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Cross-Coupling

Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions

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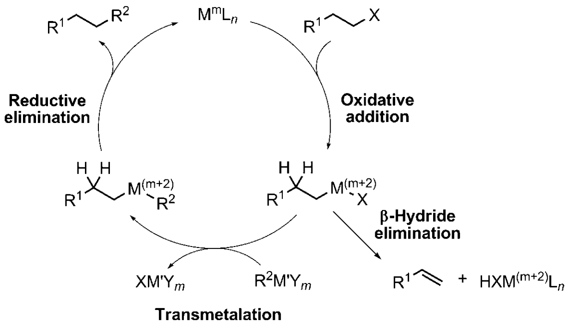
alkyl halides · cobalt · cross-coupling · iron · nickel

Enormous effort has gone into the development of metal-catalyzed cross-coupling reactions with alkyl halides as electrophilic coupling partners. Whereas a wide array of primary alkyl halides can now be used effectively in cross-coupling reactions, the synthetic potential of secondary alkyl halides is just beginning to be revealed. This Minireview summarizes selected examples of the use of secondary alkyl halides as electrophiles in cross-coupling reactions. Emphasis is placed on the transition metals employed, the mechanistic pathways involved, and implications in terms of the stereochemical outcome of reactions.

1. Introduction

Transition-metal-catalyzed reactions are widely used for carbon–carbon bond formation. The last few decades have seen huge advances in methodologies for the coupling of sp-, sp^2-, and sp^3-hybridized carbon nucleophiles with aryl or alkenyl electrophiles ($C(sp^2)-X$, in which X = I, Br, Cl, OMs, OTf, or N_2; Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl).[1] Metals such as palladium and nickel have played a central role in the development of these cross-coupling reactions and have shown wide applicability in the industrial synthesis of fine chemicals, pharmaceutically active compounds, and agricultural chemicals,[2] as well as in natural product synthesis.[3] Advances in the use of palladium and nickel can be attributed to their versatility and high functional-group tolerance, as well as the readiness and selectivity with which aryl and alkenyl electrophiles react (ease of oxidative addition and absence of β-hydride-elimination pathways).

Alkyl electrophiles containing β hydrogen atoms were originally seen as unsuitable substrates for transition-metal-catalyzed cross-coupling reactions. The oxidative addition of aliphatic C−X bonds to a metal center is considerably more difficult than the oxidative addition of aryl and alkenyl C−X bonds, as $C(sp^3)-X$ bonds are more electron-rich than $C(sp^2)-X$ bonds. The alkyl metal species that results is also substantially less stable than an aryl or alkenyl metal species owing to a lack of π electrons available to interact with the empty d orbitals of the metal center. This instability renders the alkyl metal intermediate prone to side reactions, such as β-hydride elimination or hydrodehalogenation, which can outcompete both intermolecular transmetalation and reductive elimination (Scheme 1).[4,5]



Scheme 1. Generalized catalytic cycle for the cross-coupling of alkyl electrophiles.

Since the ground-breaking studies of Kochi and Tamura,[6] Suzuki,[7] and Knochel,[8] the design of new catalyst systems has enabled the use of alkyl halides in cross-coupling reactions. A variety of transition metals, such as palladium, nickel, iron, cobalt, and copper, mediate the ready coupling of a wide range of primary alkyl halides with organometallic reagents containing zinc, boron, silicon, tin, and magnesium.[4b] In contrast, the cross-coupling of secondary alkyl halides remains a challenging task. The added steric hindrance of a secondary alkyl halide increases the energy barrier to oxidative addition and thus makes traditional transition-metal-catalyzed processes much more difficult.[9] Nevertheless, there has been a dramatic rise in the development of cross-coupling reactions of secondary alkyl halides, particularly in the last five years. The development of these

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new methodologies is significantly expanding the scope of transition-metal-catalyzed processes. Recent studies have investigated the stereochemical outcome of cross-coupling reactions and given insight into the reaction mechanisms. Asymmetric processes with racemic starting materials have also been developed. In this Minireview, we summarize recent important developments in this area with both activated and non-activated secondary electrophiles. Highlighted are the catalytic reactions with the most effective transition metals: nickel, iron, cobalt, and palladium. Each section is then further organized by reaction type.

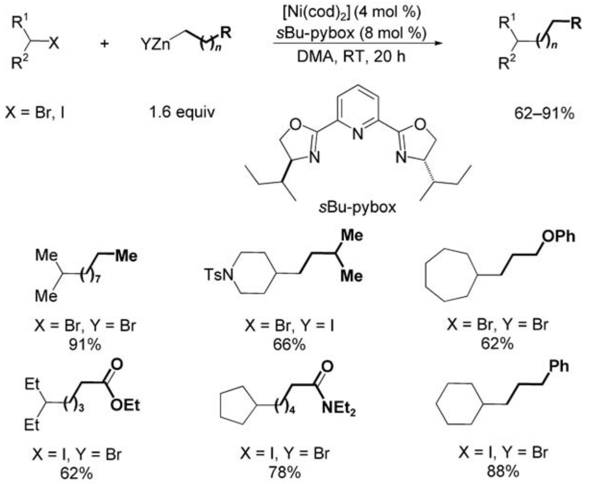
2. Nickel-Catalyzed Reactions

Nickel is by far the most versatile metal for the cross-coupling of alkyl halides. It is able to couple secondary alkyl halides with a variety of organometallic reagents, including zinc, boron, silicon, tin, and indium compounds.[4e] Asymmetric processes with racemic starting materials have also been developed with nickel catalysts.

2.1. Negishi Coupling

The first example of a nickel-catalyzed reaction of secondary alkyl bromides and iodides was reported by Zhou and Fu in 2003.[10] It was shown that $[Ni(cod)_2]$/*s*Bu-pybox in DMA could effectively catalyze the reaction of a variety of secondary alkyl electrophiles with organozinc reagents at room temperature (Scheme 2). The use of a nickel(II) catalyst led to diminished yields of the cross-coupled product, and palladium did not catalyze the desired reaction. The transformation also proceeds in the presence of various functional groups, such as sulfonamides, ethers, acetals, esters, and amides. Zhou and Fu speculated that the chelating pybox ligand disfavors β-hydride elimination, which requires a vacant coordination site on the metal center. Alkyl chlorides, alkyl tosylates, and tertiary alkyl bromides do not react under their conditions.

Fischer and Fu later reported an asymmetric version of the nickel-catalyzed Negishi reaction of secondary electrophiles. The reaction of racemic α-bromoamides under the catalysis of $NiCl_2$ and *i*Pr-pybox led to a variety of functionalized α-substituted amides in good yield and with high *ee* values (Scheme 3).[11] The reaction requires no special precautions and is carried out in air. Unfunctionalized and functionalized organozinc reagents, including those with alkene, benzyl ether, acetal, imide, and nitrile groups, participate in the coupling. The reaction is selective for the α-bromoamide in the presence of an external, unactivated primary alkyl bromide and is stereoconvergent, as racemic substrates are converted preferentially into one major enantiomer.



Scheme 2. Nickel–*s*Bu-pybox-catalyzed Negishi reaction. cod = 1,5-cyclooctadiene, DMA = *N*,*N*-dimethylacetamide, pybox = pyridine bisoxazoline, Ts = *p*-toluenesulfonyl.

A second asymmetric and stereoconvergent variant of the Negishi reaction was developed for racemic secondary benzylic bromides.[12] Under similar conditions ($NiBr_2$/*i*Pr-pybox, Scheme 4), the coupling of 1-bromoindanes proceeded in moderate to excellent yield with excellent enantioselectivity. Acyclic benzylic bromides were also coupled effectively, although the *ee* values of the products were lower. The methodology is also suitable for secondary benzylic chlorides and was found to be insensitive to moisture and oxygen.

A third example of an asymmetric Negishi reaction was developed with racemic secondary allylic chlorides and a Ni^{II}/pybox catalyst system (Scheme 5).[13] The reaction was first tested with "symmetrical" allylic chlorides, which would be

