

RECENT ADVANCES IN sp^3 - sp^3 CARBON-CARBON BOND FORMING REACTIONS

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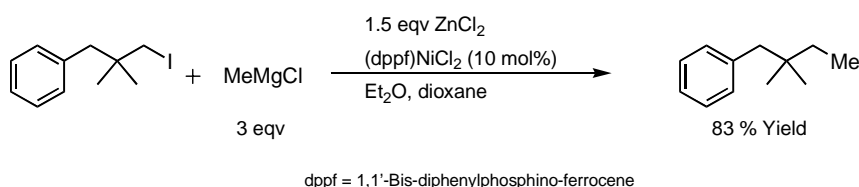
INTRODUCTION

Carbon-carbon (C-C) bond formation is among the most important processes in organic chemistry.¹ The formation of sp^3 - sp^3 C-C bonds from sp^3 -hybridized carbon electrophiles and nucleophiles. Originally, C-C bond forming reactions required harsh conditions and allowed low functional group tolerance. The Wurtz reaction, for example requires sodium metal to effect the transformation.² The development of transition metal-catalyzed reactions allowed for much more selective, mild conditions for C-C bond formation. Unfortunately, transition metal-catalyzed C-C bond-forming reactions rely on specific activating groups to be incorporated into the starting materials, thus reducing atom efficiency. This review will summarize new synthetic methods that allow for effective sp^3 - sp^3 C-C formation using activated nucleophiles and electrophiles, as well as the recently developed methods that allow for highly atom efficient reaction leading to sp^3 - sp^3 C-C bond formation.

ACTIVATED COUPLING PARTNERS – GRIGNARD REAGENTS

A reaction that employs an activated electrophile, an alkyl halide, and an alkylmagnesium species to create an sp^3 - sp^3 C-C bond was first shown by Scott in 1993 (Scheme 1).³ The use of a reagent capable of rapid oxidative addition with nickel, an alkyl iodide, and a substrate that cannot undergo β -hydride elimination produced an 83% yield of the alkylation product. This proof of concept experiment shows that if two key problems can be overcome, oxidative addition of alkyl halide reagents and β -hydride elimination transition metal mediated sp^3 - sp^3 carbon-carbon bond formation is possible.

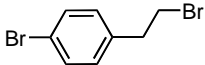
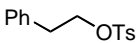
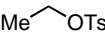
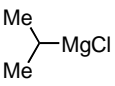
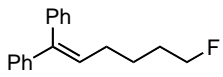
Scheme 1. Initial sp^3 - sp^3 Coupling Reaction Using Grignard Reagent



Kambe introduced the use of 1,3-butadiene in nickel-catalyzed coupling of alkyl iodide and alkyl bromide electrophiles with alkylmagnesium chloride nucleophiles.⁴ The scope of this reaction includes coupling with less-activated alkyl halides (and tosylates) and reagents that contain β -hydrogens (Table 1). The 1,3-butadiene stabilizes the Ni(0) which is generated by *in situ* reduction. Remarkably, alkyl fluorides are reactive under these conditions. Unfortunately, this reaction requires a very active Grignard

reagent, which is incompatible with many common functional groups including carbonyls, limiting the overall scope of this method.

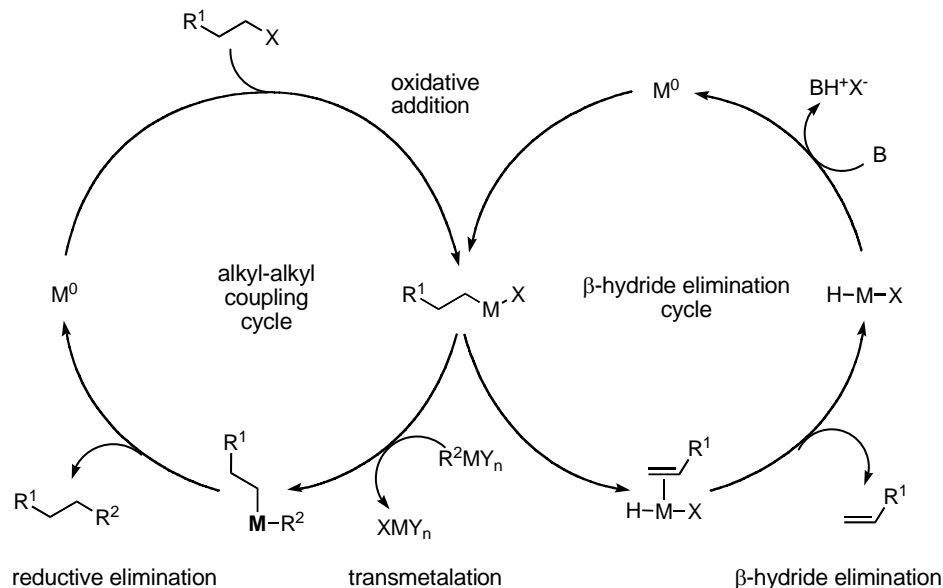
Table 1. Enhanced Scope of Grignard Nucleophile Coupling Reaction

