ACCOUNTS
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Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π-Carbon Ligand(s)

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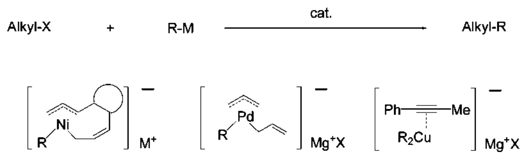
CONSPECTUS



Transition metal-catalyzed cross-coupling reactions of organic halides and pseudo-halides containing a C−X bond (X = I, Br, Cl, OTf, OTs, etc.) with organometallic reagents are among the most important transformations for carbon−carbon bond formation between a variety of sp, sp^2, and sp^3-hybridized carbon atoms.

In particular, researchers have widely employed Ni- and Pd-catalyzed cross-coupling to synthesize complex organic structures from readily available components. The catalytic cycle of this process comprises oxidative addition, transmetalation, and reductive elimination steps. In these reactions, various organometallic reagents could bear a variety of R groups (alkyl, vinyl, aryl, or allyl), but the coupling partner has been primarily limited to sp and sp^2 carbon compounds: alkynes, alkenes, and arenes. With alkyl coupling partners, these reactions typically run into two problems within the catalytic cycle. First, oxidative addition of alkyl halides to a metal catalyst is generally less efficient than that of aryl or alkenyl compounds. Second, the alkylmetal intermediates formed tend to undergo intramolecular β-hydrogen elimination.

In this Account, we describe our efforts to overcome these problems for Ni and Pd chemistry. We have developed new catalytic systems that do not involve M(0) species but proceed via an anionic complex as the key intermediate. For example, we developed a unique cross-coupling reaction of alkyl halides with organomagnesium or organozinc reagents catalyzed by using a 1,3-butadiene as the additive. This reaction follows a new catalytic pathway: the Ni or Pd catalyst reacts first with R−MgX to form an anionic complex, which then reacts with alkyl halides. Bis-dienes were also effective additives for the Ni-catalyzed cross-coupling reaction of organozinc reagents with alkyl halides. This catalytic system tolerates a wide variety of functional groups, including nitriles, ketones, amides, and esters.

In addition, we have extended the utility of Cu-catalyzed cross-coupling reactions. With 1-phenylpropyne as an additive, Cu-catalyzed reactions of alkyl chlorides, fluorides, and mesylates with Grignard reagents proceed efficiently.

These new catalytic reactions use π-carbon ligands such as π-allyl units or alkynes instead of heteroatom ligands such as phosphines or amines. Overall, these reactions provide new methodology for introducing alkyl moieties into organic molecules.

Introduction

Transition metal-catalyzed cross-coupling reactions of organic halides and pseudo-halides containing a C−X bond (X = I, Br, Cl, OTf, OTs, etc.) with organometallic reagents are among the most important transformations for carbon−carbon bond formation between a variety of sp, sp^2, and sp^3-hybridized carbon atoms.[1] For constructing new alkyl chains, of particular note are the Pd- and Ni-catalyzed cross-couplings using alkyl Grignard reagents and alkylzincs[2] and the Cu mediated cross-couplings, especially the Cu-catalyzed version permitting alkyl−alkyl coupling of wide applicability.[3] During the past decade, remarkable progress has been brought about in cross-coupling using alkyl halides by many groups using various transition metal catalysts.[4] Alkyl halides have now become even more promising candidates as substrates in transition metal catalyzed reactions.

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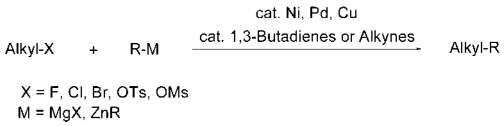
Transition metal complexes are usually classified broadly into three groups: neutral, cationic, and anionic complexes. The former two have been widely used as catalysts for organic synthesis at both bench and industrial scale, while synthetic applications of anionic complexes is less well-developed. Anionic complexes formed by the reaction of neutral complexes with organometallic reagents possess high electron densities. Consequently, it is expected that the nucleophilicity at the metal center or π-carbon ligands, as well as the electron-donating ability of the anionic complexes, would be enhanced in comparison with the corresponding neutral complexes. Our interest was to create new catalytic systems for transition metal-catalyzed cross-coupling reactions using alkyl halides by use of an anionic complex. During the course of this study, we have demonstrated that an anionic Ni, Pd, or Cu complex plays an important role in cross-coupling reactions of alkyl halides with Grignard or organozinc reagents in the presence of a π-carbon ligand (Scheme 1).

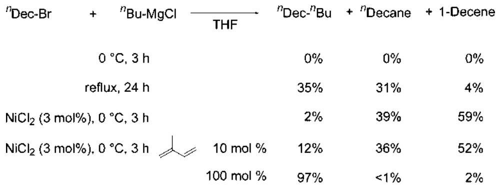
SCHEME 1. Ni-, Pd- or Cu-Catalyzed Cross-Coupling Reaction Using Alkyl Halides in the Presence of a π-Carbon Ligand



Ni-Catalyzed Cross-Coupling Reaction Using Alkyl Halides in the Presence of 1,3-Butadiene

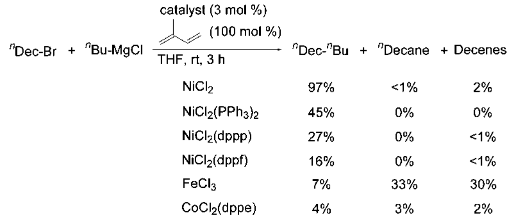
n-Decyl bromide did not react with *n*-butylmagnesium chloride at 0 °C but gave 35% yield of cross-coupling product under reflux conditions along with 31% yield of *n*-decane and 4% yield of 1-decene (Scheme 2). When the reaction was carried out in the presence of $NiCl_2$ as a catalyst, tetradecane was obtained in only 2% yield, and significant amounts of decane and decenes were formed. However, when isoprene was added to this system, a big change occurred and, on increasing the amount of isoprene, the yield of cross-coupling product increased and the formation of decane and decene was suppressed.[5]

SCHEME 2. Effect of Isoprene as an Additive



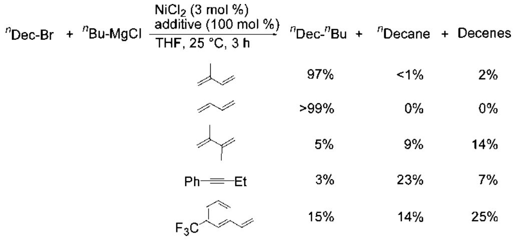
As shown in Scheme 3, the use of nickel complexes bearing phosphine ligands, such as $NiCl_2(PPh_3)_2$, $NiCl_2$(dppp), and $NiCl_2$(dppf) resulted in the decrease of yields of tetradecane. Under similar conditions, $FeCl_3$ and $CoCl_2$(dppe) were ineffective.