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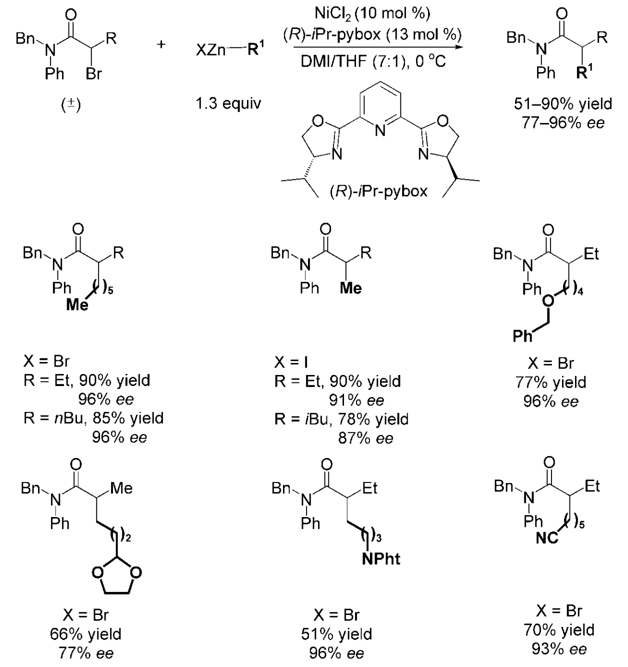
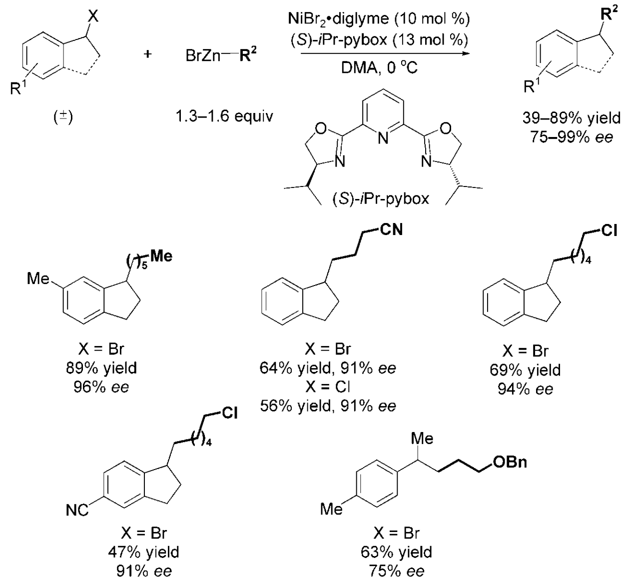
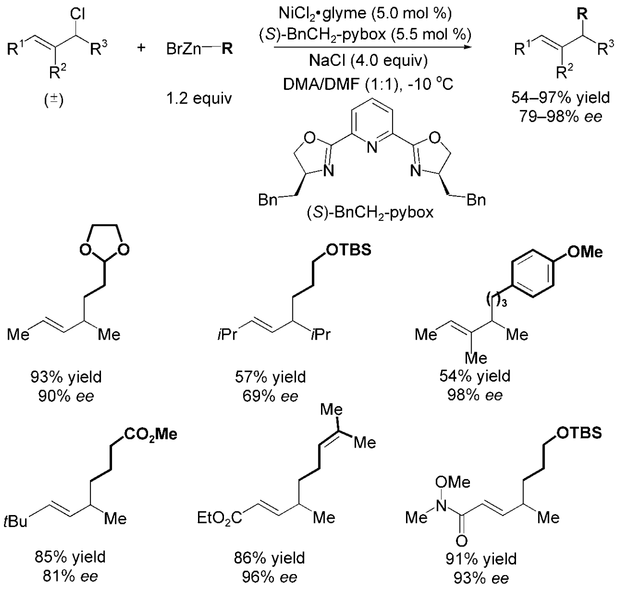


Scheme 3. Asymmetric nickel-catalyzed Negishi reaction of secondary α-bromoamides. Bn = benzyl, DMI = 1,3-dimethyl-2-imidazolidinone, Pht = phthalidimide.



Scheme 4. Asymmetric nickel-catalyzed Negishi reaction of secondary benzylic bromides.

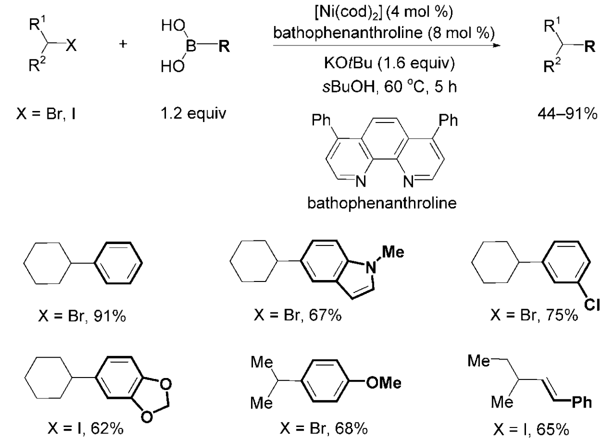
transformed into the same product regardless of the reaction site. The yield and enantioselectivity dropped dramatically as the steric bulk of the R^3 substituent α to the chloro group increased. Unsymmetrical allylic chlorides reacted at the carbon atom with the smallest substituent (R^1 or R^3) with greater than 20:1 regioselectivity, regardless of the isomeric composition of the substrate. Conjugated allylic chlorides reacted preferentially at the γ position.



Scheme 5. Asymmetric nickel-catalyzed Negishi reaction of secondary allylic chlorides. DMF = N,N-dimethylformamide, TBS = *tert*-butyldimethylsilyl.

2.2. Suzuki Coupling

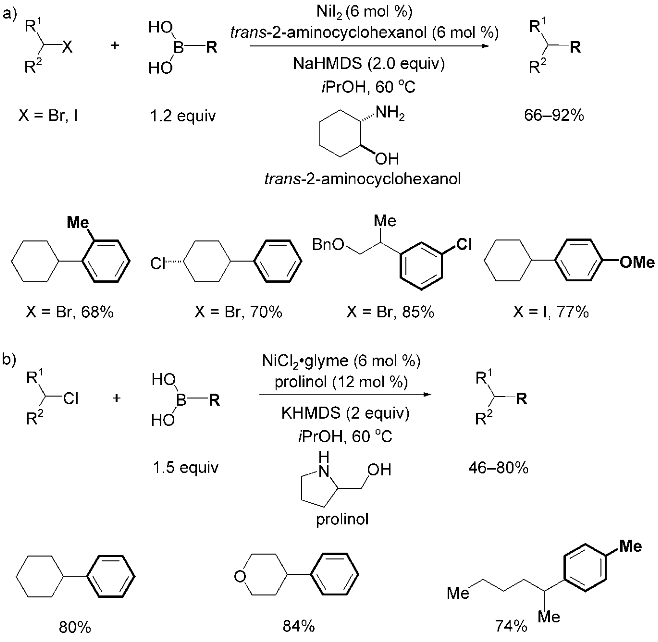
The Suzuki reaction is one of the most versatile and widely used cross-coupling reactions. Among the reasons for its appeal are the commercial availability of a large range of boronic acids, the ease with which these reagents can be handled, and their high functional-group compatibility. On the basis of the pioneering work of Suzuki and co-workers in 1992,[7] efforts by the Fu research group since 2001[4c] led to the catalytic coupling of primary alkyl halides. Extending their progress in this field, Zhou and Fu developed the first Suzuki coupling of unactivated secondary alkyl bromides and iodides in 2004.[14] The cross-coupling was carried out with [Ni(cod)$_2$] and the bidentate pyridine ligand bathophenanthroline (Scheme 6). Other metals, such as palladium, displayed no activity. A range of cyclic and acyclic secondary



Scheme 6. Nickel-catalyzed Suzuki coupling of secondary alkyl bromides and iodides.

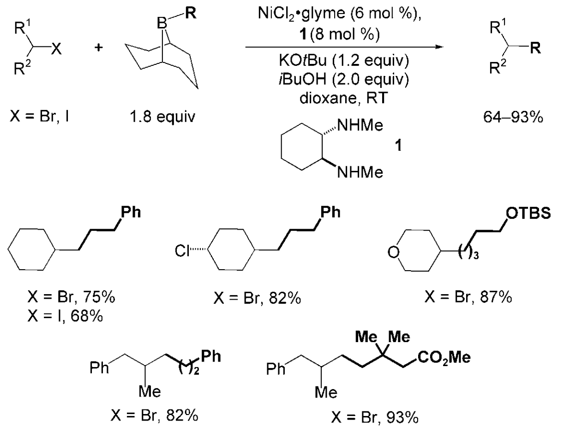
alkyl bromides and iodides were coupled with substituted aryl, heteroaryl, and alkenyl boronic acids. Primary, tertiary, and functionalized alkyl bromides, alkyl chlorides, alkyl boronic acids, and *ortho*-substituted aryl boronic acids could not be used as substrates under the specified conditions.

González-Bobes and Fu later reported more robust conditions that addressed the shortcomings of the initial Suzuki coupling methodology.[15] With a NiI$_2$/2-aminocyclohexanol catalyst system, unactivated and functionalized cyclic and acyclic secondary alkyl bromides and iodides underwent the coupling reaction; *ortho* substituents were also tolerated on the aryl boronic acid (Scheme 7a). A slightly modified catalyst system, NiCl$_2$/prolinol, enabled the first Suzuki coupling of unactivated secondary alkyl chlorides (Scheme 7b). Duncton et al. demonstrated the applicability of this methodology in the coupling of 3-iodooxetanes and azetidines to give the corresponding aryl oxetanes and aryl azetidines, which are important motifs in medicinal chemistry.[16]



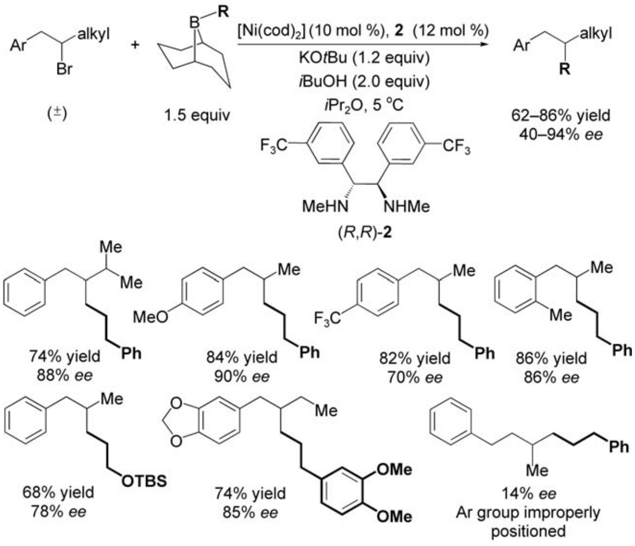
Scheme 7. Nickel–amino alcohol catalyzed Suzuki coupling of secondary alkyl bromides, iodides, and chlorides.

