃) ₂ PdCl ₂ ^g	80	50	CF ₃ (CH ₂) ₂ CO ₂ H (61)
((CF ₂) ₂ CH ₂ CHMeI) ₂	H ₂ O/KF	Co ₂ (CO) ₈ ^g	80	50	(CF ₂ (CH ₂) ₂ CO ₂ H) ₂ (97)
((CF ₂) ₃ (CH ₂) ₂ I) ₂	H ₂ O/KF	Co ₂ (CO) ₈ ^g	80	50	((CF ₂) ₂ CH ₂ CHMeCO ₂ H) ₂ (69)
((CF ₂) ₂ CH ₂ CHMeI) ₂	H ₂ O/KF	Co ₂ (CO) ₈ ^g	80	50	((CF ₂) ₃ (CH ₂) ₂ CO ₂ H) ₂ (94)
C ₈ H ₁₇ I	H ₂ O/Bu ₄ NF	Mo(CO) ₆ ^h	40–60	HCO ₂ Me	((CF ₂) ₂ CH ₂ CHMeCO ₂ H) ₂ (67)
C ₈ F ₁₇ (CH ₂) ₂ I	Et ₂ NH	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₈ H ₁₇ CO ₂ C ₈ H ₁₇ (70)
C ₈ F ₁₇ (CH ₂) ₂ I	piperidine	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₈ F ₁₇ (CH ₂) ₂ CONEt ₂ (12)
C ₆ F ₁₃ (CH ₂) ₂ I	<i>t</i> -BuNH ₂	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₈ F ₁₇ (CH ₂) ₂ COCONEt ₂ (56)
C ₄ F ₉ (CH ₂) ₂ I	<i>n</i> -Pr ₂ NH	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₈ F ₁₇ (CH ₂) ₂ COCONC ₆ H ₁₁ (21)
<i>i</i> -C ₃ F ₇ (CH ₂) ₂ I	Et ₂ NH	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₆ F ₁₃ (CH ₂) ₂ COCONH <i>t</i> -Bu (36)
C ₂ F ₅ (CH ₂) ₂ I	Et ₂ NH	(PPh ₃) ₂ PdCl ₂ ⁱ	100	50	C ₄ F ₉ (CH ₂) ₂ CON(<i>n</i> -Pr) ₂ (17)
CF ₃ (CH ₂) ₂ I	Pr ₂ NH	(PPh ₃) ₂ PdCl ₂ ^g	100	50	C ₄ F ₉ (CH ₂) ₂ COCON(<i>n</i> -Pr) ₂ (56)
CF ₃ (CH ₂) ₂ I	<i>t</i> -BuNH ₂	(PPh ₃) ₂ PdCl ₂ ^g	100	50	<i>i</i> -C ₃ F ₇ (CH ₂) ₂ CONEt ₂ (22)
CF ₃ CH ₂ CHMeI	Et ₂ NH	(PPh ₃) ₂ PdCl ₂ ^g	100	50	<i>i</i> -C ₃ F ₇ (CH ₂) ₂ COCONEt ₂ (38)
EtO ₂ CCH ₂ CHMeI	EtOH/TMU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₂ F ₅ (CH ₂) ₂ CONEt ₂ (1)
C ₈ H ₁₇ I	EtOH/TMU	Co ₂ (CO) ₈ ⁱ	100	50	C ₂ F ₅ (CH ₂) ₂ COCONEt ₂ (36)
C ₈ H ₁₇ I	EtOH/DMPU	Co ₂ (CO) ₈ ⁱ	100	50	CF ₃ (CH ₂) ₂ CONPr ₂ (7)
C ₈ H ₁₇ I	EtOH/DMPU	Co ₂ (CO) ₈ ⁱ	100	50	CF ₃ (CH ₂) ₂ COCONPr ₂ (50)
C ₈ H ₁₇ I	H ₂ O/TMU	Co ₂ (CO) ₈ ⁱ	100	50	CF ₃ (CH ₂) ₂ COCONH <i>t</i> -Bu (53)
C ₈ H ₁₇ Br	EtOH/TMU	Co ₂ (CO) ₈ ⁱ	100	50	CF ₃ CH ₂ CHMeCONEt ₂ (14)
C ₁₀ H ₂₁ I	EtOH/DMPU	Co ₂ (CO) ₈ ⁱ	100	50	CF ₃ CH ₂ CHMeCOCONEt ₂ (66)
MeO(CH ₂) ₃ I	MeOH/TMU	Co ₂ (CO) ₈ ⁱ	100	50	EtO ₂ CCHMeCH ₂ CO ₂ Et (71)
MeOCO(CH ₂) ₂ I	MeOH/TMU	Co ₂ (CO) ₈ ⁱ	100	50	EtO ₂ C(CH ₂) ₃ CO ₂ Et (5)
<i>c</i> -C ₆ H ₁₁ I	EtOH/TMU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (86)
<i>c</i> -C ₆ H ₁₁ I	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (67)
<i>c</i> -C ₆ H ₁₁ I	H ₂ O/TMU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (84)
C ₆ H ₁₃ CHMeI	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ H (97) ^m
C ₈ H ₁₇ I	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (61)
C ₁₀ H ₂₁ I	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₁₀ H ₂₁ CO ₂ Et (88)
MeO(CH ₂) ₃ I	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	MeO(CH ₂) ₃ CO ₂ Me (91)
MeO ₂ CCH ₂ CHMeI	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	MeOCO(CH ₂) ₂ CO ₂ Me (65)
<i>c</i> -C ₆ H ₁₁ I	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ Et (70)
<i>c</i> -C ₆ H ₁₁ I	H ₂ O/TMU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ Et (70)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ H (76) ^m
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₆ H ₁₃ CHMeCO ₂ Et (51)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (77) ^m
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₁₀ H ₂₁ CO ₂ Et (82) ^m
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	MeO(CH ₂) ₃ CO ₂ Et (75)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ Et (80)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	MeOCOCH ₂ CHMeCO ₂ Et (81)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ H (57)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (72)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (63)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (72)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (80)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (74)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (37)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (56)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (57)
C ₈ H ₁₇ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₈ H ₁₇ CO ₂ Et (53)
C ₁₂ H ₂₅ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₁₂ H ₂₅ CO ₂ Et (79)
C ₁₂ H ₂₅ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	C ₁₂ H ₂₅ CO ₂ Et (75)
Ph(CH ₂) ₂ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	Ph(CH ₂) ₂ CO ₂ Et (61)
EtO(CH ₂) ₃ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	EtO(CH ₂) ₃ CO ₂ Et (56)
CH ₂ =CH(CH ₂) ₄ OTs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	CH ₂ =CH(CH ₂) ₄ CO ₂ Et (73)
Me ₂ C=CH(CH ₂) ₂ -CHMe(CH ₂) ₂ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	Me ₂ C=CH(CH ₂) ₂ CHMe-(CH ₂) ₂ CO ₂ Et (76)
MsO(CH ₂) ₄ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	EtO ₂ C(CH ₂) ₄ CO ₂ Et (78)
MeCH(OH)(CH ₂) ₂ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	 (48) ^m
<i>c</i> -C ₆ H ₁₁ OMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	<i>c</i> -C ₆ H ₁₁ CO ₂ Et (34)
EtO ₂ CCH ₂ CHMeOMs	EtOH/DMPU	(PPh ₃) ₂ PdCl ₂ ^j	100	50	EtO ₂ CCHMeCH ₂ CO ₂ Et (36)