SCHEME 3. Effect of Catalysts



The effect of additives is summarized in Scheme 4. Unsubstituted 1,3-butadiene shows the highest activity for this cross-coupling reaction. 2,3-Dimethyl-1,3-butadiene, alkynes, and alkenes are far less effective under the same conditions. Optimization of the reaction revealed that use of 1 mol % $NiCl_2$ and 10 mol % 1,3-butadiene based on the halides at 0 °C afforded desired coupling products quantitatively in 30 min.

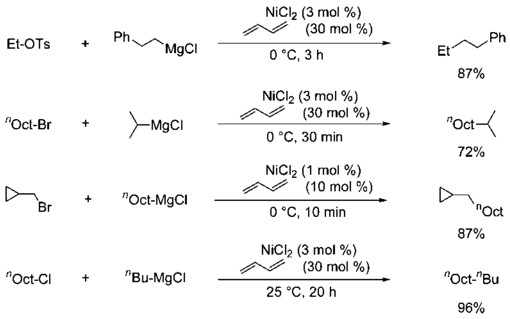
SCHEME 4. Effect of π-Carbon Ligands



Aryl and secondary alkyl Grignard reagents also afforded the corresponding products in moderate to good yields. This cross-coupling reaction proceeds efficiently by using alkyl tosylates (Scheme 5). Reaction of (bromomethyl)cyclopropane with *n*-Oct-MgCl gave nonylcyclopropane as the sole coupling product in 87% yield without formation of 1-dodecene, which may arise from ring-opening of the cyclopropylmethyl radical.[6] This result rules out a radical mechanism.[7] Interestingly, alkyl chlorides can also undergo this cross-coupling reaction, giving rise to the desired products in high yields. This is the first example of cross-coupling reactions using unactivated alkyl chlorides catalyzed by transition metals.[8] The present catalytic system is highly advantageous, particularly for large-scale production, since the reaction proceeds efficiently using less expensive alkyl chlorides as the reagent, $NiCl_2$ as the catalyst, and 1,3-butadiene as the additive instead of using phosphines or other heteroatom ligands.

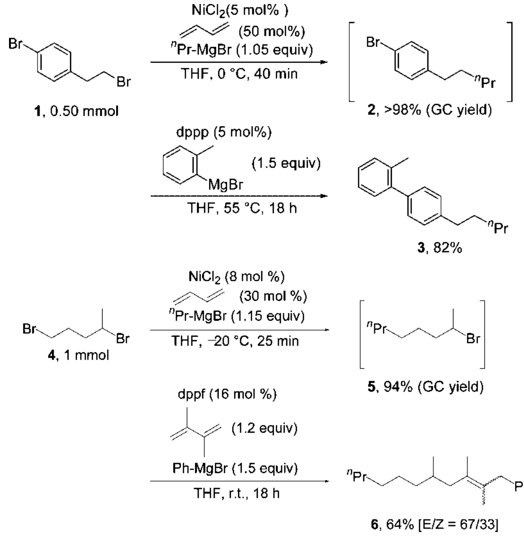
It is noteworthy that (sp^2)C−Br bonds are tolerant to the present system. This remarkable difference in reactivity between (sp^3)C−Br bond and (sp^2)C−Br bond prompted us to perform a site-selective sequential cross-coupling reaction

SCHEME 5. Scope of Ni-Catalyzed Cross-Coupling Using Alkyl Halides



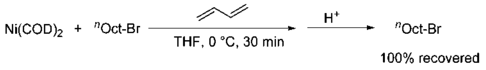
using dibromide **1** (Scheme 6). Into a solution of **2** prepared in situ from **1** according to our method were added dppp (5 mol %) and *o*-tolyl Grignard reagent (0.75 mmol). After the mixture was stirred at 55 °C for 18 h, the desired coupling product **3** was obtained in 82% yield, in which *n*-propyl and *o*-tolyl groups are introduced site selectively to the phenethyl skeleton.

SCHEME 6. Site-Selective Seqential Cross-Coupling Using Unsymmetrical Dibromides



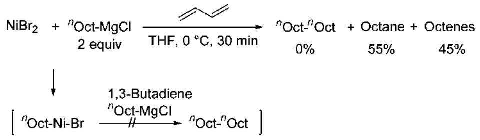
No reaction took place with secondary alkyl bromides under similar conditions as in Scheme 5. This reactivity allows the successful synthesis of 2-octyl bromide (**5**) in high yield by using 1,4-dibromopentane and *n*-propyl Grignard reagent (Scheme 6). As a synthetic application of this reaction, **5** was subjected to successive C−C bond formation by Ni-catalyzed three-component coupling developed separately.[9] Into a solution of **5** prepared in situ from **4** were added dppf (16 mol %), 2,3-dimethyl-1,3-butadiene (1.2 mmol), and Grignard reagent (1.5 mmol). After the reaction was stirred at 25 °C for 18 h, the corresponding three-component coupling product **6** was obtained in 64% yield (Scheme 6).

To shed light on the mechanism, we carried out a stoichiometric reaction of $Ni(COD)_2$ with *n*-decyl bromide in the presence of isoprene. After the reaction was stirred at 25 °C for 30 min, *n*-decyl bromide was recovered unchanged (eq 1). This result may imply that the present coupling reaction does not involve a process of oxidative addition of alkyl halides to Ni(0) giving alkyl−Ni−X under these conditions.



(1)

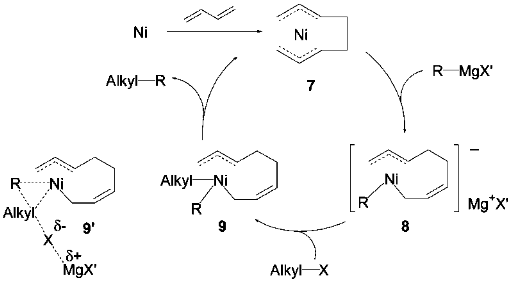
We then performed a reaction of $NiBr_2$ with 2 equiv of *n*-octylmagnesium chloride in the presence of 1,3-butadiene at 25 °C for 15 min. Octane and 1-octene were formed in 55% and 45% yields, respectively; however, the homocoupling product, *n*-hexadecane, was not obtained. This result also suggests that our cross-coupling reaction does not involve an oxidative addition intermediate (*n*-Oct−Ni−Br), which should arise from a reaction of $NiBr_2$ with *n*-octylmagnesium chloride (eq 2).