The scope of nickel-catalyzed Suzuki reactions with unactivated secondary alkyl bromides was further expanded to include alkyl boranes as coupling partners.[17] The coupling proceeds efficiently at room temperature with *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**1**) as the ligand (Scheme 8). The methodology is effective for a variety of cyclic and acyclic alkyl bromides and cyclic alkyl iodides. Functionality is tolerated on both the alkyl halide and the alkyl borane.



Scheme 8. Nickel-catalyzed Suzuki reaction of secondary alkyl bromides with alkyl boranes.

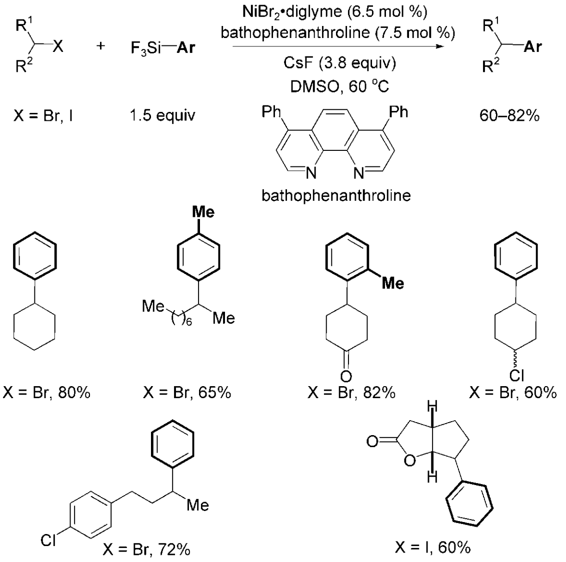
Saito and Fu discovered that this catalyst system with the chiral ligand (*R*,*R*)-**1** could be used to couple racemic secondary alkyl bromides with alkyl boranes to give enantiomerically enriched products.[18] Fine-tuning of the nickel source, ligand, solvent, and reaction temperature led to general reaction conditions ($[\mathrm{Ni(cod)_2}]$, ligand **2**, $i\mathrm{Pr_2O}$, 5 °C in the presence of KO*t*Bu and *i*BuOH) for the asymmetric Suzuki coupling of racemic acyclic secondary homobenzylic bromides with alkyl boranes (Scheme 9). Proper positioning of the aromatic group is essential for good enantioselectivity, as the catalyst system seems to differentiate between the CH$_2$Ar group and the alkyl group of the homobenzylic bromide. The enantioselectivity is somewhat diminished if the aryl group contains an electron-withdrawing substituent. Heteroatom-containing electrophiles and alkyl boranes are good coupling partners, although the products are generally isolated with lower *ee* values than those observed when unfunctionalized substrates are used.



Scheme 9. Asymmetric nickel-catalyzed Suzuki reaction of secondary homobenzylic bromides with alkyl boranes.

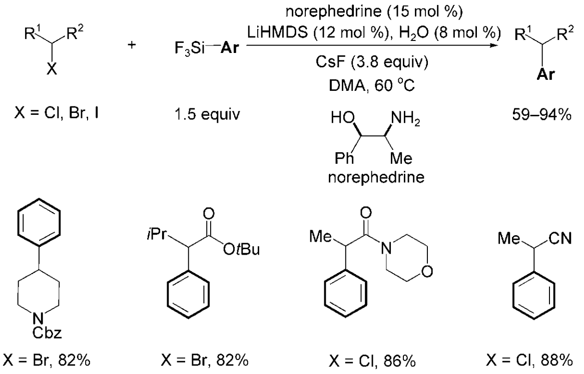
2.3. Hiyama Coupling

Organosilicon reagents have many of the attractions of organoboron reagents, including availability, low toxicity, and high functional-group compatibility. Further increasing the scope of cross-coupling reactions with secondary alkyl electrophiles, Powell and Fu developed a nickel-catalyzed coupling of aryl trifluorosilanes.[19] In this method, a Ni^{II}/bathophenanthroline catalyst system is used for the cross-coupling in the presence of CsF (Scheme 10). The use of a nickel(0) source led to a drop in yield, and palladium did not promote the reaction. A variety of cyclic and acyclic secondary bromides and cyclic iodides can be used, and the substrates can contain ether, imide, ketone, and carbamate functional groups.



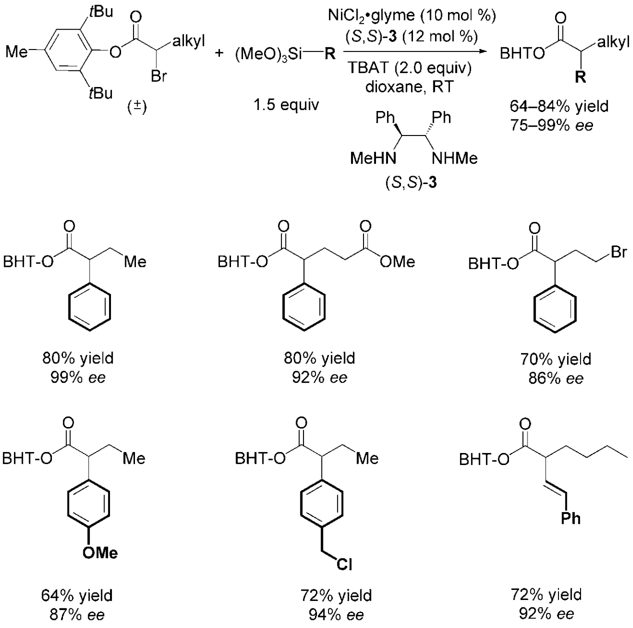
Scheme 10. Nickel-catalyzed Hiyama coupling of secondary alkyl bromides and iodides with aryl trifluorosilanes. DMSO = dimethyl sulfoxide.

Fu and co-workers later developed a more active catalyst system.[20] The use of norephedrine as the ligand enables the coupling of unactivated secondary bromides and iodides in much higher yield than with the first-generation $NiBr_2$/bathophenanthroline catalyst system (Scheme 11). Activated secondary bromides also underwent cross-coupling with this system. Furthermore, this system catalyzes the reaction of activated secondary alkyl chlorides and thus expands the scope of the Hiyama coupling significantly.



Scheme 11. Nickel–amino alcohol catalyzed Hiyama coupling of secondary alkyl chlorides, bromides, and iodides. Cbz = carbobenzyloxy, LiHMDS = lithium hexamethyldisilazide.

An asymmetric version of the nickel-catalyzed Hiyama coupling was developed with racemic secondary α-bromoesters and the chiral diamine ligand **3** (Scheme 12).[21] The ligand, organosilane, and fluoride activator all play a critical role in the enantioselectivity of this reaction. Under the optimized conditions, a variety of functionalized α-bromoesters, which may contain additional ester, ether, and alkene functional groups, can be coupled in high yield with excellent enantioselectivity. Interestingly, when norephedrine (see Scheme 11) was used as the chiral ligand under these optimized conditions, the product was formed with less than 5 % *ee*. Remarkably, the coupling of the activated secondary alkyl bromide occurs preferentially in the presence of an unactivated primary alkyl bromide. The reaction is sensitive to the steric bulk of both the alkyl and the ester moieties. The α-bromoesters underwent arylation and alkenylation with high enantioselectivity.

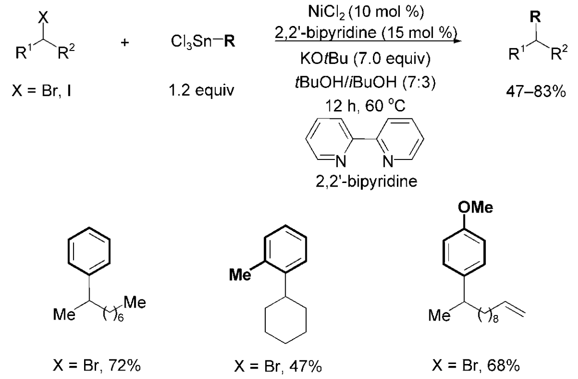


Scheme 12. Asymmetric Hiyama coupling of racemic secondary α-bromoesters. BHT = 2,6-di-*tert*-butyl-4-methylphenyl, TBAT = $[F_2SiPh_3]^-[NBu_4]^+$.