^a Reference 29. ^b Reference 30. ^c Reference 31. ^d Reference 32. ^e Reference 33. ^f Reference 34. ^g Reference 35. ^h Reference 36. ⁱ Reference 37. ^j Reference 38. ^k Reference 39. ^l Reference 40. ^m GLC yields. DCHEA, dicyclohexylethylamine; DMI, 1,3-dimethyl-2-imidazolidinone; TMU, *N,N,N,N*-tetramethylurea; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; NMP, *N*-methylpyrrolidone; [1,5-HDRhCl]₂, 1,5-hexadienerhodium(I) chloride dimer.

Table 7. Formation of Ketones from Pd(PPh₃)₄-Catalyzed Carbonylative Cross-Coupling of Alkyl Iodides with Alkyl-9-BBN^a

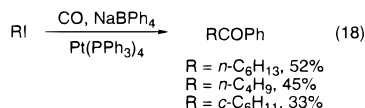
$$R^1I \xrightarrow[\text{(PPh}_3)_4\text{Pd}]{R^2\text{-9-BBN, CO, } h\nu} R^1COR^2$$

R ¹	R ²	% yield
C ₆ H ₁₃	C ₈ H ₁₇	67 ^b
<i>c</i> -C ₆ H ₁₁	C ₈ H ₁₇	65 ^b
<i>t</i> -Bu	C ₈ H ₁₇	69 ^b
		73
		65 ^c
NC(CH ₂) ₃	PhCH ₂ O(CH ₂) ₄	70
MeO ₂ C(CH ₂) ₃	NCC ₁₀ H ₂₀	65

^a Reference 44. ^b GLC yields. ^c The product was contaminated by 11% of the *cis*-isomer.

3. Formation of Ketones

Alkyl aryl ketones can be prepared from the (PPh₃)₄Pt-catalyzed carbonylative cross-coupling of alkyl iodides with NaBPh₄ in moderate yields (eq 18). In addition, benzophenone and triphenylmethane are commonly formed as byproducts.⁴³



Unsymmetrical dialkyl ketones are obtained from the palladium-catalyzed carbonylative cross-coupling reaction of alkyl-9-BBN derivatives with iodoalkanes under a CO atmosphere (Table 7 and eq 18).⁴⁴ Direct exposure to visible light accelerates the reaction. Primary, secondary, and tertiary iodoalkanes can all be carbonylated and coupled with alkyl-9-BBN's. More importantly, acetal, nitrile, and ester groups can be tolerated under the reaction conditions.

Carbonylative cross-coupling reaction of β -perfluoroalkyl-substituted alkyl halides with organostannanes can also be performed in the presence of a palladium-catalyst (Table 8).⁴⁵

4. Formation of Silyl Enol Ethers

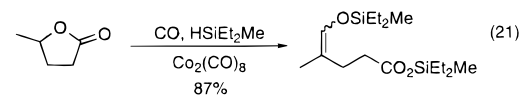
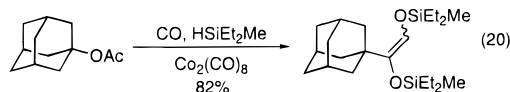
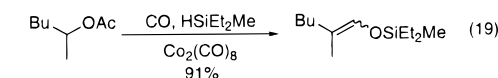
In the presence of HSiEt₂Me and a catalytic amount of Co₂(CO)₈, secondary alkyl acetates undergo clean incorporation of CO to give enol silyl ethers (eqs 19–21 and Table 9).^{46,47} Lactones behave similarly. It is interesting to note that primary alkyl acetates give several products in a nonselective fashion. On the other hand, no incorporation of CO takes place in tertiary alkyl esters besides bridgehead acetates.

Table 8. Carbonylative-Coupling Reaction of β -(Perfluoroalkyl)ethyl Iodides with Organostannanes^a

$$R_fCH_2CH_2I \xrightarrow[\text{Pd}]{\text{CO, R}^1\text{Sn(Bu)}_3} R_fCH_2CH_2COR^1$$

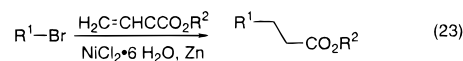
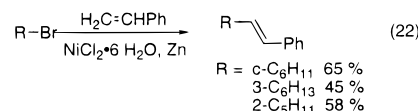
R _f	R ¹	% yield ^b
C ₈ F ₁₇	Ph	97
CF ₃	Ph	66
C ₆ F ₁₃	Ph	97
C ₈ F ₁₇	allyl	39 (R ¹ = MeCH=CH)
		16 (R ¹ = allyl)
C ₈ F ₁₇	allyl	61 (R ¹ = MeCH=CH)
C ₈ F ₁₇	PPhC≡C	48
C ₈ F ₁₇	PhCH=CH	79

^a Reference 45. ^b GLC yields.