(2)

A proposed reaction pathway is depicted in Scheme 7. Ni(0) reacts with 2 molar amounts of 1,3-butadiene to afford the bis(η^3-allyl)nickel complex **7**,[10] which reacts with Grignard reagents to form the anionic bis(η^1,η^3-allyl)nickel complex **8**.[11] This complexation might enhance the nucleophilicity of Ni toward alkyl halides. A coupling product is formed by nucleophilic substitution of alkyl halides by the attack of the nickel in **8** yielding the dialkylnickel complex **9**, which undergoes reductive elimination to give the product or direct substitution via **9′**. In this system, cationic magnesium of the nickelate **8** would act as Lewis acid and accelerate the cleavage of C−X bonds by a strong Mg−X interaction. 1,3-Butadienes play an important role to convert Ni(0) to Ni(II) complex **7**, which is inert toward organic halides but readily reacts with R−MgX′ to form an anionic complex **8**. Complex **8** is coordinately saturated, and thus, β-hydrogen elimination process is suppressed. 2,3-Dimethyl-1,3-butadiene can also form a similar bis(η^3-allyl)nickel complex, but it is thermodynamically less stable than the complexes of 1,3-butadiene or isoprene and cannot promote the catalytic reaction. This is supported by the evidence that rates of Ni-catalyzed dimerization of butadienes, which involves similar bis-π-allyl Ni intermediates, decrease in the order 1,3-butadiene > 2-methyl-1,3-butadiene > 2,3-dimethyl-1,3-butadiene. Besides, the 2,3-dimethyl-1,3-butadiene complex might be less reactive toward R–MgX′ due to steric reasons hindering formation of anionic complexes.

SCHEME 7. Proposed Catalytic Cycle for the Case of 1,3-Butadiene as an Additive



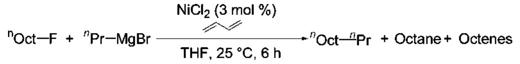
As shown in Scheme 7, the present reaction proceeds via a new catalytic pathway; that is, the Ni catalyst in this system reacts first with R–MgX′ to form an anionic complex and then with alkyl halides. This is in large contrast to conventional cross-coupling reactions using Ni or Pd, where low-valent metals react first with halides and then with R–MgX′.

Ni-Catalyzed Cross-Coupling Reaction Using Alkyl Fluorides in the Presence of 1,3-Butadiene

The successful result of cross-coupling reaction using alkyl chlorides prompted us to examine alkyl fluorides as the substrate. Theoretical calculations by the G2 method using Gaussian 98 program on the thermodynamic properties of coupling reaction (Me–X + R–MgCl to Me–R + X–MgCl) suggests that alkyl fluorides are not unfavorable energetically as substances for reactions with R–MgCl. Calculated bond energies of X–MgCl are 142, 112, and 101 kcal/mol and those of Me–X are 112, 85, and 74 kcal/mol for X = F, Cl, and Br, respectively. Consequently, energy differences between these two bonds for F, Cl, and Br are similar (30, 28, and 27 kcal/mol, respectively), indicating that the formation of a strong F–MgCl bond can compensate for destabilization arising from C–F bond cleavage.

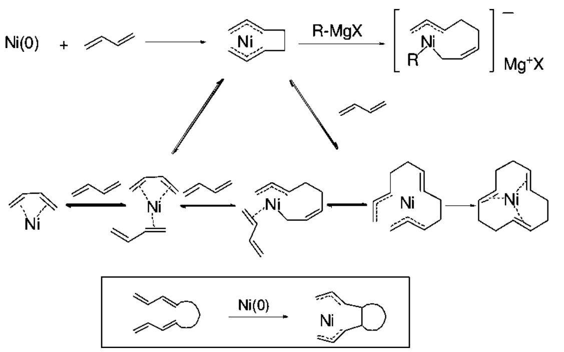
The reaction of *n*-octyl fluoride with *n*-PrMgBr did not take place at rt even in the presence of Ni catalysts such as $(PPh)_3NiCl_2$, $(dppf)NiCl_2$, and $NiCl_2$. Addition of 1,3-butadiene was also found to be effective giving rise to cross-coupling products (Scheme 8). On increasing the amount of 1,3-butadiene up to 100 mol %, the yield of undecane improved to 64%. However, further increase of 1,3-butadiene did not lead to improvement of the product yield.[12] This is probably because, under high concentrations of 1,3-butadiene, Ni(0) reacts with more than two 1,3-butadiene molecules to give nickel–butadiene trimer complexes resulting in low concentrations of bis(η^3-allyl)nickel complex (Scheme 9).[13]

SCHEME 8. Cross-Coupling Reaction of Alkyl-F

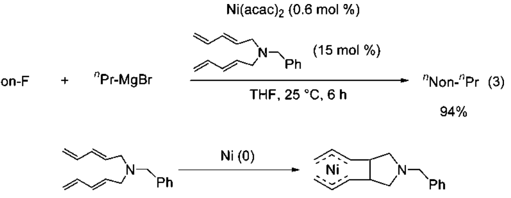


(mol %)			
0	0%	0%	0%
10	9%	1%	0%
100	64%	4%	2%
400	65%	3%	2%

SCHEME 9. Reaction of Ni(0) with 1,3-Butadiene and Tetraenes

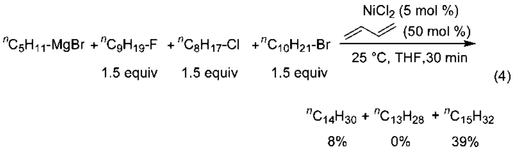


Since it is known that tetraenes react with Ni(0) species exclusively to form bis(η^3-allyl)nickel complexes, we examined the effect of tetraene as an additive.[14] The yield was dramatically improved by the use of only 0.6 mol % of Ni catalyst and 15 mol % of tetraene **10** (eq 3).[15] This result provides supporting evidence for the intermediary of bis(η^3-allyl)nickel complexes.



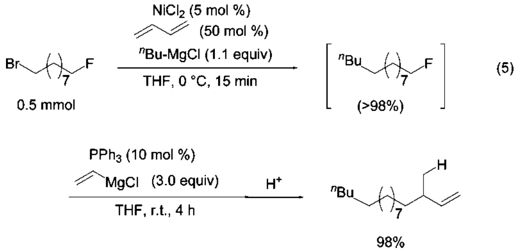
10

We then examined the relative reactivities of alkyl halides (RX; X = F, Cl, Br) by competitive experiments using n-$C_5H_{11}MgBr$. The reactivities of alkyl halides increase in the order chloride < fluoride < bromide (eq 4). When this reaction was carried out at 0 °C, the selective formation of *n*-pentadecane from decyl bromide was observed. The strong interaction between leaving F anion and Mg cation at the transition state to form **9** from **8** or as exemplified by **9′** in Scheme 7 would explain the rapid reaction of alkyl fluorides in comparison to alkyl chlorides where a much weaker Cl–Mg interaction is expected. As a related system, for the reaction of alkyl-X with R_2CuLi, it is proposed that interaction between Li and X plays an important role in C–X bond fission.[16]



(4)

This reactivity allows selective synthesis of 1-tridecyl fluoride by the cross-coupling reaction of 1-fluoro-9-bromononane with *n*-BuMgCl. We undertook sequential C−C bond formation by successive Ni-catalyzed alkylative dimerization of vinyl Grignard reagents using thus formed alkyl fluoride (eq 5).[17] Into a THF solution of tridecyl fluoride formed in situ from 1-bromo-9-fluorononane were added an excess amount of vinyl Grignard reagent (1.5 mmol) and PPh_3 (10 mol %). After the reaction was stirred at 25 °C for 4 h followed by quenching with 1 N HCl, the desired coupling product 3-methylhexadecene was obtained in 98% yield.