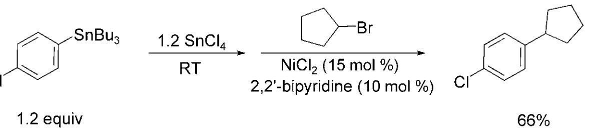
2.4. Stille Coupling

Nickel-catalyzed processes with secondary electrophiles were also extended to the Stille reaction by using monoorganotin reagents.[22] Monoorganotin reagents are especially useful, as they are not as toxic as triorganotin reagents and do not make product purification as difficult. A $NiCl_2$/2,2′-bipyridine catalyst system was used in the presence of KO*t*Bu for the coupling of a range of unactivated secondary alkyl bromides and iodides with aryl trichlorotin reagents

(Scheme 13). Readily available aryl and alkenyl tributylstannanes are themselves not effective in the coupling but can be converted into the aryl and alkenyl trichlorostannanes in a redistribution reaction with $SnCl_4$. These trichlorostannanes can then undergo carbon–carbon bond formation under the optimized cross-coupling conditions [Eq. (1)].



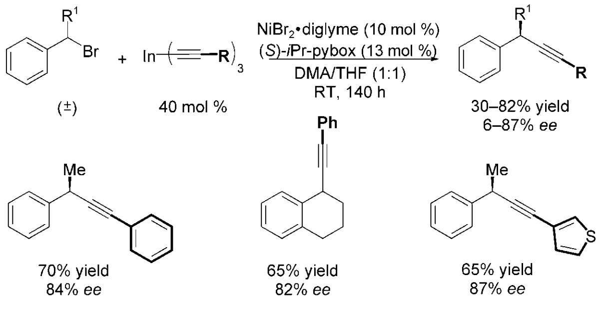
Scheme 13. Nickel-catalyzed Stille coupling of unactivated secondary alkyl halides with monoorganotin reagents.



(1)

2.5. Sonogashira-Type Coupling

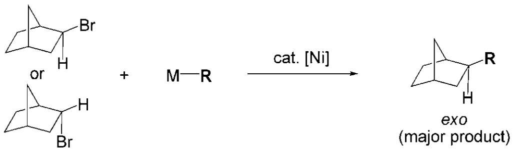
The first enantioselective sp–sp^3 cross-coupling of alkynyl organometallic reagents and racemic secondary benzyl bromides was recently described by Caeiro et al.[23] A substoichiometric amount of a trialkynyl indium reagent is used as the nucleophilic component in the reaction, as the indium reagent is able to transfer all three organic groups to the electrophile (Scheme 14). The coupling is catalyzed by a $NiBr_2$/*i*Pr-pybox catalyst system and proceeds at room temperature to give the desired product in moderate to good yields and enantioselectivities. Palladium is also able to catalyze this transformation, although the products are formed with less than 10% *ee*. The reaction is stereoconvergent and enables the coupling of a variety of functionalized alkyl groups.



Scheme 14. Asymmetric nickel-catalyzed coupling of trialkynyl indium reagents with racemic secondary benzylic bromides.

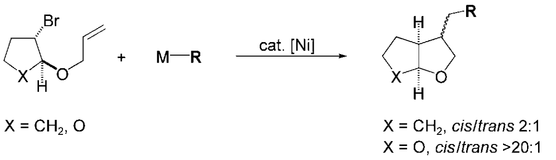
2.6. Mechanistic Considerations

Alkyl halides are known to oxidize low-valent transition-metal compounds by single-electron processes to afford an alkyl radical and X^-.[24] It is assumed that many of the nickel-catalyzed reactions summarized in the previous sections proceed by radical mechanisms. Cross-coupling reactions of both *exo*- and *endo*-2-bromonorbornane with various organometallic reagents produced the *exo* product predominantly, which suggests that both substrates react via the same planar (radical) intermediate [Eq. (2)].[14,15,19]



(2)

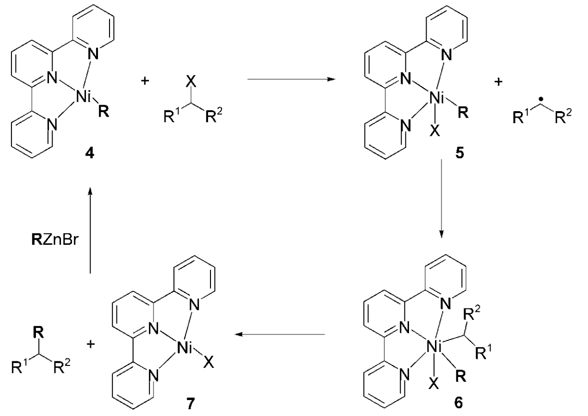
Secondary alkyl halides with a pendant olefin tend to undergo an intramolecular cyclization prior to cross-coupling [Eq. (3)].[15,22,26] These cyclizations proceed with the same *cis*/*trans* selectivity regardless of the organometallic coupling partner or the ligand used in the reaction. The same *cis*/*trans* selectivity is also observed under known radical conditions.[25] Cárdenas and co-workers conducted a thorough investigation of this cyclization/cross-coupling sequence with organozinc reagents and found strong indications of a radical mechanism via a nickel(I) intermediate.[26]



(3)

The asymmetric cross-coupling reactions of secondary alkyl halides reported in this section proceed with stereoconvergence rather than through kinetic resolution of the starting material, which suggests that both enantiomers of the substrate react to give a planar radical intermediate. The stereoselectivity of the coupling reaction is then determined by the configuration of the catalyst ligand.

Vicic and co-workers carried out extensive studies on the electronic structure and reactivity of (terpyridine)nickel–alkyl complexes **4** (Scheme 15), which are known to be involved in alkyl–alkyl Negishi cross-coupling reactions.[24] From these studies, they reached the following conclusions: 1) A (terpyridine)nickel(0) complex does not react by oxidative addition (a two-electron process) of the alkyl halide followed by simple transmetalation to afford the cross-coupled product. 2) Complex **4** can be best described as a



Scheme 15. Possible mechanism for the nickel-catalyzed alkyl–alkyl cross-coupling reactions with organozinc reagents.

nickel(II)–alkyl cation bound to a reduced terpyridine ligand containing a single unpaired electron. Central to the results of this investigation was the finding that this single unpaired electron was localized mostly on the ligand. 3) Complex **4** reduces the alkyl halide through the transfer of a single electron from the ligand to give complex **5** and an alkyl radical. It is postulated that the alkyl radical remains in close proximity to the metal center, where an oxidative radical addition occurs to give a nickel(III)–dialkyl complex **6**. Fast reductive elimination of the alkyl groups affords the coupled product and complex **7**, which has been shown to be a viable catalyst for the cross-coupling reaction. Vicic and co-workers state that this mechanism can account for the stereoconvergence observed in asymmetric coupling reactions, if the nickel catalyst contains a chiral ligand. In this case, enantioselective addition of the alkyl radical to the nickel center may take place to afford a chiral product.

Density functional theory calculations by Lin and Phillips[27] provided further evidence for the mechanism proposed by Vicic and co-workers. Their results also showed that a traditional two-electron redox mechanism is energetically unfavorable. By using *n*-propyl iodide and isopropyl iodide in their calculations, they found that the transfer of the iodide to the catalyst (as in the formation of **5**, Scheme 15) is the rate-determining step, although the energy difference may be lower with isopropyl iodide. For secondary alkyl halides, the decomposition of the nickel(III) intermediate **6** is kinetically favored over reductive elimination and may lead to lower yields of the cross-coupled product. These studies also showed that the catalytic cycle is plausible, even though the regeneration of intermediate **4** from **7** is slightly disfavored in terms of free energy.

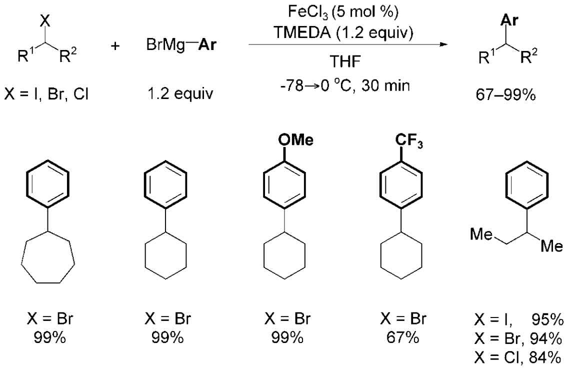
3. Iron-Catalyzed Reactions

Kochi and co-workers showed in the 1970s that cross-coupling under iron catalysis is possible.[28] Iron compounds offer many advantages over some of the more "popular" transition-metal catalysts, as iron is extremely cheap, in abundant supply, nontoxic, and environmentally benign. Iron catalysts have shown a great deal of promise in the cross-coupling of alkyl electrophiles and are rapidly becoming attractive alternatives for transition-metal catalysis.[4d]

3.1. Kumada-Type Coupling

The ready availability and low cost of Grignard reagents make the Kumada coupling a valuable reaction for the formation of carbon–carbon bonds. Iron-catalyzed Kumada coupling reactions of secondary alky halides encompass nearly the entire reaction spectrum through bond formation with aryl, alkenyl, and alkyl Grignard reagents.