C. Reductive Heck Reactions

When alkyl halides are treated with styrene in the presence of a Ni(0) catalyst, β -alkylstyrenes are obtained as the major products (eq 22).⁴⁸ However, when electron-deficient olefins are employed, conjugate-addition products become predominant (Table 10 and eqs 23 and 24).^{48–51} Zn powder^{48,51,52} and borohydride exchange resin (BER)^{49,50} are commonly used for the in situ generation of active Ni(0) catalyst from the corresponding Ni(II) compounds. Alternatively, electrochemical reduction has also been reported.⁵³ Iodocalcitriol derivatives **18** react with ethyl acrylate under the nickel-catalyzed conditions to give **19**.⁵²



R¹ = *c*-C₆H₁₁; R² = Me, in MeCN 36%
 R¹ = 2-C₅H₁₁; R² = Me, in MeCN 41%
 R¹ = 1-C₆H₁₇; R² = Et, in THF 69%
 R¹ = *c*-C₆H₁₁; R² = Et, in THF 65%
 R¹ = 1,1-dimethylpropyl; R² = Et, in THF 79%

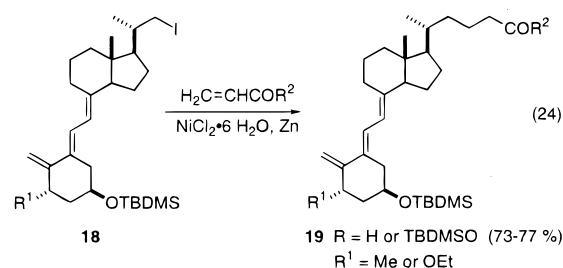
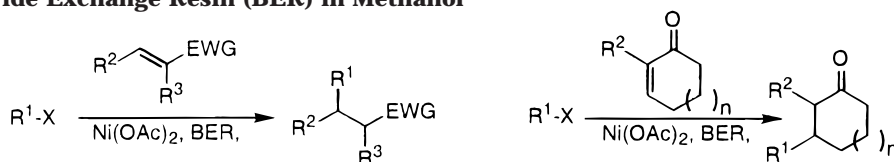


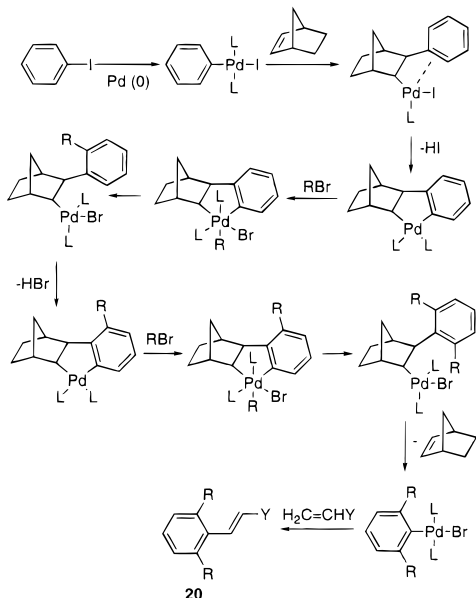
Table 9. Conversion of Alkyl Esters to (Siloxymethylene)Alkanes by $\text{Co}_2(\text{CO})_8$ -Catalyzed Reaction with Hydrosilane and CO^a

R ¹ OAc	product (% yield)	R ¹ OAc	product (% yield)
	(75) ^b		(75) ^b
	(60)		(57)
	(91) ^b		(40)
	(49) ^b		(64) ^b
	(65) R = SiEt ₂ Me		(47) ^b
	(56) ^b R = SiEt ₂ Me		(63) ^b
	(90)		(67) ^b
	(73) ^b		(68) ^b
	(67) ^b		(87) ^b
	(70) ^b		(73)
	(74) ^b		(85) ^b
	(79) ^b		(87) ^b
	(71) ^b		(82)
	(78)		(4)
	(17)		(63)
	(19)		

^a References 46 and 47. ^b GLC yields.

Table 10. Conjugate Addition of Alkyl Halides with α,β -Unsaturated Compounds Using Nickel Acetate–Borohydride Exchange Resin (BER) in Methanol^a

alkyl halides	α,β -unsaturated compd	% yield	alkyl halide	α,β -unsaturated compd	% yield
<i>c</i> -C ₆ H ₁₁ I	MeCH=CHCO ₂ Me	85	C ₈ H ₁₇ I	CH ₃ CH=CHCO ₂ Me	68
	CH ₂ =CMeCO ₂ Me	93		CH ₂ =CMeCO ₂ Me	88
	CH ₂ =CHCO ₂ Et	93		CH ₂ =CHCO ₂ Et	86
	MeCH=CHCN	93		MeCH=CHCN	80
	CH ₂ =CMeCN	91		CH ₂ =CMeCN	81
	CH ₂ =CHCN	90		PhCH=CHCN	77
	MeCH=CHCOEt	81		MeCH=CHCOEt	73
	CH ₂ =CHCOMe	54		PhCH=CHCOMe	60
	OC(CH ₂) ₂ CH=CMe	85		OC(CH ₂) ₂ CH=CMe	72
	OC(CH ₂) ₂ CH=CH	72		BuOCH(OEt)CH ₂ I	CH ₂ =CHCO ₂ Et
OC(CH ₂) ₃ CH=CH	66	CH ₂ =CHCN	81		
CH ₂ =CHCOEt	84	CH ₂ =CHCO ₂ Et	76		
<i>c</i> -C ₆ H ₁₁ Br	MeCH=CHCN	40	Et ₂ NCO(CH ₂) ₄ I	CH ₂ =CHCN	65
	OC(CH ₂) ₂ CH=CMe	56		Ph(CH ₂) ₂ I	68
	CH ₂ =CHCOEt	92		NC(CH ₂) ₄ I	78
<i>s</i> -C ₆ H ₁₃ I	MeCH=CHCN	92	EtCH=CH(CH ₂) ₂ I	MeCH=CHCOEt	68
	CH ₂ =CHCO ₂ Et	92		CH ₂ =CMeCO ₂ Et	70
<i>s</i> -C ₈ H ₁₇ I	MeCH=CHCOEt	84	Me ₂ C=CH(CH ₂) ₂ I	CH ₂ =CMeCN	76
	CH ₂ =CHCOEt	89		CH ₂ =CHCO ₂ Et	65
	OC(CH ₂) ₂ CH=CH	80		CH ₂ =CHCN	74