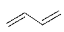
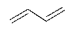
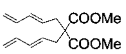
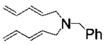
(5)

Ni-Catalyzed Cross-Coupling Using Organozinc Reagents

A serious drawback of the cross-coupling reaction using Grignard reagents is the limited tolerance of functional groups due to the high reactivity of Grignard reagents. Thus, we tried to extend this catalytic system to organozinc reagents instead of Grignard reagents.[18] Although our Ni-butadiene system could be applied to Negishi-type cross-coupling reactions, only moderate yields of coupling products were obtained even in the presence of large amounts of butadiene. We could also solve this problem again by employing tetraenes as additives (Scheme 10).

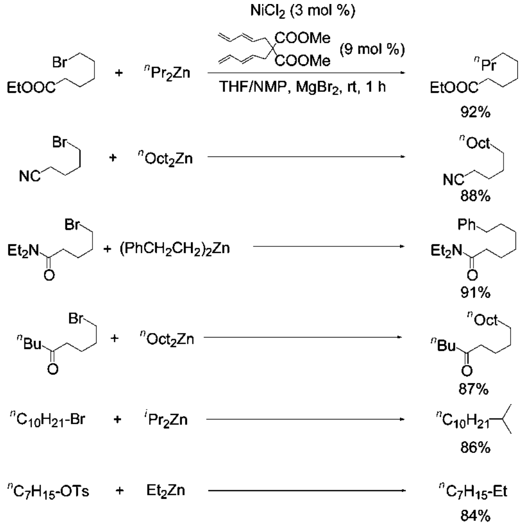
SCHEME 10. Ni-Catalyzed Cross-Coupling Reaction Using Et_2Zn

$$^{n}\text{Dec-Br} + Et_2Zn \xrightarrow[\text{THF/NMP, MgBr}_2\text{, rt}]{\text{NiCl}_2\text{ (3 mol \%)}} {}^{n}\text{Dec-Et} + {}^{n}\text{Decane} + \text{Decenes}$$

additive	mol%	time			
none	0	48 h	0%	0%	0%
	100	48 h	45%	20%	11%
	400	48 h	73%	2%	2%
	9	1 h	>99%	0%	0%
	9	1 h	>99%	0%	0%

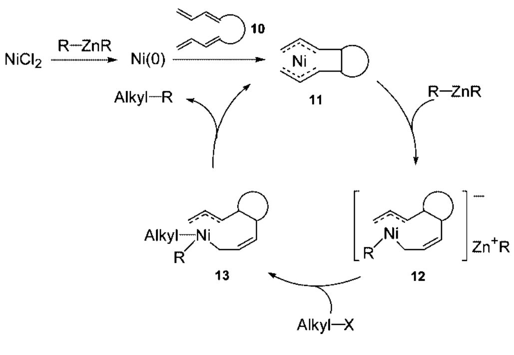
This catalytic system tolerates ketones, esters, nitriles, and amides. Secondary alkylzinc and alkyl tosylate can also undergo this reaction efficiently under mild conditions (Scheme 11).

SCHEME 11. Ni-Catalyzed Cross-Coupling Reaction Using Organozinc Reagents



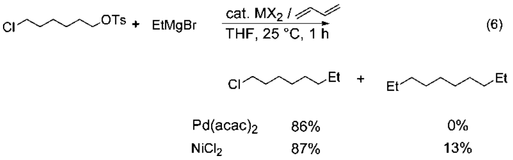
A proposed reaction pathway is shown in Scheme 12 for the case of organozinc reagents. Bis(η^3-allyl)nickel complex **11** is formed by the oxidative cycloaddition of Ni(0) with two butadiene moieties of a tetraene **10**. Organozinc reagent attacks **11** to generate anionic (η^1,η^3-allyl)nickel complex **12**, which then reacts with alkyl halides to give **13**. Subsequent reductive elimination affords the coupling product along with **11** to complete the catalytic cycle. Selective and efficient formation of **11** from Ni(0) and **10** in comparison to the case of 1,3-butadiene would facilitate the generation of ate complex **12**. These tetraene ligands have broadened the scope of reagents, both of the alkyl halides and of the organometallic reagents, and dramatically improved the efficiency of the Ni-catalyzed cross-coupling reaction.

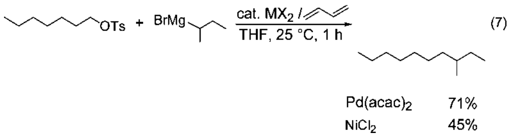
SCHEME 12. Proposed Catalytic Cycle for the Case of a Tetraene as an Additive



Pd-Catalyzed Cross-Coupling Reaction Using Alkyl Halides in the Presence of 1,3-Butadiene

Palladium also catalyzes the cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents in the presence of 1,3-butadiene as an additive.[19] Because alkyl chlorides were somewhat more sluggish in Pd-catalyzed reactions, selective synthesis of the alkyl chloride from 6-chlorohexyl tosylate could be achieved (eq 6). When $NiCl_2$ was used as catalyst under the same conditions, the dialkylated product was obtained in 13% yield. Pd catalyst afforded better yields than Ni for the reaction of aryl and *sec*-alkyl Grignard reagents (eq 7). This Pd-catalyzed cross-coupling would proceed by a similar pathway via the corresponding bis(η^3-allyl)palladium complex as proposed for the Ni-catalyzed reaction shown in Scheme 7.





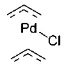
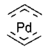
Cross-Coupling Reaction Using Bis(η^3-allyl)metal Complexes as Catalysts

Cross-coupling of alkyl bromides or tosylates with Grignard reagents proceeds in the presence of a catalytic amount of bis(η^3-allyl)nickel or -palladium complexes as a catalyst without using butadienes (Scheme 13).[20] Bis(η^3-allyl)palladium complex afforded a moderate yield of cross-coupling product, and bis(η^3-allyl)nickel catalyst showed much higher activity. It was also revealed that two allyl ligands are essential to attain high yields of the cross-coupling products. However, $PdCl_2$ and (η^3-allyl)palladium chloride gave less than 10% yield of cross-coupling product along with significant amounts of decane and decenes. These results suggest that while both allyl groups on the metal play important roles, the ethylene tether (CH_2CH_2) between two allyl ligands of **7** in Scheme 7 is not essential. A proposed reaction pathway similar to Scheme 7 is depicted in Scheme 14.