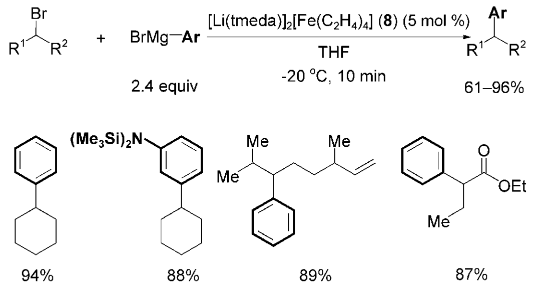
Nakamura and co-workers demonstrated the successful coupling of secondary alkyl halides with aryl Grignard reagents under iron catalysis.[29] The products were formed in excellent yields with $FeCl_3$ (5 mol %), a slight excess of the Grignard reagent, and TMEDA as an additive (Scheme 16).



Scheme 16. Iron-catalyzed Kumada coupling of secondary alkyl halides with aryl Grignard reagents. TMEDA = tetramethylethylenediamine.

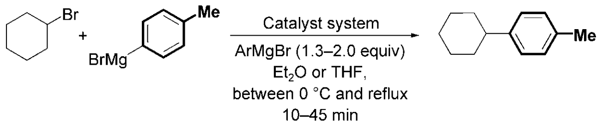
For the cross-coupled product to be formed in high yield, a solution of the aryl Grignard reagent and TMEDA must be added slowly to a solution of the alkyl bromide and the catalyst at −78 °C with a syringe pump. TMEDA is required to suppress the formation of olefinic products through a formal loss of HX. Tertiary monoamines were not effective as additives, and stronger bases, such as DABCO, were also less effective. Nakamura and co-workers reported that phosphine ligands, alkyl Grignard reagents, and organozinc reagents are not compatible with this methodology.

Although the mechanisms of iron-catalyzed cross-coupling reactions have not been elucidated (see Section 3.3), it has been postulated that highly reduced iron–magnesium clusters containing an iron(−II) center, such as $[Fe(MgX)_2]_n$, may play an important role in the catalytic cycle. Martin and Fürstner probed this theory by testing the known, well-defined iron(−II) complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ (**8**), which was first described by Jonas and co-workers,[30a,b] as a catalyst for cross-coupling reactions.[30c] Indeed, **8** is a very active catalyst for the coupling of aryl Grignard reagents with alkyl electrophiles, including secondary alkyl bromides (Scheme 17). The coupling reactions proceed within 10 min at −20 °C and show remarkable functional-group compati-



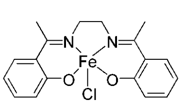
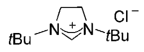
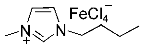
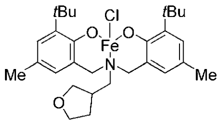
Scheme 17. Coupling of secondary alkyl bromides with aryl Grignard reagents under the catalysis of $[Li(tmeda)]_2[Fe(C_2H_4)_4]$.

bility. Most importantly, the iron-catalyzed activation of the alkyl bromide outcompetes the nucleophilic attack of the Grignard reagent on functional groups such as keto, ester, chloride, and nitrile groups, which makes this method extremely powerful.



Scheme 18. Iron-catalyzed cross-coupling of *p*-tolylmagnesium bromide with bromocyclohexane (see Table 1).

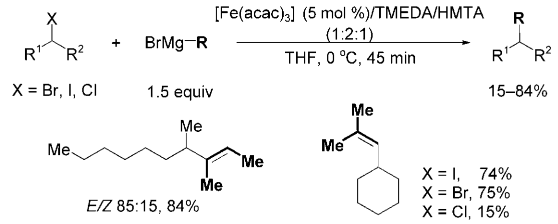
Table 1: Conditions developed for the iron-catalyzed cross-coupling of *p*-tolylmagnesium bromide with bromocyclohexane (see Scheme 18).[a]

	Catalyst system	Yield [%]	Ref.
A	$[Fe(acac)_3]$ (5 mol%)	69[b]	[31]
B	 (2.5 mol%)	90	[32]
C	$FeCl_3$ (10 mol%), Et_3N (20 mol%)	79	[33]
	$FeCl_3$ (10 mol%), DABCO (10 mol%)	79	
D	$FeCl_3$ (10 mol%), PCy_3 (20 mol%)	85	[34]
	$FeCl_3$ (10 mol%), dpph (10 mol%)	85	
	$FeCl_3$ (10 mol%), $P(OC_6H_3\text{-}2,4\text{-}t\text{Bu}_2)_3$ (20 mol%)	88	
	$FeCl_3$ (10 mol%),  (20 mol%)	97	
E	 ([bmim]$FeCl_4$, 5 mol%)	89[b]	[35]
F[c]	$[Fe(acac)_3]$ (5 mol%), TMEDA (10 mol%), HMTA (5 mol%)	90[b]	[36]
	$[(FeCl_3)_2(tmeda)_3]$ (5 mol%)	91[b]	
G	 (5 mol%)	99	[37]

[a] acac = acetylacetonate, Cy = cyclohexyl, DABCO = 1,4-diazabicyclo-[2.2.2]octane, HMTA = hexamethylenetetramine. [b] Yield of the isolated product. [c] Yields for the reaction with phenylmagnesium bromide.

Several catalytic systems have been developed for the efficient coupling of secondary alkyl electrophiles with aryl Grignard reagents (Scheme 18 and Table 1). Nagano and Hayashi reported that $[Fe(acac)_3]$ (5 mol%) in refluxing diethyl ether is an effective catalyst without other ligands or additives (Table 1, conditions A).[31] Studies conducted by Bedford and co-workers showed that a wide variety of ligands are suitable for the alkyl–aryl coupling, such as salen (Table 1, conditions B),[32] mono- and bidentate tertiary amines (Et_3N and DABCO, conditions C),[33] and various phosphines, phosphites, arsines, and carbenes (conditions D).[34] Bica and Gaertner showed that an iron-containing ionic liquid, butylmethylimidazolium tetrachloroferrate ([bmim]$FeCl_4$), can also catalyze the reactions of secondary alkyl bromides, iodides, and chlorides (Table 1, conditions E).[35] Interested in developing this cross-coupling reaction for large-scale use, Cahiez et al. showed that $[Fe(acac)_3]$/TMEDA/HMTA (1:2:1) and the preformed complex $[(FeCl_3)_2(tmeda)_3]$ catalyze the alkyl–aryl cross-coupling reaction effectively on a gram scale (alkyl bromide: 10 mmol; Table 1, conditions F).[36] Most recently, Kozak and co-workers developed an Fe^{III}/amine–bis(phenolate) catalyst (Table 1, conditions G).[37]

The coupling of alkenyl and alkyl Grignard reagents is also possible. Cahiez et al. were able to extend the coupling of secondary bromides to a variety of alkenyl Grignard reagents[38] by using the catalyst system developed previously ($FeCl_3$/TMEDA/HMTA) for the coupling of aryl Grignard reagents (Scheme 19).[36] Secondary alkyl iodides can also be coupled with this catalyst system; however, the corresponding chlorides react sluggishly. The same *Z*/*E* ratio was found for the coupled products as that of the starting alkenyl magnesium bromides.

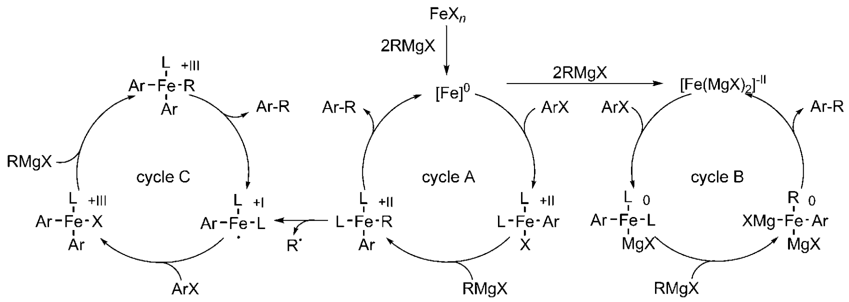


Scheme 19. Iron-catalyzed coupling of secondary alkyl halides with alkenyl Grignard reagents.

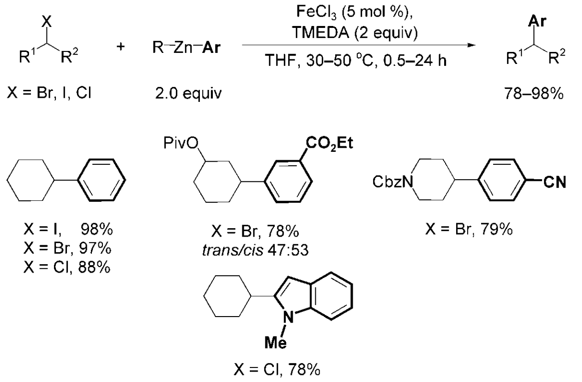
Cossy and co-workers reported that the alkenylation of secondary alkyl bromides is possible with an $FeCl_3$/TMEDA system under mild conditions.[39] However, an almost twofold excess of TMEDA was required with respect to the alkyl bromide, as well as the slow addition of the Grignard reagent. To date, only one example of the coupling of secondary alkyl halides with alkyl Grignard reagents has been reported.[40] In this case, Chai and co-workers used an iron(II) catalyst derived from $Fe(OAc)_2$ and the bidentate phosphine ligand xantphos (4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene).