^a References 49 and 50.**Scheme 3****D. Miscellaneous Reactions**

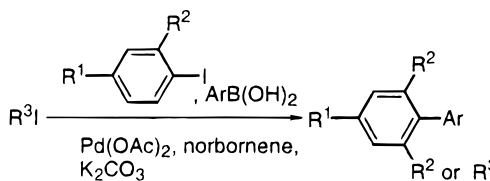
A novel palladium-catalyzed three component synthesis of bis-ortho-substituted styrenes **20** from iodobenzene, alkyl iodides, and alkenes has recently been uncovered.^{54–57} Norbornene is required as a promoter for these reactions. A plausible mechanism is shown in Scheme 3. Representative examples are summarized in Table 11. By using a similar strategy,

Table 11. Reaction of Alkyl Iodides and Aryl Iodides with Terminal Olefins in the Presence of K₂CO₃, KOAc, Norbornene, and Pd(OAc)₂^a

R ¹	R ²	R ³	Y	% yield ^{b,c}
H	H	Bu	MeO ₂ C	93
H	H	C ₈ H ₁₇	MeO ₂ C	95
H	H	Ph(CH ₂) ₂	MeO ₂ C	95
Me	H	Bu	MeO ₂ C	93
MeO ₂ C	H	Bu	MeO ₂ C	89
H	H	Bu	MeO ₂ C	90
H	H	Bu	Ph	91
H	H	Bu	C ₆ H ₁₃	90
H	Me	Pr	MeO ₂ C	84
H	Me	Bu	MeO ₂ C	81
H	Et	Pr	MeO ₂ C	93
H	Bu	Pr	MeO ₂ C	76
H	Bu	C ₈ H ₁₇	MeO ₂ C	73
H	Bu	<i>i</i> -Pr	MeO ₂ C	25
H	<i>i</i> -Pr	Bu	MeO ₂ C	60
H	<i>t</i> -Bu	Pr	MeO ₂ C	42
H	Bu	Pr	MeCO	71
H	Bu	Pr	N=C	43
H	Bu	Pr	Ph	46
H	Bu	Pr	4-MeC ₆ H ₄	50
H	Bu	Pr	4-FC ₆ H ₄	67

^a Reference 54–56. ^b When R² = H, both ortho positions are substituted by R³. ^c Conversion yields.

2,6-dialkyl-substituted biaryl compounds could also be prepared in high yields (Table 12).⁵⁷

Table 12. Reaction of Alkyl Bromides, Aryl Iodides, and Arylboronic Acids in the Presence of Norbornene, Pd(OAc)₂, and K₂CO₃^a


R ¹	R ²	R ³	Ar	% yield ^b
H	H	Pr	Ph	90
H	H	Bu	Ph	81
MeO ₂ C	H	Bu	Ph	89 ^c
Me	H	Bu	Ph	63
Me	H	Bu	4-MeC ₆ H ₄	84
H	H	Bu	4-MeC ₆ H ₄	66
H	H	Bu	4-FC ₆ H ₄	59
H	Me	Bu	Ph	89 ^c
H	Bu	Pr	Ph	70 ^c
H	Pr ⁱ	Bu	Ph	82 ^c
H	Pr ⁱ	Pr	Ph	71 ^c

^a Reference 57. ^b When R² = H, both ortho positions are substituted by R³. ^c GC yields.

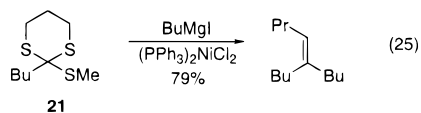
III. α -Heteroatom-Substituted C–X Bond Activation

In the previous section, the reactions are mainly concerned with the cleavage of the C–I bond. For less reactive C–X bonds, some kind of activation is essential. It is well-documented that the bond strength may play a significant role in the oxidative addition reaction.^{4–6} Since the C–X bond energy decreases with an increasing number of these bonds attached to this carbon atom, the presence of a α -heteroatom may weaken the corresponding C–X bond and therefore transition-metal-catalyzed activation of such C–X bond becomes more facile.

A. Cross-Coupling Reactions

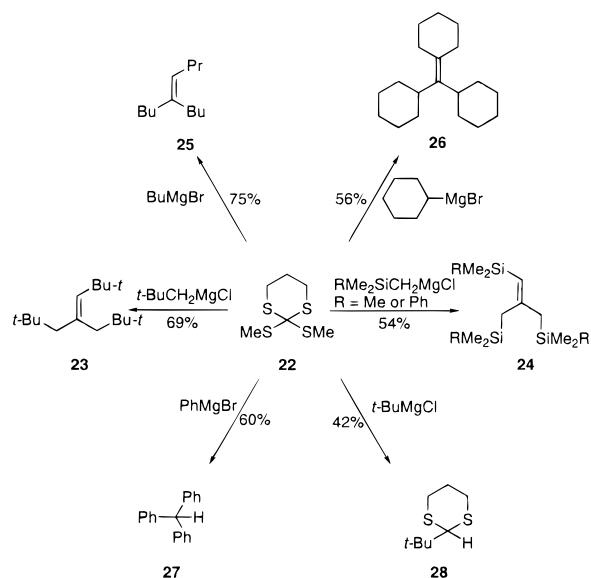
1. Kumada–Corriu Reaction

The extension of Kumada–Corriu reaction to organosulfur compounds has been well-documented. Vinylic and allylic thioethers are known to undergo nickel-catalyzed cross-coupling reactions with Grignard reagents.^{58–60} More recently, benzylic and allylic dithioacetal functionalities have been shown to undergo nickel-catalyzed olefination reactions and geminal dimethylation reactions in good to excellent yields.^{61–63} The corresponding unactivated aliphatic substrates are unreactive under these conditions. Nevertheless, the C–S bonds in trithioortho esters **21** (eq 25)



or tetrathioorthocarbonate **22** (Scheme 4), which are relatively weak, have been found to undergo alkylative olefination reactions in the presence of a nickel catalyst.^{64,65} A mechanism similar to that described