Alkyl halide	+	Grignard Reagent	$\xrightarrow[\text{THF, 0}^\circ\text{C}]{\text{NiCl}_2 (1-3 \text{ mol}\%), \text{1,3-butadiene}}$	Alkylated Product
alkyl halide		Grignard reagent		yield (%)
		<i>n</i> -BuMgCl		100
		EtMgBr		87
		PhMgBr		56
<i>n</i> -OctylBr				72
<i>n</i> -OctylCl		<i>n</i> -BuMgCl		96
		<i>i</i> -PrMgBr		72

ACTIVATED COUPLING PARTNERS – BORON REAGENTS


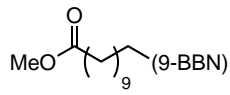
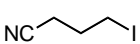
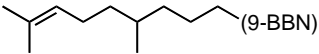
The Suzuki coupling reaction is generally applied for the construction of sp^2 - sp^2 and sp^2 - sp^3 bonds. However, sp^3 - sp^3 bonds formation using this method present a particular challenge.⁵ A general catalytic cycle for the sp^3 - sp^3 coupling of alkyl groups, similar to known Suzuki-coupling catalytic cycle is shown in Figure 1. This modified cycle demonstrates the potential problems with the sp^3 - sp^3 coupling as there is a competing cycle that leads to olefin formation. Suzuki first showed the coupling of alkyl boranes (alkyl-(9BBN)) to alkyl iodides that contain β -hydrogens (Table 2).⁵

Figure 1. General Suzuki and Negishi Catalytic Cycle with Alkyl Halides



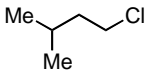
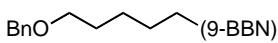
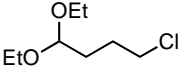
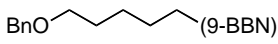
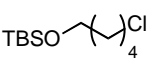
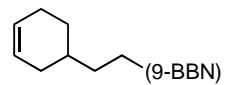
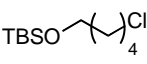
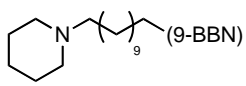
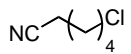
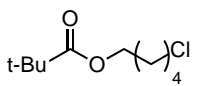
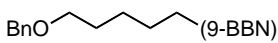
9-BBN is particularly useful because only one alkyl group can be transformed effectively. The process is hydroxide dependent, as a transient boron-ate complex is invoked as the active transmetalating agent. Palladium(0) functions well as a low valent transition-metal capable of oxidative addition to reactive alkyl iodides.

Table 2. Coupling of Alkylboranes and Alkyl Iodides

Alkyl-I	+	Alkyl-(9-BBN)	$\xrightarrow[\text{THF, 60}^\circ\text{C}]{\text{Pd(PPh}_3)_4 \text{ (3 mol\%)} \\ \text{3 eqv K}_3\text{PO}_4 \cdot \text{H}_2\text{O}}$	Alkylated Product
alkyl-I		alkyl-(9-BBN)		yield (%)
MeI		<i>n</i> -hexyl-(9BBN)		71
				45
				61

To suppress β -hydride elimination, Fu introduced a new class of alkylphosphine ligands in 2002.⁶ These phosphines drastically increase the yield and maintain the enhanced functional group tolerance of the relatively mild reaction conditions (Table 3).

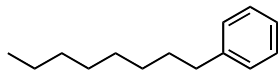
Table 3. Modified Conditions for Suzuki Coupling of Boranes

Alkyl-Cl	+	Alkyl-(9-BBN) 1.2 eqv	$\xrightarrow[\text{dioxane, 90}^\circ\text{C}]{\text{Pd}_2(\text{dba})_3 \text{ (5 mol\%)} \\ \text{PCy}_3 \text{ (20 mol\%)} \\ \text{1.1 eqv CsOH} \cdot \text{H}_2\text{O}}$	Alkylated Product
alkyl-Cl		alkyl-(9-BBN)		yield (%)
				74
				70
				72
				73
		<i>n</i> -oct(9-BBN)		73
				65

The alkylboranes used in the previously described systems are still problematic for the development of a widely used method. These reagents are air sensitive and require specific laboratory procedures. Commercially available, air stable boronic acids has been introduced as replacements.