3.2. Negishi Coupling

Nakamura and co-workers expanded the scope of the iron-catalyzed cross-coupling of secondary alkyl halides to include aryl zinc reagents as nucleophiles.[41] Interestingly, it is necessary to use a diorganozinc reagent prepared from a Grignard reagent for the cross-coupling to occur (Scheme 20). The presence of a magnesium salt (formed in the generation of the diorganozinc reagent) appears to be necessary for conversion. The reaction can be used to couple secondary alkyl iodides, bromides, and chlorides and shows functional-group tolerance for alkene, trimethylsilyl, alkyne, ester, and nitrile groups. Both functionalized aryl zinc reagents and heteroaryl zinc reagents are good substrates for the reaction.



Scheme 21. Interconnected mechanisms of iron-catalyzed cross-coupling reactions.



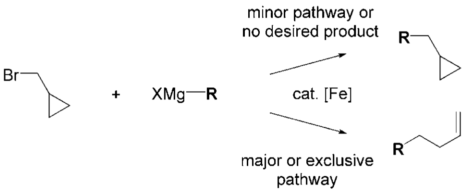
Scheme 20. Iron-catalyzed Negishi reaction of secondary alkyl halides. Piv = pivaloyl.

3.3. Mechanistic Considerations

Until recently, little was known about the mechanisms and catalytically active species of iron-catalyzed reactions. Fürstner et al. studied iron-catalyzed cross-coupling reactions of Grignard reagents extensively with various electrophiles in an attempt to elucidate the mechanistic pathways of these processes.[42] Their results suggest that carbon–carbon bond formation can occur by more than one mechanism, as redox couples with the formal oxidation states Fe^{I}/Fe^{III}, Fe^{0}/Fe^{II}, and Fe^{-II}/Fe^{0} are possible. It is thought that these different possibilities are interconnected, which makes it difficult to determine the dominant redox cycle for a given reaction. Any of these three proposed redox variants may begin with the reduction of an Fe^{II} or Fe^{III} salt to the Fe^{0} species by 2 equivalents of the Grignard reagent (Scheme 21). The Fe^{0} species may then enter the Fe^{0}/Fe^{II} redox cycle (cycle A), or it may be further reduced by another 2 equivalents of the Grignard reagent to the low-valent Fe^{-II} species (cycle B). Another possibility is that an electron-rich, low-valent iron species in cycle A may undergo single-electron transfer to initiate another redox process between the Fe^{I} and Fe^{III} oxidation states (cycle C). However, other possible scenarios exist in terms of interconnected mechanisms for these transformations.

In their mechanistic studies of cross-coupling reactions of both primary and secondary alkyl halides with aromatic Grignard reagents, Fürstner and co-workers were able to demonstrate that well-defined iron complexes of oxidation states +III, +II, +I, 0, and −II (such as catalyst **8**) are all catalytically competent. However, as previously shown (Scheme 17), complex **8** is an extremely active catalyst for the cross-coupling of alkyl halides. It outperforms all other iron complexes of higher oxidation states in terms of product yield and reaction rate.

There is further data to suggest that single-electron-transfer processes intervene in iron-catalyzed alkyl–aryl cross-coupling reactions: 1) The reaction of chiral substrates with aryl Grignard reagents and an iron catalyst leads to a racemic coupled products, which indicates that a radical intermediate is involved.[29,30,42] 2) As described earlier [Eq. (2), Section 2.6], two diastereomeric substrates give the same isomer of the coupled product, which also suggests that a common radical intermediate is involved and the more thermodynamically favored product is formed.[29] 3) Alkyl halides bearing a pendant olefin preferentially undergo cyclization prior to coupling with the Grignard reagent [Eq. (3), Section 2.6],[30,33,34,41,42] presumably via a radical intermediate. 4) In the iron-catalyzed reaction of (bromomethyl)cyclopropane with a Grignard reagent, the coupled product expected from an oxidative-addition pathway is not obtained; instead, the ring-opened product is obtained, which further supports a radical pathway [Eq. (4)].[33,34,39–42] Therefore, it appears that highly reduced iron species (such as the iron(−II) complex **8**) are the dominant catalytic species in the cross-coupling of alkyl halides with aryl Grignard reagents, although other redox couples, such as Fe^{0}/Fe^{II} and Fe^{I}/Fe^{III}, are also viable.



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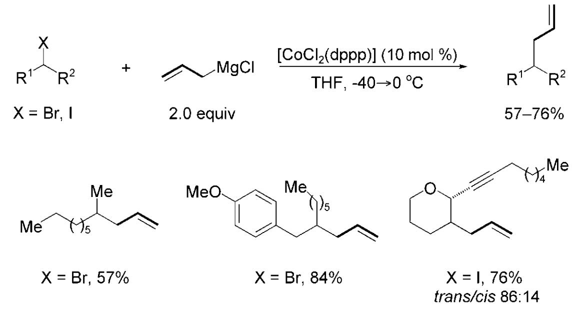
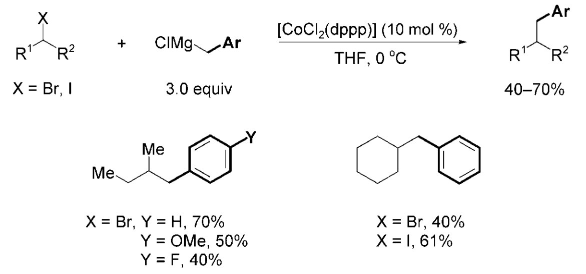
4. Cobalt-Catalyzed Reactions

4.1. Kumada Coupling

Cobalt catalysis has a great deal of potential with regard to the cross-coupling of alkyl halides. Oshima and co-workers highlighted this remarkable activity in a series of studies, in which they developed the coupling of primary, secondary, and even tertiary alkyl electrophiles. They demonstrated in a seminal report that secondary alkyl bromides could undergo coupling with allylic Grignard reagents (Scheme 22)[43] and later that benzylic Grignard reagents were also suitable coupling partners in this transformation (Scheme 23).[44] The reactions are catalyzed by $CoCl_2$ and the bidentate phosphine ligand 1,3-bis(diphenylphosphanyl)propane (dppp) in THF at temperatures between −40°C and room temperature. An excess of the Grignard reagent is required, and in contrast to iron-catalyzed processes, functional groups such as amides, esters, and carbamates did not survive under the reaction conditions.

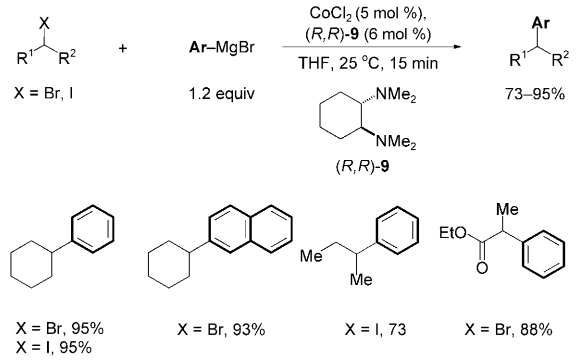


Scheme 22. Cobalt-catalyzed allylation of secondary alkyl bromides and iodides.



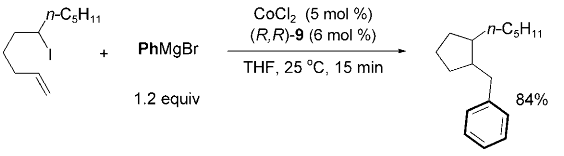
Scheme 23. Cobalt-catalyzed benzylation of secondary alkyl bromides and iodides.

The scope of the cobalt-catalyzed coupling of secondary alkyl halides and aryl Grignard reagents is limited when a phosphine ligand is used,[45] but with a diamine ligand,[46] the reaction is quite efficient (Scheme 24). In the presence of $CoCl_2$ (5 mol%) and (*R*,*R*)-*trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (**9**), and with a slight excess of the aryl Grignard reagent (1.2 equiv), the reactions of secondary alkyl bromides and iodides were complete within 15 min at room temperature. With alkyl chlorides, the desired products were formed in poor yields. Alkenyl Grignard reagents and ester groups were compatible with the reaction conditions.



Scheme 24. Cobalt–diamine-catalyzed arylation of secondary alkyl bromides and iodides.

In the reaction of 6-iodo-1-undecene with phenylmagnesium bromide, an intramolecular cyclization was followed by intermolecular coupling to give 1-benzyl-2-pentylcyclopentane [Eq. (5)]. No enantioselectivity was observed in the 5-*exo*-trig cyclization step in the presence of the chiral diamine ligand. However, modest enantioselectivity was observed in the phenylation of some cyclic halides [Eq. (6)], which opens the door for an asymmetric process from racemic starting materials. In the coupling of Ueno–Stork acetals (which contain a stereogenic center next to the halogenated carbon atom), the phenylation of tetrahydrofurans was highly diastereoselective [Eq. (7)].