Scheme 4

**Table 13. Stille Cross-Coupling Reaction of Organostannanes with α -Haloethers or α -Halothioethers^a**

R ¹ CHR ² X		R ³ SnBu ₃		(Ph ₃ P) ₄ Pd		R ¹ CHR ² –R ³	% yield
R ¹	R ²	X	R ³				
C ₈ H ₁₇ O	H	Br	CH ₂ =CH				84
	H	Br	PhC≡C				55
	H	Cl	CH ₂ =CH				82
	H	Cl	PhC≡C				71
	H	Cl	Ph				86
	H	Cl	CH ₂ =C(OEt)				81
TMS(CH ₂) ₂ O	H	Cl	PhC≡C				61
HC≡C(CH ₂) ₄ O	H	Cl	PhC≡C				61
PhCH ₂ O	H	Cl	CH ₂ =CH				75
PhCH ₂ O	H	Cl	PhC≡C				73
PhS	H	Cl	PhC≡C				67
MeO	Ph	Cl	PhC≡C				71
MeO	Ph(CH ₂) ₂	Cl	PhC≡C				65

^a Reference 66.

for the cross-couplings of benzylic or allylic dithioacetals also applies here.^{61–63} In other words, as soon as the first C–S bond is activated, the following steps involving the reactions of the remaining C–S bonds would be a cascade process.

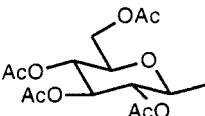
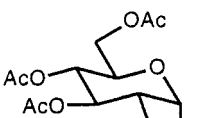
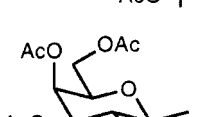
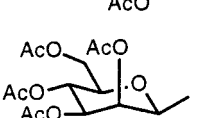
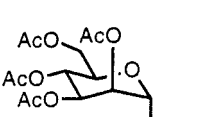
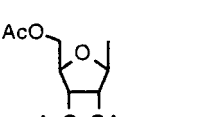
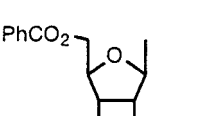
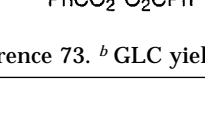
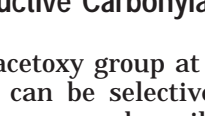
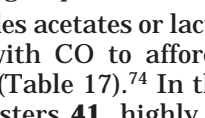
As shown in Scheme 4, sterically hindered neopentyl or trimethylsilylmethyl Grignard reagents can couple with **22** to give **23** and **24**, respectively. Since there is no hydrogen for β -elimination, the reaction of **22** with PhMgBr under the same conditions gives triphenylmethane **27**. The reaction of **22** with *t*-BuMgCl under these coupling conditions affords **28**. No further reaction is observed. These coupling reactions provide convenient routes for the synthesis of polysubstituted alkenes, while **22** can be considered to serve as a C⁴⁺ synthon.^{63–65}

2. Stille Reaction

Pd(0) mediates the cross-coupling of organostannanes with a variety of α -haloethers or α -halothioethers in moderate to good yields (Table 13).⁶⁶ It is

Table 17. $\text{Co}_2(\text{CO})_8$ -Catalyzed Siloxymethylation of Glycosyl Acetates with HSiR_3 and CO^a

$$\text{glycosyl-OAc} \xrightarrow[\text{Co}_2(\text{CO})_8]{\text{CO, HSiR}_3} \text{glycosyl-CH}_2\text{OSiR}_3$$

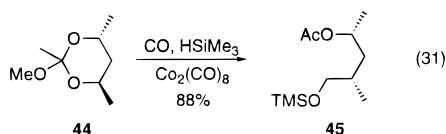
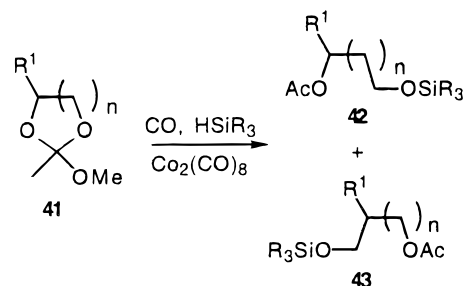
glycosyl group	HSiR_3	% yield ^b
	HSiMe_3	75 (β)
	HSiEt_2Me	82 (β)
	HSiMe_3	78 (β)
	HSiMe_3	82 (β)
	HSiMe_3	51 (α)
	HSiMe_3	45 (α)
	HSiEt_2Me	19 (α)
	HSiEt_2Me	31 (β)
	HSiEt_2Me	70 (β)
	HSiEt_2Me	75 (β)

^a Reference 73. ^b GLC yields.

C. Reductive Carbonylation

The acetoxy group at the anomeric center of glycosides can be selectively replaced with a siloxymethyl group under mild conditions (Table 17).⁷³

Besides acetates or lactones, cyclic ortho esters also react with CO to afford the corresponding homologues (Table 17).⁷⁴ In the case of substituted cyclic ortho esters **41**, highly regioselective ring opening occurs at the primary carbon center as the major products **42** (Table 18). The stereospecificity of the ring opening reaction has been demonstrated in the siloxymethylation of **44** to yield **45** with an inversion of configuration (eq 31).