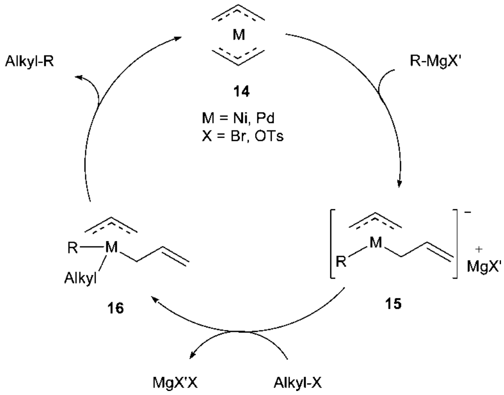
To confirm the validity of this pathway, we examined the stoichiometric reaction of alkyl halides with the anionic complex **15**. Into a solution of bis(η^1,η^3-allyl)palladate complex (**15′**),[21] generated by the reaction of bis(η^3-allyl)palladium[22] with EtMgBr, was added *n*-hexyl bromide at −60 °C. After 2 h at the same temperature, NMR analysis showed formation of nearly equal amounts of octane and bis(η^3-allyl)palladium (**14′**) (eq 8). It should be noted that no evidence for the formation of coupling products involving an allyl group such as 1-pentene or 1-nonene was detected, suggesting that alkyl−alkyl reductive elimination proceeds exclusively from **16**. This fact is consistent with evidence that reductive elimination of R-H from $(PPh_3)_2Pt(H)R$ proceeds preferentially with alkyl groups compared with an allyl group.[23]

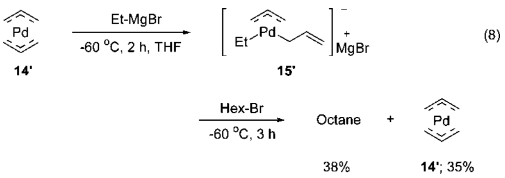
SCHEME 13. Bis(η^3-allyl)metal-Catalyzed Cross-Coupling Reaction

$$^{n}\text{Dec-Br} + \underset{1.3\ \text{equiv}}{^{n}\text{Bu-MgCl}} \xrightarrow[0\ ^{\circ}\text{C},\ 3\ \text{h}]{\text{cat. (10 mol\%)}} {}^{n}\text{Dec-}^{n}\text{Bu} + \text{Decane} + \text{Decenes}$$

cat.	yield (%)		
$PdCl_2$	3	54	26
$(PPh_3)_2PdCl_2$	2	1	1
	10	26	23
	58	13	12
	94	4	2

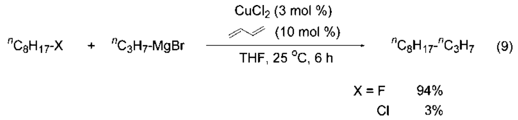
SCHEME 14. Proposed Catalytic Cycle for the Case of Bis(η^3-allyl)metal as an Catalyst





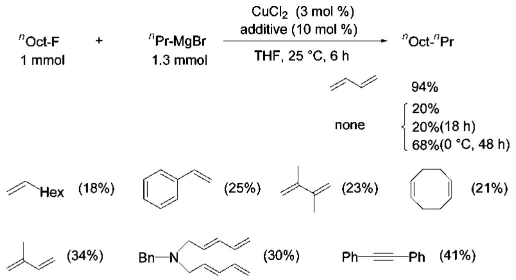
Cu-Catalyzed Cross-Coupling Reaction Using Alkyl Chorides and Fluorides

Cu-catalyzed cross-coupling reaction of alkyl halides or sulfonates with alkyl Grignard reagents has become one of the most straightforward methods for constructing methylene chains.[3] However, no successful application to alkyl chlorides and fluorides is available.[24] This is probably due to the strong C−Cl or C−F bond compared with C−I and C−Br bonds. In 2003, we reported the first example of Cu-catalyzed cross-coupling reactions of nonactivated alkyl fluorides with Grignard reagents in the presence of 1,3-butadienes as additives under mild conditions (eq 9).[12] Interestingly, alkyl chlorides are less reactive than fluorides and gave only 3% yields of the cross-coupling products from octyl chloride under the same conditions of eq 9.



For the cross-coupling reaction of primary alkyl fluorides with Grignard reagents in the presence of 1,3-butadiene, $CuCl_2$ and CuCl showed the highest activities. The coupling product was obtained in 20% yield even in the absence of 1,3-butadiene at 25 °C for 6 h; however, prolonged reaction times did not improve the yield (Scheme 15). Isoprene, tetraene **10**, and diphenylacetylene were less effective under these conditions. 1-Octene, styrene, 2,3-dimethyl-1,3-butadiene, and 1,5-cyclooctadiene were also ineffective. When the reaction was carried out at −20 °C, the coupling reaction proceeded slowly without significant loss of catalytic activity even in the absence of 1,3-butadiene resulting in formation of undecane in 68% yield after 48 h.

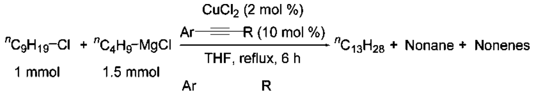
SCHEME 15. Cu-Catalyzed Cross-Coupling Reactions Using Alkyl Fluorides



In 2007, we reported that Cu-catalyzed cross-coupling reactions of alkyl chlorides with primary, secondary, and tertiary alkyl and phenyl Grignard reagents proceeded efficiently in the presence of 1-phenylpropyne as additive.[25] For example, *n*-nonyl chloride reacted with *n*BuMgCl in the presence of a catalytic amount of $CuCl_2$ and 1-phenylpropyne under THF reflux conditions for 6 h to give tridecane in >98% yield. In the absence of 1-phenylpropyne, tridecane was obtained in only 3% yield and 95% of *n*-nonyl chloride was recovered. Li_2CuCl_4 alone was not effective either toward *n*-nonyl chloride; however, in the presence of 1-phenylpropyne, 86% yield of tridecane was obtained in refluxing THF.

The effects of other 1-arylalkynes in the present cross-coupling reaction were examined (Scheme 16). On increasing the length of the alkyl chain from methyl to butyl, the yield of tridecane gradually decreased. The *o*-methyl substituent on the aryl ring decreased the yield; however, the *p*-methyl substituent did not affect the reaction. These results suggest that the present cross-coupling reaction is sensitive to steric hindrance around the C−C triple bond of alkynes.