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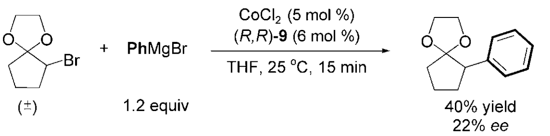

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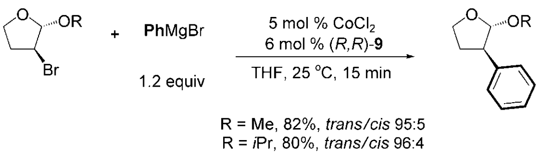
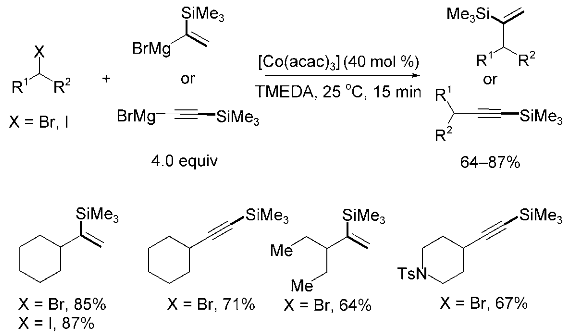


(7)

Oshima and co-workers also developed an alkenylation and alkynylation of secondary alkyl bromides and iodides with 1-(trimethylsilyl)ethenylmagnesium bromide and 2-trimethylsilylethynylmagnesium bromide.[47] The reactions are relatively inefficient, as they require 40 mol% of the catalyst and 4 equivalents of the Grignard reagent in TMEDA as the



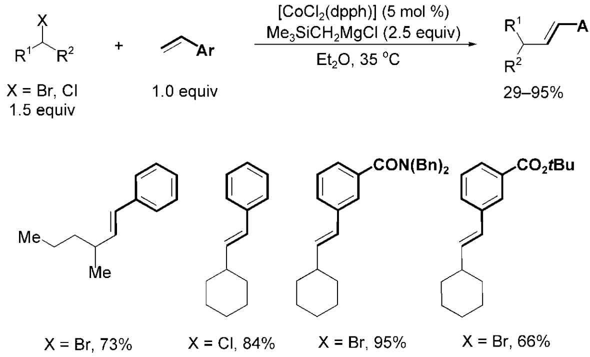
Scheme 25. Cobalt-catalyzed alkynylation of secondary alkyl halides with magnesium reagents.

solvent (Scheme 25); however, there have been very few examples of the alkynylation of secondary alkyl halides.

The same research group also discovered that carbene ligands are effective in cobalt-catalyzed cyclization/cross-coupling reactions of 6-halo 1-hexene derivatives with trialkylsilylmethyl and 1-alkynyl Grignard reagents.[48] Such Grignard reagents were not effective under previously developed reaction conditions with phosphine and amine ligands.

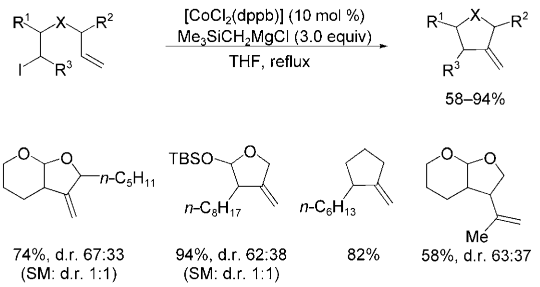
4.2. Heck-Type Reactions with Organometallic Nucleophiles

The Heck reaction is one of the most powerful carbon–carbon bond-forming reactions. However, the Heck reaction of alkyl halides still requires further development. Oshima and co-workers were able to develop a cobalt-catalyzed version for the coupling of secondary alkyl bromides with styrene derivatives.[49] The reaction requires 1,6-(diphenylphosphanyl)hexane (dpph) to be used as the ligand and the alkyl halide to be used in excess (1.5 equiv). Trimethylsilylmethylmagnesium bromide is necessary as a reagent, but is not incorporated into the product (Scheme 26). Other trialkylsilylmethyl Grignard reagents, such as $PhMe_2SiCH_2MgCl$, also effect the coupling reaction, but methyl, ethyl, neopentyl, and phenyl Grignard reagents only afforded a trace amount of the desired product. It is thought that the Grignard reagent coordinates to the catalyst and thus makes it more electron-rich. Secondary alkyl chlorides also participated in the coupling reaction, as well as a variety of styrene derivatives. Owing to the low reactivity of Me_3SiCH_2MgBr, a *tert*-butoxycarbonyl group and a carbamoyl group were tolerated.



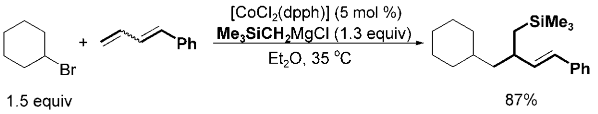
Scheme 26. Cobalt-catalyzed Heck-type coupling of secondary alkyl halides with styrene derivatives.

This methodology was extended to an intramolecular Heck-type coupling of secondary 6-iodo-1-hexene derivatives to afford *exo*-methylenecyclopentanes (Scheme 27).[50] Although the authors do not comment on the differing isomeric compositions of the substrates and products, it appears likely that the mechanism involves a planar intermediate.



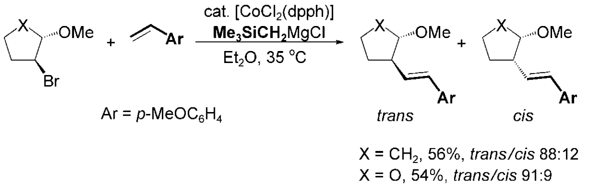
Scheme 27. Cobalt-catalyzed intramolecular Heck-type coupling. dppb = 1,4-bis(diphenylphosphanyl)butane, SM = starting material.

During their investigations into the Heck-type coupling of styrene derivatives (Scheme 26),[49] Oshima and co-workers found that the reaction of 1,3-dienes resulted in an unexpected three-component coupling in which the Grignard reagent was incorporated into the product.[51] In the presence of $CoCl_2$ and dpph, and with a slight excess of trimethylsilylmethylmagnesium chloride (1.3 equiv), the coupled product was obtained with high selectivity for the *E* double bond [Eq. (8)].



(8)

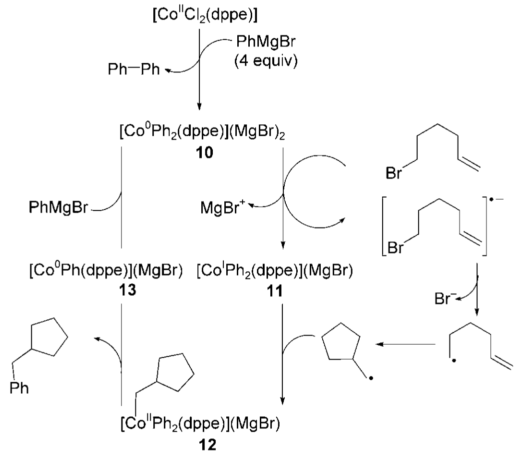
Cyclic secondary alkyl bromides containing a stereocenter next to the brominated carbon atom were also investigated in the Heck-type coupling [Eq. (9)].[52] The best *trans*/*cis* selectivity was observed with five-membered rings; in particular, better selectivity was observed for cyclic acetals than for carbocycles.



(9)

4.3. Mechanistic Considerations

Evidence exists that cobalt-catalyzed reactions of alkyl halides also proceed through radical mechanisms.[44,45,52] For example, in the reactions of substrates containing an ether linkage β to the halide substituent [Eq. (7) and Scheme 27], no allylic alcohol products (which would result from an oxidative addition and subsequent β-alkoxy elimination) were detected.[49] On the basis of crystallographic and spectroscopic evidence, Oshima and co-workers proposed a mechanism for both the cobalt-catalyzed coupling of 6-halo 1-hexene derivatives with aryl Grignard reagents[45] and the cobalt-catalyzed Heck-type reaction.[52] The radical mechanism of the cobalt-catalyzed cyclization/phenylation of 6-bromo-1-hexene is shown in Scheme 28 as an example: The reaction of [Co^{II}Cl$_2$(dppe)] with 4 equivalents of the Grignard reagent (relative to Co) affords the catalytically active species **10** and 1 equivalent of biphenyl. Single-electron transfer from the 17-electron ate complex **10** to the substrate yields a radical anion and the Co^{I} complex **11**. Loss of the halide anion then affords the 5-hexenyl radical intermediate, which undergoes cyclization to give the cyclopentylmethyl radical. The Co^{I} complex **11** recombines with the cyclopentylmethyl radical to afford the Co^{II} complex **12**. Reductive elimination then gives the product and the Co^{0} species **13**, which is converted into the active species **10** with additional Grignard reagent.



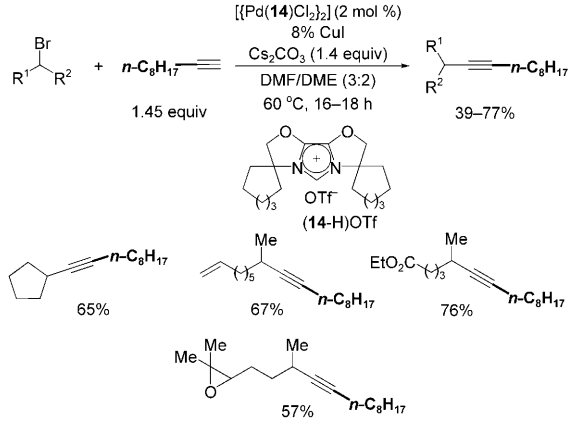
Scheme 28. Mechanism of the cobalt-catalyzed cyclization/arylation reaction of 6-bromo-1-hexene. dppe = 1,2-bis(diphenylphosphanyl)-ethane.