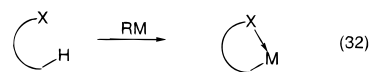
**Table 18.** $\text{Co}_2(\text{CO})_8$ -Catalyzed Reaction of Cyclic Ortho esters with Hydrosilanes and Carbon Monoxide^a

R^1	n	hydrosilane	% yield (ratio of 42 : 43) ^b
H	1	HSiEt_2Me	94
Me	1	HSiEt_2Me	57 (91:9)
Bu	1	HSiEt_2Me	69 (95:5)
Bu	1	HSiMe_3	72 (94:6)
ClCH_2	1	HSiMe_3	32 (100:0)
MOM	1	HSiMe_3	41 (100:0)
Ph	1	HSiMe_3	45 (0:100)
Ph	1	HSiMe_3	56 (0:100)
H	2	HSiMe_3	89
H	2	HSiEt_2Me	61
Me	2	HSiEt_2Me	34 (90:10)
Me	2	HSiMe_3	50 (94:6)
H	3	HSiEt_2Me	41

^a Reference 74. ^b GLC yields.

IV. Chelation Assisted Activation of a Proximal C–X Bond

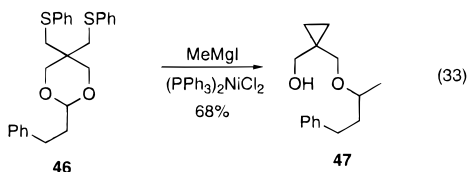
It is well-documented that chelation demonstrates a unique role to direct regioselective metalation of a neighboring C–H bond (eq 32).^{75–77}



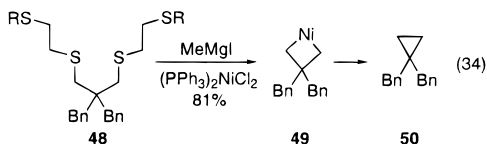
The use of this strategy to activate aliphatic C–X bond in the transition metal-catalyzed reactions has been explored recently. Since the neighboring heteroatom can also serve as a leaving group, such a chelative activation can be considered as the *symbiotic* interaction of the chelating ligands to the metal center.⁷⁸ Either or both of the carbon–heteroatom bonds can thus be activated leading to the C–C bond formation.

A. Desulfurative Cyclopropanation of 1,3-Bis-(thioethers)

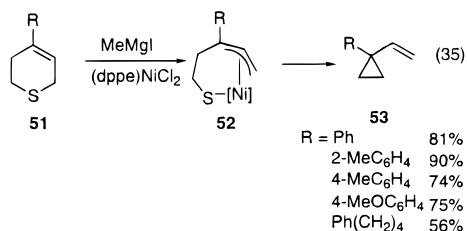
It is known that the C–S bonds in certain coordinated complexes are activated.⁷⁹ Poly(thioethers) are known to form chelate complexes.^{80,81} Similar to the chelate-assisted activation of a proximal C–H bond, the sulfur moieties in poly(thioethers) can interact *symbiotically* with a metallic species such that these C–S bonds can be cleaved selectively. Thus, reaction of the bis(thioether) **46** affords the corresponding cyclopropane derivative **47** in 68% yield (eq 33).⁸² It is noteworthy that the acetal group in **46** also undergoes an alkylative ring opening reaction^{78,83} with a Grignard reagent.



This reaction can be extended to poly(thioethers) **48**. Due to chelate interaction of the sulfur atoms with the nickel catalyst, all C–S bonds are cleaved leading to a possible nickelacyclobutane intermediate **49**. Reductive elimination of **49** produces the corresponding cyclopropane **50** in good yield (eq 34).⁸²



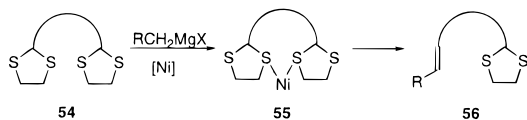
5,6-Dihydro-2*H*-thiapyran **51** has two kinds of C–S bonds, one allylic and the other aliphatic. The reaction may proceed via an initial cleavage of the more reactive allylic C–S bond to give the π -allyl intermediate **52**. The remaining C–S bond may be cleaved due to chelation leading eventually to the corresponding vinylcyclopropanes **53** in 56–90% yields (eq 35).⁸²



B. Olefination of Dithioacetals

As mentioned earlier, simple aliphatic dithioacetals are unreactive toward the transition metal-catalyzed cross-coupling reaction, due to the low reactivity of these C–S bonds in the oxidative addition process. Based on the chelation model described in the previous section, a strategy for the olefination of aliphatic bisdithioacetals is outlined in Scheme 6.^{82,84} The two

Scheme 6



proximal dithioacetal moieties in **54** may form a chelation complex **55** with the nickel catalyst. Accordingly, the C–S bond is activated and olefination of one of the dithioacetal moieties may occur to give **56**. The remaining dithioacetal group in **56**, which is aliphatic in nature, remains intact. This reaction can be considered as a selective modification of one of the two carbonyl equivalents.

Either (PPh₃)₂NiCl₂ or complexes having bidentate ligands can be used as the catalyst in these reactions.