Optimized reaction conditions using KO*t*-Bu as an additive and *di-t*-butyl(methyl)phosphine as a bulky, electron-rich-ligand to effect sp³-sp³ C-C bond formation with the less reactive alkylboronic acids and alkyl halides has been developed (Table 4).⁷

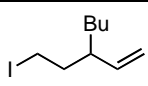
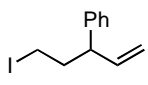
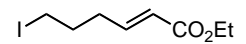
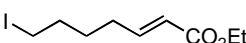
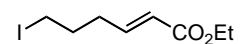
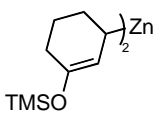
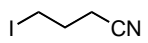
Table 4. Boronic Acids in sp³-sp³ Suzuki Coupling Reaction

n -octylBr + (HO) ₂ B-Ph 1.5 eqv		Pd(OAc) ₂ (5 mol%) phosphine ligand (10 mol%) 3 eqv KO <i>t</i> -Bu <i>t</i> -amyl-alcohol, rt		
additive	solvent	ligand	yield (%)	
K ₃ PO ₄ H ₂ O	THF	PCy ₃	<2	
KO <i>t</i> -Bu	THF	PCy ₃	11	
KO <i>t</i> -Bu	<i>t</i> -amyl alcohol	PCy ₃	63	
KO <i>t</i> -Bu	<i>t</i> -amyl alcohol	P(<i>t</i> -Bu) ₂ Me	85	

ACTIVATED COUPLING PARTNERS – ZINC REAGENTS

Despite the utility of organoboron reagents in the coupling process, they are limited in reactivity and scope. Organozinc reagents are more reactive and are known to participate in transition-metal catalyzed reactions. In 1995, Knochel demonstrated the use of a nickel-catalyzed sp³-sp³ coupling reaction using a dialkylzinc reagent and LiI as an activator.⁸ Although many alkylzinc reagents are effective coupling partners, a tethered double bond the reactive alkyl halide bond is required for the cross coupling reaction (Table 5).

Table 5. Initial Scope of Negishi sp³-sp³ Coupling

Alkyl Iodide	+	R ₂ Zn	Ni(acac) ₂ (7.5 mol%) LiI (20 mol%) THF, -35°C	Alkylated Product
alkyl halide		organozinc		yield (%)
		n-pentyl ₂ Zn		72
		t-Bu-C(=O)-O-(CH ₂) ₂ -Zn		90
		n-pentyl ₂ Zn		83
		AcO-(CH ₂) ₂ -Zn		78
				65
		n-pentyl ₂ Zn		52

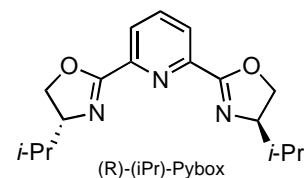
Fu employs designed phosphine ligands to effect coupling of commercially available alkylzinc halides with alkyl halides (Table 6).⁹ Enantioselective sp^3 - sp^3 carbon-carbon bond formation has been achieved with racemic α -bromoamides as coupling partners with organozinc reagents in the presence of commercially available Pybox ligands (Table 7).¹⁰

Table 6. Alkylation with Alkylzinc Halides

Alkyl halide	+	Organozinc 1.3 eqv	$\xrightarrow[\text{2:1 THF:NMP, 80}^\circ\text{C}]{\text{Pd}_2(\text{dba})_3 \text{ (2 mol\%)}PCyp_3 \text{ (8 mol\%)}1.2 \text{ eqv NMI}}$	Alkylated Product
alkyl halide		organozinc		yield (%)
<i>n</i> -DecBr				89
				76
				83
<i>n</i> -DecBr				52
BnO-CH ₂ -CH ₂ -CH ₂ -Br				68
TBSO-CH ₂ -CH ₂ -CH ₂ -Br				67
NC-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -Br				65

Table 7. Enantioselective sp^3 - sp^3 Bond Formation with Zinc Reagents

	+	R^2ZnBr 1 eqv	$\xrightarrow[\text{7:1 DMI:THF, 0}^\circ\text{C}]{\text{NiCl}_2\text{:glyme (10 mol\%)}(\text{R})\text{-(i-Pr)-Pybox (13 mol\%)}}$	
R ¹		R ²		yield (%) er
Et				78 39:1
Et				77 49:1
Me				66 7.7:1
Et				51 49:1
Et				70 27:1