5. Palladium-Catalyzed Reactions

Palladium-catalyzed reactions of secondary alkyl halides are still in their infancy. A seminal report by Sustmann et al. in 1986 showed that palladium-catalyzed Stille coupling reactions with a secondary benzylic bromide were possible.[53] Simultaneously, Castle and Widdowson disclosed their results for a palladium-catalyzed reaction of a secondary alkyl iodide with Grignard reagents,[54] which was later disputed by Yuan and Scott.[55] Several carbonylation reactions of secondary alkyl electrophiles were reported between 1988 and 1992.[56] It is remarkable that reports on these cross-coupling reactions have emerged, as more recent investigations showed that the energy barrier to the oxidative addition of secondary electrophiles to palladium is very high.[9] This high activation barrier should in principle make such a reaction very difficult. Furthermore, the mechanisms by which palladium-catalyzed cross-coupling reactions occur differ greatly from those of the nickel-, iron-, and cobalt-catalyzed processes discussed herein.

5.1. Sonogashira Coupling

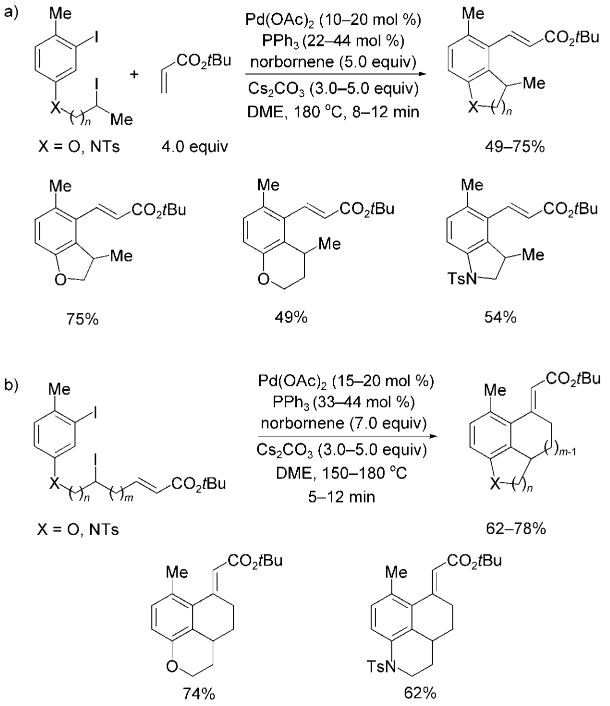
In 2006, the first Sonogashira coupling of unactivated secondary alkyl bromides was reported.[57] The reaction proceeds well in the presence of a palladium complex with an N-heterocyclic carbene (NHC) ligand at elevated reaction temperatures in polar solvents (Scheme 29). The ligand, **14**, is from a family of bisoxazoline-derived NHCs that are electron-rich and sterically demanding but exhibit a degree of conformational flexibility. The reaction does not proceed with phosphine ligands. Different alkyl and cycloalkyl bromides were coupled with 1-octyne under these conditions. In some cases, the presence of a catalytic amount of 1,2-diaminocyclohexane proved to be beneficial. The use of enantiomerically pure (*R*)-2-bromooctane led to the racemic coupled product.



Scheme 29. Palladium-catalyzed Sonogashira coupling of secondary alkyl bromides. DME = 1,2-dimethoxyethane.

5.2. The Catellani Reaction

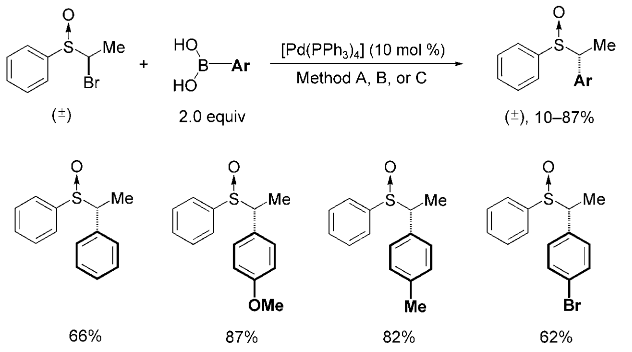
The Catellani reaction is a norbornene-mediated palladium-catalyzed cross-coupling reaction for the *ortho* functionalization of aryl halides by alkyl or aryl electrophiles. The process requires norbornene, although it is not incorporated in the coupling product. This domino reaction affords functionalized arenes as the final products.[58] Catellani and co-workers were the first to show, in two separate instances, that isopropyl iodide could be used in an intermolecular *ortho* alkylation with moderate to good conversion.[59] Lautens and co-workers reported an intramolecular reaction of secondary alkyl iodides.[60] Readily available $Pd(OAc)_2/PPh_3$ was used as the catalyst, and elevated temperatures (180 °C) were required to generate bicyclic (Scheme 30 a) or tricyclic heterocycles (Scheme 30 b). The use of enantiomerically enriched substrates showed that the palladium-catalyzed annulation proceeds with inversion of configuration at the stereogenic center. Minimal erosion of the *ee* value was observed. According to the proposed mechanism, oxidative addition of the alkyl iodide to the Pd^{II} complex generates a Pd^{IV} intermediate, which undergoes rapid elimination to afford the *ortho*-alkylated arene. It was proposed that the inversion of configuration occurs during oxidative addition, and that reductive elimination occurs with retention of configuration.



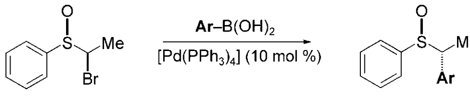
Scheme 30. Palladium-catalyzed annulation of aryl iodides with secondary alkyl iodides.

5.3. Suzuki Coupling

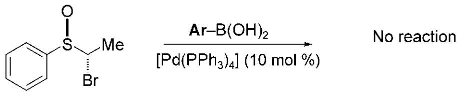
Asensio and co-workers reported a Suzuki coupling reaction of activated secondary bromo sulfoxides with aryl boronic acids.[61] An array of boronic acids were coupled with bromo sulfoxides under standard Suzuki conditions (Scheme 31). The reaction occurs in a stereospecific manner, with inversion of configuration at the stereogenic center. The authors proposed that inversion of configuration occurs during the oxidative addition of the bromo sulfoxide to the Pd^0 center and that reductive elimination from the Pd^{II} complex occurs with retention of configuration. In an experiment with a mixture of the diastereomeric bromo sulfoxides **7a** and **7b**, only the *cis* diastereomer **7a** underwent coupling with a variety of boronic acids, whereas **7b** remained untouched [Eq. (10) and (11)]. This result may pave the way for the development of an asymmetric process based on the resolution of racemic starting materials.



Scheme 31. Palladium-catalyzed coupling of secondary bromo sulfoxides with aryl boronic acids. A) aqueous Na_2CO_3, MeOH; B) CsF, THF; C) CsF, *tert*-amyl alcohol.



(±)-**7a** (±) (10)



(±)-**7b** (11)

5.3. Mechanistic Considerations

Whereas coupling reactions of secondary alkyl halides under nickel, iron, and cobalt catalysis appear to proceed by radical mechanisms, the stereospecificity observed in palladium-catalyzed reactions would suggest the involvement of a two-electron redox process (see Sections 5.2 and 5.3). The inversion of configuration at the stereocenter implies that the oxidative addition of the secondary alkyl halide to the Pd center (either Pd^0 or Pd^{II}) probably occurs by an S_N2 mechanism.[62] The sensitivity of S_N2 mechanisms to the steric bulk of the substrate might provide an explanation as to why palladium-catalyzed transformations of secondary alkyl halides are scarce in the literature in comparison to those developed with primary alkyl halides. However, as the development of methodologies is still in its early stages, generalization of the mechanisms may be risky, especially considering that the Sonogashira coupling reaction proceeded with a complete lack of stereospecificity when a chiral substrate was employed (see Section 5.1).

6. Summary

Significant advances have been made in transition-metal-catalyzed cross-coupling reactions of secondary alkyl halides over the last five years. Nickel, iron, cobalt, and more recently palladium catalysts all show excellent activity towards secondary alkyl electrophiles. Examples of the use of other transition metals, such as zinc, copper, silver, zirconium, chromium, and vanadium, in these challenging transformations are also beginning to appear in the literature.[63] A wide range of coupling reactions inspired by known reactions, such as the Kumada, Negishi, Stille, Suzuki, Sonogashira, and Hiyama coupling, are now possible. Thus, the scope of application of cross-coupling processes has been expanded significantly. Asymmetric processes with racemic starting materials have also been demonstrated, as well as stereospecific reactions.

Most of the cross-coupling reactions highlighted herein proceed by a radical mechanism; therefore, it would be of interest to see whether more two-electron redox processes are viable with secondary alkyl electrophiles. The development of more active catalyst systems is still necessary to enable lower catalyst loadings than those currently used. Furthermore, to improve functional-group compatibility, the range of possible nucleophilic coupling partners needs to be expanded.

An increase in the repertoire of asymmetric transformations with secondary alkyl halides would have a large impact on organic synthesis. Such powerful transformations would be particularly useful in the synthesis of complex molecules and natural products.

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