Table 19. (PPh₃)₂NiCl₂-Catalyzed Reaction of Bisdithioacetals with Grignard Reagents^a

R = Me, Me₃SiCH₂, Ph

substrate	product (% yield)

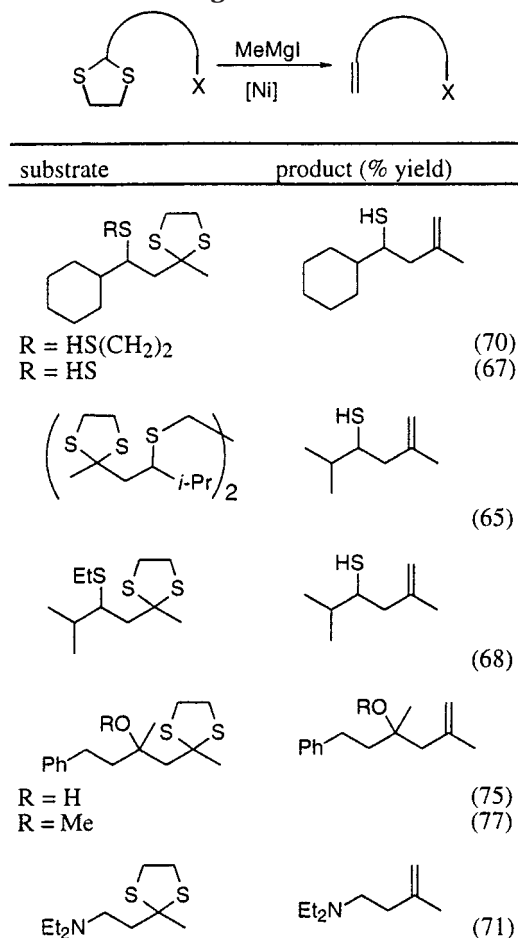
^a References 82 and 84.

As shown in Table 19, a wide range of Grignard reagents react smoothly with bisdithioacetals to give the monoolefination products.^{82,84}

The ability of the two sulfur moieties to coordinate simultaneously to a nickel catalyst is the criterion for the success of these transformations. Substrates (e.g. **57**) which are unable to form a chelation complex with a nickel catalyst fail to react under these reaction conditions.⁸²



The extension of the cross-coupling reactions to thioether–dithioacetals gives regioselectively homoallylic thiols (Table 20).⁸² The regioselective formation of the double bond suggests the formation of a chelation intermediate **58** which may determine the

Table 20. (Ph₃P)₂NiCl₂-Catalyzed Reactions of Dithioacetals Having a Proximal Heteroatom Substituent with MeMgI^a

orientation of the β -hydride elimination, preferentially leading to the formation of the corresponding homoallylic thioethers. It is noteworthy that the C–S bonds of these thioethers may also be cleaved under these conditions.

Like sulfur auxiliaries, proximal substituents such as hydroxy, methoxy, or amino groups also assist the alkenation of aliphatic dithioacetals to give the corresponding homoallylic alcohols, ethers, and amines, respectively, in reasonably good yields (Table 20).⁸²

The heteroatom-assisted olefination of dithioacetals has been extended to a sugar derivative **59**. Under nickel-catalyzed cross-coupling conditions, the oxygen-atom-assisted olefination together with the regioselective ring opening of both acetonide moieties occurs to give **60**. In the absence of a nickel catalyst, **61** is obtained and the C–S bonds remain intact (eq 36).⁸⁵

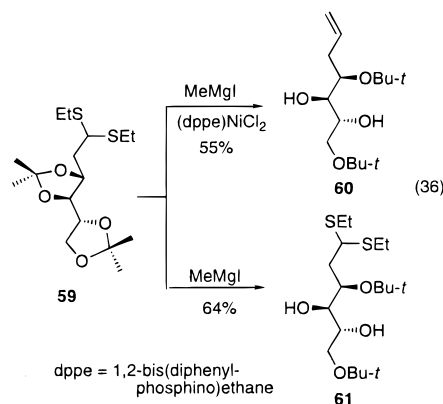
C. Chelation Assisted Activation of Aliphatic Carbon–Halogen Bonds

A remote double bond has also been found to serve as a chelation auxiliary to activate the C–I and C–Br bonds in the cross-coupling reactions with a wide range of organozinc reagents in the presence of

Table 21. Ni(acac)₂-Catalyzed Cross-Coupling Reaction of Alkyl Iodides with Dialkylzinc Reagents^a

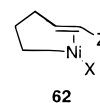
$$R^1I \xrightarrow[Ni(acac)_2]{(R^2)_2Zn} R^1-R^2$$

R ¹	R ²	% yield
CH ₂ =CH(Ph)(CH ₂) ₂	C ₅ H ₁₁	80
	PivO(CH ₂) ₃	90
CH ₂ =CH(Bu)(CH ₂) ₂	C ₅ H ₁₁	72
	PivO(CH ₂) ₃	70
EtO ₂ CCH=CH(CH ₂) ₃	C ₅ H ₁₁	83
	PivO(CH ₂) ₃	79
	TMSO-	65
EtO ₂ CCH=CH(CH ₂) ₄	Et	84
	AcO(CH ₂) ₅	78
	PivO(CH ₂) ₆	73
N≡C(CH ₂) ₂	C ₅ H ₁₁	64
N≡C(CH ₂) ₃	C ₅ H ₁₁	52
N≡C(CH ₂) ₄	C ₅ H ₁₁	39

^a References 86–88.

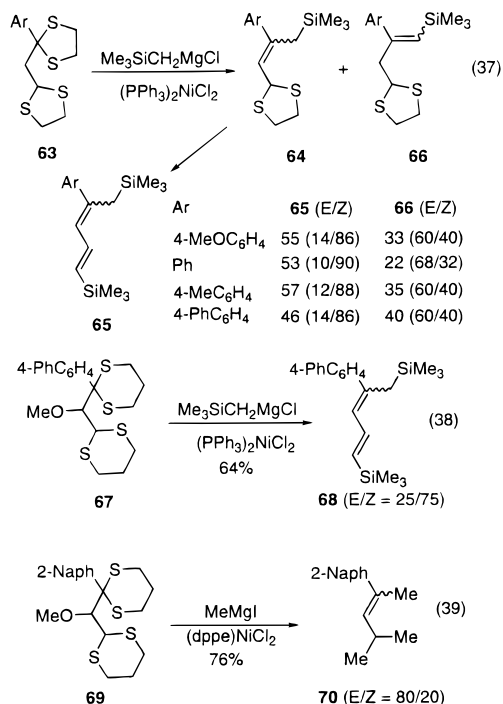
Ni(acac)₂ catalyst (Table 21).^{86–88} Thus, the efficiency of Ni(acac)₂-catalyzed cross-coupling reactions of dialkylzinc and alkyl halides with a double bond located in close proximity is enhanced. A variety of functional group remains intact under these conditions (Table 22). It is particularly noteworthy that a proximal thioether or dithioacetal functionality show a significant accelerating effect on the reaction rate. A remote nitrile or carbonyl group can also assist the cross-coupling reaction.