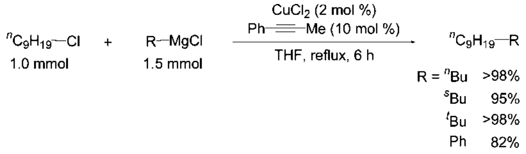
SCHEME 16. Effect of Internal Alkyne



Ar	R	$^nC_{13}H_{28}$	Nonane	Nonenes
Ph	CH_3	98%	1%	0%
	$^nC_9H_{19}$	13%	12%	1%
	$^tC_4H_9$	5%	15%	2%
o-tol	C_2H_5	6%	18%	2%
p-tol	C_2H_5	82%	5%	3%

As illustrated in Scheme 5, Ni-catalyzed cross-coupling reactions of a primary alkyl chloride with *n*-BuMgCl in the presence of 1,3-butadiene afforded a good yield of the product. However, this reaction using alkyl chlorides cannot be applied to *s*- and *t*-butyl and aryl Grignard reagents. On the other hand, Cu-catalyzed cross-coupling reactions proceed efficiently using a variety of alkyl and phenyl Grignard reagents, as shown in Scheme 17. In addition, all yields are higher than 98% yield for n-C_9H_{19}−X (X = F, Br, and OTs[26]) regardless of the nature of the Grignard reagent. However, methyl and vinyl Grignard reagents did not give coupling products in good yields.

SCHEME 17. Cu-Catalyzed Cross-Coupling Reactions Using 1-Phenyl-1-Propyne as an Additive



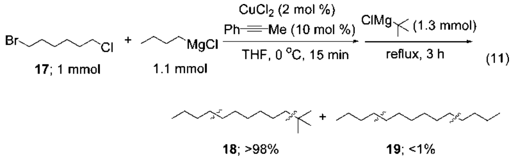
To examine the relative reactivities of alkyl halides (alkyl-X; X = F, Cl, Br) in the present reaction, we performed the following competitive experiments. To a mixture of equimolar amounts of *n*-octyl fluoride, *n*-nonyl chloride, and *n*-decyl bromide were added $CuCl_2$, 1-phenylpropyne, and a THF solution of *n*-BuMgCl. After the reaction was stirred for 30 min in THF at reflux, GC analysis of the resulting mixture indicated the selective formation of tetradecane in 98% yield along with 2% yield of dodecane (eq 10). A similar reaction using only alkyl fluorides and chlorides gave dodecane and tridecane in 95% and 5% yields, respectively. These results indicate the reactivity of alkyl halides to be in the order chloride < fluoride < bromide.

We then attempted a site-selective sequential cross-coupling reaction using dihaloalkanes. When a reaction of

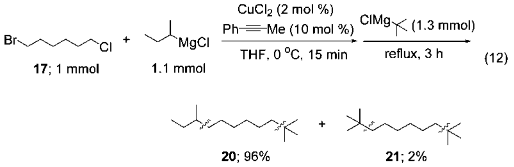
$$\underset{\text{1 mmol}}{{}^nC_4H_9\text{-MgCl}} + \underset{\text{5 mmol}}{{}^nC_8H_{17}\text{-F}} + \underset{\text{5 mmol}}{{}^nC_9H_{19}\text{-Cl}} + \underset{\text{(5 mmol)}}{{}^nC_{10}H_{21}\text{-Br}} \xrightarrow[\text{THF, reflux, 30 min}]{\text{CuCl}_2\text{ (2 mol \%)},\ \text{Ph}{\equiv}\text{Me (10 mol \%)}} \quad (10)$$

	${}^nC_4H_9\text{-}{}^nC_8H_{17}$	${}^nC_4H_9\text{-}{}^nC_9H_{19}$	${}^nC_4H_9\text{-}{}^nC_{10}H_{21}$
with ${}^nC_{10}H_{21}\text{-Br}$	2%	0%	98%
without ${}^nC_{10}H_{21}\text{-Br}$	95%	5%	–

1-bromo-6-chlorohexane (**17**) with *n*-BuMgCl (1.1 equiv) was conducted in the presence of catalytic amounts of $CuCl_2$ and 1-phenylpropyne at 0 °C for 15 min followed by successive addition of *t*-BuMgCl (1.3 equiv), nearly quantitative yield of 2,2-dimethyldodecane (**18**) was obtained along with less than 1% of tetradecane (**19**) (eq 11). The use of *s*-BuMgCl instead of *n*-BuMgCl under the identical conditions as in eq 11 produced 2,2,9-trimethylundecane (**20**) in 96% yield accompanied by 2% yield of 2,2,9,9-tetramethyldecane (**21**) (eq 12).

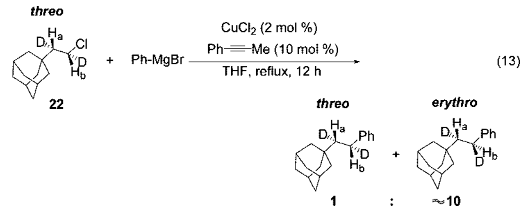


(11)



(12)

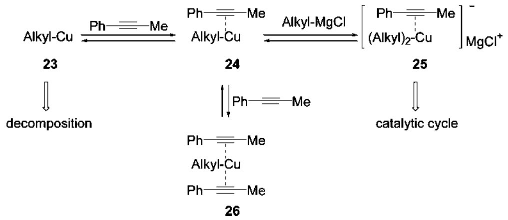
Stereochemistry of the reaction of *primary* alkyl fluoride was examined using pure α,*β*-d_2-*β*-adamantylethyl chloride **22** and PhMgBr (eq 13). The ^{1}H NMR analysis of the products indicated that substitution occurs primarily with inversion of configuration with ca. 10:1 selectivity.[27] This result suggests that cross-coupling reactions of *primary* alkyl fluorides proceeds predominantly via an S_N2 mechanism.



(13)

Although the role of 1-phenylpropyne in the present catalytic reaction has not been clarified yet, a proposed reaction pathway is shown in Scheme 18. Coordination of alkynes to the thermally unstable alkylcopper(I) intermediates **23**[28] would form more stable alkyne−alkylcopper(I) complex **24**[29] and a bis(alkyne)copper(I) complex **26**.[30] The complex **26** might be a resting state of the catalyst, because high concentrations of alkynes retarded the reaction. Complexation of alkyne−alkylcopper(I) complex **24** with Grignard reagent forms an ate complex **25**, which would react with alkyl halides as a key species in the present cross-coupling reaction.[31]

SCHEME 18. A Proposed Reaction Pathway



Concluding Remarks

We have developed a unique cross-coupling reaction system using 1,3-butadiene derivatives, where the metal catalyst reacts first with R−MgX to form an anionic complex and then with alkyl halides. This is similar to Cu-catalyzed reactions but in strong contrast to conventional cross-couplings using Ni or Pd with phosphine ligands. We have also achieved the efficient Cu-catalyzed cross-coupling of alkyl chlorides by the use of 1-phenylpropane as an additive. The present catalytic systems have several advantages over conventional systems for large scale production since the reaction proceeds efficiently under mild conditions using less expensive Ni, Pd, and Cu salts as the catalysts and hydrocarbon additives instead of heteroatom ligands involving N, P, S, etc.