A double bond-coordinated nickel intermediate **62** is speculated. It is interesting to note that the presence of an electron-withdrawing group such as an ester group at the double bond may strengthen the nickel–olefin bond and, hence, has a beneficial effect. However, when the zinc reagent contains a bulky alkyl group, which will prevent the complexation of the double bond with the nickel, halogen–zinc exchange occurs readily and no coupling product is observed. Pd(II) catalyst is ineffective for this reaction. Again, only halogen–zinc exchange is observed.¹⁵ A radical mechanism has been suggested.⁸⁸



V. Tandem Olefination Reactions of Dithioacetals

Another way to activate the unreactive C_{sp}³-X bond is to design a substrate which can under the reaction conditions generate a double bond, so that the originally unreactive C-X moiety becomes allylic and reactive. Consequently, further coupling with the nucleophile can take place. Thus, bisdithioacetal **63** contains one benzylic dithioacetal moiety and one aliphatic dithioacetal group located at the C-3 position relative to the benzylic dithioacetal functionality. In the presence of the nickel catalyst, the benzylic dithioacetal reacts first with the Grignard reagent generating intermediate **64** which subsequently reacts with the Grignard reagent under the reaction conditions leading to diene **65** (eq 37).⁸⁹ Unfortunately, undesired side product **66** is formed in significant amount. Alternatively, introduction of a heteroatom substituent at the C-2 position (e.g. **67**) will lead to elimination of this substituent under the reaction conditions. As such, allylic dithioacetal intermediate **64** is formed regioselectively and further reaction with the silylmethyl Grignard reagent under the nickel catalyzed conditions yields the corresponding diene **68** (eq 38).⁹⁰ In a similar manner, the (dppe)NiCl₂-catalyzed reaction of **69** with MeMgI under similar conditions affords the isopropylstyrene **70** in 76% yield (eq 39).



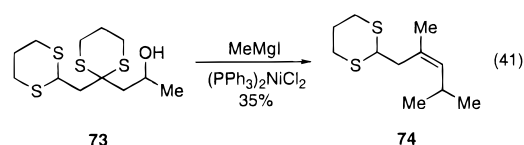
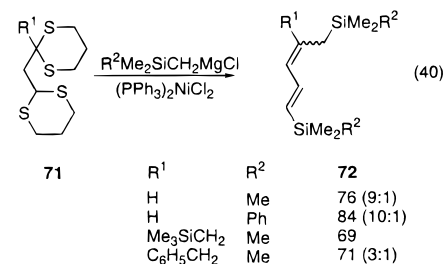
As discussed in section IV.B, 1,3-bisdithioacetals derived from diketones undergo cross-coupling reactions to give homoallylic dithioketals. Interestingly, when one of these two sulfur heterocycles is derived from an aldehyde group, treatment of these substrates **71** with RMe₂SiCH₂MgCl (R = Me and Ph) under similar conditions affords the corresponding silyl-substituted dienes **72** in good yields (eq 40).⁸² In a similar manner, the reaction of **73** with MeMgI

Table 22. Ni(acac)₂-Catalyzed Cross-Coupling Reaction of Alkyl Iodides with Dialkylzinc Reagents in the Presence of Cocatalyst^{a,b}

R ¹	R ²	% yield
PhS(CH ₂) ₃	C ₅ H ₁₁	71
PivO(CH ₂) ₅	C ₅ H ₁₁	78
PivO(CH ₂) ₆	C ₅ H ₁₁	59
PhCO(CH ₂) ₃	C ₅ H ₁₁	88
	PivO(CH ₂) ₃	76
	myrtanyl	66
PhCO(CH ₂) ₅	myrtanyl	74
4-MeOC ₆ H ₄ CO(CH ₂) ₃	C ₅ H ₁₁	71
3-CF ₃ C ₆ H ₄ CO(CH ₂) ₃	C ₅ H ₁₁	92
4-NCC ₆ H ₄ CO(CH ₂) ₃	C ₅ H ₁₁	81
BuCO(CH ₂) ₃	PivO(CH ₂) ₃	68
	EtO ₂ C(CH ₂) ₂	58
BuCO ₂ (CH ₂) ₂	C ₅ H ₁₁	76
EtCO ₂ (CH ₂) ₂	C ₅ H ₁₁	72
	PivO(CH ₂) ₃	60
	C ₅ H ₁₁	70
	PivO(CH ₂) ₃	68
	PivO(CH ₂) ₄	64
	C ₅ H ₁₁	67
	PivO(CH ₂) ₃	70
	C ₅ H ₁₁	78
	PivO(CH ₂) ₃	70
	PivO(CH ₂) ₅	67

^a Cocatalyst: *m*-trifluoromethylstyrene, acetophenone, or ethyl crotonate. ^b References 86–88.

in the presence of the nickel catalyst yields **74** (eq 41).⁹¹



VI. Conclusions

The chemistry described herein summarizes recent developments in the transition metal-catalyzed reac-

tions of unactivated aliphatic C–X bonds. Under appropriate conditions, simple alkyl iodides undergo a variety of cross-coupling, carbonylation, and olefin insertion reactions leading to carbon–carbon bond formation. For less reactive C–X bonds, specially designed substrates are normally required. This includes activation by an α -heteroatom substituent which will weaken the corresponding C–X bonds and enable the transition metal-catalyzed reaction to be more facile. Alternatively, chelation has served as a powerful tool for the activation of a number of C–X bonds. By using this strategy, dithioacetals as well as alkyl halides can successfully couple with nucleophiles in the presence of a nickel catalyst. The investigation is still in the preliminary stages, and scope for future development emanating from the present research abounds.

VII. Acknowledgments

This work has been supported by the National Science Council of the Republic of China.

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CR990272O