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FOOTNOTES

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REFERENCES

1 For recent extensive reviews, see: (a) Negishi, E. Palladium-Catalyzed Reactions Involving Reductive Elimination. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. I, pp 213−1119. (b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 1−916.

2 For seminal papers on Pd- or Ni-catalyzed alkylation with alkyl-MX ($M = Mg$, Zn), see: (a) Tamao, K.; Sumitani, K.; Kumada, M. Selective Carbon−Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickel−Phosphine Complexes. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Hayashi, T.; Konishi, M.; Kumada, M. Dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II): An Effective Catalyst for Cross-Coupling Reaction of a Secondary Alkyl Grignard Reagent with Organic Halides. *Tetrahedron Lett.* **1979**, *21*, 1871–1874. (c) Negishi, E.; Valente, L. F.; Kobayashi, M. Palladium-Catalyzed Cross-Coupling Reaction of Homoallylic or Homopropargylic Organozincs with Alkenyl Halides as a New Selective Route to 1,5-Dienes and 1,5-Enynes. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299.

3 (a) For a seminal paper on the reaction of alkyl Grignard reagents with alkyl electrophiles catalyzed by Li_2CuCl_4, see: Tamura, M.; Kochi, J. K. Copper-Catalyzed Coupling of Grignard Reagents and Alkyl Halides in Tetrahydrofuran Solutions. *J. Organomet. Chem.* **1972**, *42*, 205–228. (b) For Cu-promoted alkylation, see: Posner, G. H. Substitution Reactions Using Organocopper Reagents. *Org. React.* **1975**, *22*, 253–400. (c) For Cu-promoted and Cu-catalyzed alkylation, see: Lipshutz, B. H.; Sengupta, S. Organocopper Reagents: Substitution, Conjugate Addition, Carbo/Metallocupration, and Other Reactions. *Org. React.* **1992**, *41*, 135–631.

4 For reviews, see: (a) Cárdenas, D. J. Towards Efficient and Wide-Scope Metal-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018–3020. (b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. Transition Metal-Catalyzed Activation of Aliphatic C-X Bonds in Carbon-Carbon Bond Formation. *Chem. Rev.* **2000**, *100*, 3187–3204. (c) Cárdenas, D. J. Advances In Functional-Group-Tolerant Metal-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387. (d) Netherton, M. R.; Fu, G. C. Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides and Pseudohalides with Organometallic Compounds. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (e) Terao, J.; Kambe, N. Cross-Coupling Reaction of Alkyl Halides with Organometallic Reagents Using Transition-Metal Catalysts. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1192–1203. (f) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (g) Netherton, M. R.; Fu, G. C. Palladium-Catalyzed Cross-Coupling Reactions of Unactivated Alkyl Electrophiles with Organometallic Compounds. In *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Topics in Organometallic Chemistry; Springer: New York, 2005; pp 85−108. (h) Furstner, A.; Martin, R. Advances in Iron Catalyzed Cross Coupling Reactions. *Chem. Lett.* **2005**, *34*, 624–629.

5 Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Halides and Tosylates: Remarkable Effect of 1,3-Butadienes. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223.

6 Maillard, B.; Forrest, D.; Ingold, U. K. Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. 27. Isomerization of Cyclopropylcarbinyl to Allylcarbinyl. *J. Am. Chem. Soc.* **1976**, *98*, 7024–7026.

7 Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. Palladium-Catalyzed Alkyl-Alkyl Cross-Coupling Reaction of 9-Alkyl-9-BBN Derivatives with Iodoalkanes Possessing β-Hydrogens. *Chem. Lett.* **1992**, 691–694.

8 For seminal papers on cross-coupling reaction using alkyl chlorides, see: (a) Kirchhoff, J. H.; Dai, C.; Fu, G. C. A Method for Palladium-Catalyzed Cross-Couplings of Simple Alkyl Chlorides: Suzuki Reactions Catalyzed by $[Pd_2(dba)_3]/PCy_3$. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947. (b) Frisch, N.; Shaikh, A. C.; Zapf, A.; Beller, M. Palladium-Catalyzed Coupling of Alkyl Chlorides and Grignard Reagents. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059. (c) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.

9 Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. Nickel-Catalyzed Regioselective Three Component Coupling Reaction of Alkyl Halides, Butadienes, and Ar-M ($M = MgX$, ZnX). *Adv. Synth. Catal.* **2004**, *346*, 905–908.

10 Benn, R.; Büssemeier, B.; Holle, S.; Jolly, P. W.; Mynott, R.; Tkatchenko, I.; Wilke, G. Transition Metal Allyls: VI. The Stoichiometric Reaction of 1,3-Dienes with Ligand Modified Zerovalent-Nickel Systems. *J. Organomet. Chem.* **1985**, *279*, 63–86.

11 (a) Kaschube, W.; Pörschke, K. R.; Angermund, K.; Krüger, C.; Wilke, G. On the Lewis Acidity of Nickel(0). X. Diorganylmagnesium complexes of Nickel(0): $(TMEDA)MgCH_3(\mu\text{-}CH_3)Ni(C_2H_4)_2$. *Chem. Ber.* **1988**, *121*, 1921–1929. (b) Holle, S.; Jolly, P. W.; Mynott, R.; Salz, R. η^3-Allyl-Stabilized Ate Complexes of Nickel, Palladium and Platinum. *Z. Naturforsch., B: Anorg. Chem. Org. Chem.* **1982**, *37*, 675–676.

12 Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. Ni- or Cu-Catalyzed Cross-Coupling Reaction of Alkyl Fluorides with Grignard Reagents. *J. Am. Chem. Soc.* **2003**, *125*, 5646.

13 Tobisch, S. Structure-Reactivity Relationships in the Cyclo-oligomerization of 1,3-Butadiene Catalyzed by Zerovalent Nickel Complexes. *Adv. Organomet. Chem.* **2003**, *49*, 167–224.

14 Wender, P. A.; Tebbe, M. J. Nickel(0)-Catalyzed Intramolecular [4 + 4] Cycloadditions: 5. The Type II Reaction in the Synthesis of Bicyclo [5.3.1] Undecadienes. *Synthesis* **1991**, 1089–1094.

15 Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. Nickel-Catalyzed Cross-Coupling Reaction of Alkyl Halides with Organozinc and Grignard Reagents Using 1,3,8,10-Tetraenes as Additives. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182.

16 Nakamura, E.; Mori, S.; Morokuma, K. Mechanism of S_N2 Alkylation Reactions of Lithium Organocuprate Clusters with Alkyl Halides and Epoxides. Solvent Effects, BF_3 Effects, and Trans-Diaxial Epoxide Opening. *J. Am. Chem. Soc.* **2000**, *122*, 7294–7307.

17 Terao, J.; Watabe, H.; Kambe, N. Ni-Catalyzed Alkylative Dimerization of Vinyl Grignard Reagents Using Alkyl Fluorides. *J. Am. Chem. Soc.* **2005**, *127*, 3656–3657.

18 For seminal papers on transition metal catalyzed Negishi coupling using alkyl halides, see: (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. A New Nickel-Catalyzed Cross-Coupling Reaction Between sp^3 Carbon Centers. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723–2725. (b) Zhou, J.; Fu, G. C. Palladium-Catalyzed Negishi Cross-Coupling Reactions of Unactivated Alkyl Iodides, Bromides, Chlorides, and Tosylates. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (c) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α-Bromo Amides with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (d) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. Iron-Catalyzed Chemoselective Cross-coupling of Primary and Secondary Alkyl Halides with Arylzinc Reagents. *Synlett* **2005**, *11*, 1794–1798. (e) Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K. Novel Rh Catalysis in Cross-Coupling between Alkyl Halides and Arylzinc Compounds Possessing *ortho*-COX ($X = OR$, NMe_2, or Ph) Groups. *Org. Lett.* **2006**, *8*, 3037–3040. (f) Gong, H.; Sinisi, R.; Gagne, M. R. A Room Temperature Negishi Cross-Coupling Approach to C-Alkyl Glycosides. *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909.

19 Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. Pd-Catalyzed Cross-Coupling Reaction of Alkyl Tosylates and Bromides with Grignard Reagents in the Presence of 1,3-Butadiene. *Chem. Lett.* **2003**, *32*, 890–891.

20 Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. Cross-coupling of Alkyl Halides with Grignard Reagents Using Nickel and Palladium Complexes Bearing η-Allyl Ligand as Catalysts. *Chem. Commun.* **2007**, *825*, 827.

21 Henc, B.; Jolly, P. W.; Salz, R.; Wilke, G.; Benn, R.; Hoffmann, E. G.; Mynott, R.; Schroth, G.; Seevogel, K.; Sekutowski, J. C.; Krüger, C. Transition Metal Allyls: III. The $(\eta^3\text{-allyl})_2M$ Complexes of Nickel, Palladium and Platinum: Structural Considerations. *J. Organomet. Chem.* **1980**, *191*, 425–448.

22 (a) Jolly, P. W. η^3-Allylpalladium Compounds. *Angew. Chem., Int. Ed.* **1985**, *24*, 283–295. (b) Bogdanović, B.; Huckett, S. C.; Wilczok, U.; Rufińska, A. Organobimetallic Mg-Pd Complexes as Intermediates in the Formation of Amorphous MgPdCxHy from $Mg(C_2H_5)_2$ and $[Pd(\eta^3\text{-}C_3H_5)_2]$. *Angew. Chem., Int. Ed.* **1988**, *27*, 1513–1516. (c) Alberti, D.; Goddard, R.; Rufińska, A.; Pörschke, K.-R. π-Allyl Nickelate(II) and Palladate(II) Complexes. *Organometallics* **2003**, *22*, 4025–4029.

23 Abis, L.; Sen, A.; Halpern, J. Intramolecular Reductive Elimination of Alkanes from *cis*-Hydridoalkylbis(phosphine)platinum(II) Complexes. *J. Am. Chem. Soc.* **1978**, *100*, 2915–2916.

24 Ashby, E. C.; Lin, J. J. Reactions of New Organocuprates. 2. Substitution Reactions of Alkyl, Cycloalkyl, and Aryl halides with Lithium Trimethyldicuprate, Dilithium Trimethylcuprate, and Dilithium Pentamethyltricuprate. *J. Org. Chem.* **1977**, *42*, 2805–2808.

25 Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. Cu-Catalyzed Cross-Coupling Reaction of Grignard Reagents with primary-Alkyl Chlorides: Remerkable Effect of 1-Phenylpropyne. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089.

26 Burns, D. H.; Miller, J. D.; Chan, H. K.; Delaney, M. O. Scope and Utility of a New Soluble Copper Catalyst [CuBr-LiSPh-LiBr-THF]: A Comparison with Other Copper Catalysts in Their Ability to Couple One Equivalent of a Grignard Reagent with an Alkyl Sulfonate. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133.

27 (a) Lipshutz, B. H.; Wilhelm, R. S. Chemistry of Higher Order, Mixed Organocuprates. 4. The Stereochemical Outcome of Substitution Reactions at Unactivated Secondary Centers Using Organocopper Reagents. *J. Am. Chem. Soc.* **1982**, *104*, 4696–4698. (b) Guo, C.-y.; Brownawell, M. L.; San Filippo, J. *a*-Deuterium and Carbon-13 Kinetic Isotope Effects Associated with the S_N2 Displacement of Iodide and Tosylate by Lithium Organocuprates. *J. Am. Chem. Soc.* **1985**, *107*, 6028–6030. (c) Mori, S.; Nakamura, E.; Morokuma, K. Mechanism of S_N2 Alkylation Reactions of Lithium Organocuprate Clusters with Alkyl Halides and Epoxides. Solvent Effects, BF_3 Effects, and Trans-Diaxial Epoxide Opening. *J. Am. Chem. Soc.* **2000**, *122*, 7294–7307.

28 Miyashita, A.; Yamamoto, T.; Yamamoto, A. Thermal Stability of Alkylcopper(I) Complexes Coordinated with Tertiary Phosphines. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1109–1117.

29 Schulte, P.; Behrens, U. Metallorganische Verbindungen des Kupfers und Silbers XV1. Synthese und Struktur von Alkin-Silber(I)-Komplexen des Typs[AgX(η^2-Cycloalkin)] ($X{=}NO_3$, NO_2, CN, BF_4, OSO_2CF_3, CH_3 COO, CF_3COO, Hexafluoracetylacetonat; Cycloalkin 3,3,6,6 Tetramethyl-1-thia-4-cycloheptin und 3,3,6,6-Tetramethyl-1-thia-4-cycloheptin-1,1-dioxid). *J. Organomet. Chem.* **1998**, *563*, 235–249.

30 Gröger, G.; Behrens, U.; Olbrich, F. Monomeric and Dimeric Cyclooctyne-Stabilized Complexes of Copper(I). *Organometallics* **2000**, *19*, 3354–3360.

31 (a) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; p 372. (b) Klunder, J. M.; Posner, G. H. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.;Pergamon: Oxford, U.K., 1991; Vol. 3, p 207. (c) Nakamura, E.; Mori, S.; Morokuma, K. Theoretical Studies on S_N2-Reaction of MeBr with $Me_2CuLi \cdot LiCl$. Solvent and Cluster Effects on Oxidative Addition/Reductive Elimination Pathway. *J. Am. Chem. Soc.* **1998**, *120*, 8273–8274.