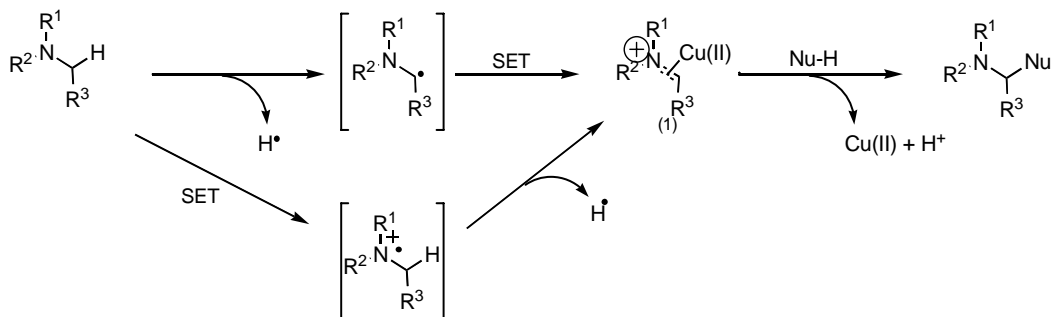
DIRECT COUPLING PARTNERS LEADING TO sp^3 - sp^3 COUPLING

A direct sp^3 - sp^3 , C-C, cross-coupling reaction from two sp^3 C-H bonds has demonstrated the potential for milder and more selective transformations using less expensive starting materials.¹¹ The use of catalytic quantities of copper bromide, in the presence of *tert*-butyl hydrogen peroxide (TBHP), allows for the coupling of *N*-methyl and *N*-methylene groups to NO_2 activated nucleophiles, in a process similar to a nitro-Mannich or aza-Henry reaction (Table 8). This reaction is thought to proceed through an iminium intermediate (**1**) that arises through hydride abstraction from the starting material (Figure 2).¹² This method can also incorporate other nucleophiles including malonates and malononitriles.¹³

Table 8. Coupling Next to N with Nitroalkane

$\begin{array}{c} \text{R}^1 \\ \\ \text{R}^2\text{N}-\text{CH}_2 \\ \\ \text{R}^3 \end{array} + \begin{array}{c} \text{R}^4 \\ \\ \text{H}-\text{C}-\text{NO}_2 \\ \\ \text{2 eqv} \end{array}$		$\xrightarrow[\text{5.5M decane, rt}]{\begin{array}{c} \text{CuBr (5 mol\%)} \\ \text{1.2 eqv TBHP} \end{array}}$		$\begin{array}{c} \text{R}^1 \\ \\ \text{R}^2\text{N}-\text{CH}(\text{R}^3)-\text{CH}(\text{R}^4)-\text{NO}_2 \end{array}$
alkyl amine	nitro alkane	yield (%)	product	
	MeNO_2	65		
	EtNO_2	52		
	EtNO_2	51		
	MeNO_2	62		

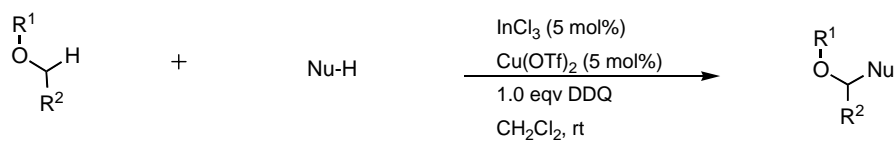
Figure 2. Proposed Mechanism for Coupling Next to Nitrogen

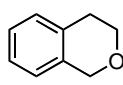
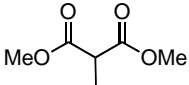
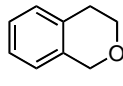
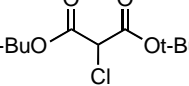
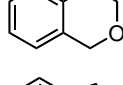
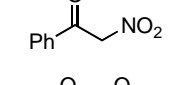
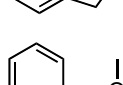
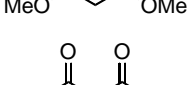
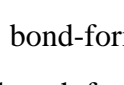
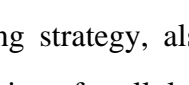


These methods rely on nitrogen as a positive-charge-stabilizing heteroatom next to the activated hydrogen atom. Nitrogen is not unique as other heteroatoms can be used to create similar sp^3 - sp^3 , C-C bonds from activated C-H bonds. Oxygen is also effective at stabilizing reactive intermediates for the direct coupling of benzyl ether carbons with malonates.^{14,15} This method, developed by Li, employs

indium and copper, along with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as the terminal oxidant. Pronucleophilic sp^3 sites are coupled to sp^3 atoms next to the stabilizing oxygen atom through a mechanism that closely resembles the nitrogen system discussed previously (Table 9). The proposed mechanism involves a hydride abstraction from the carbon next to oxygen to generate an oxocarbenium ion, which can then couple with the diester enolate.¹⁶ The scope of the reaction also includes simple enolizable ketones.¹⁷

Table 9. Coupling Next to Oxygen with Malonate



substrate	nucleophile	yield (%)
		53
		64
		72
		48
		17

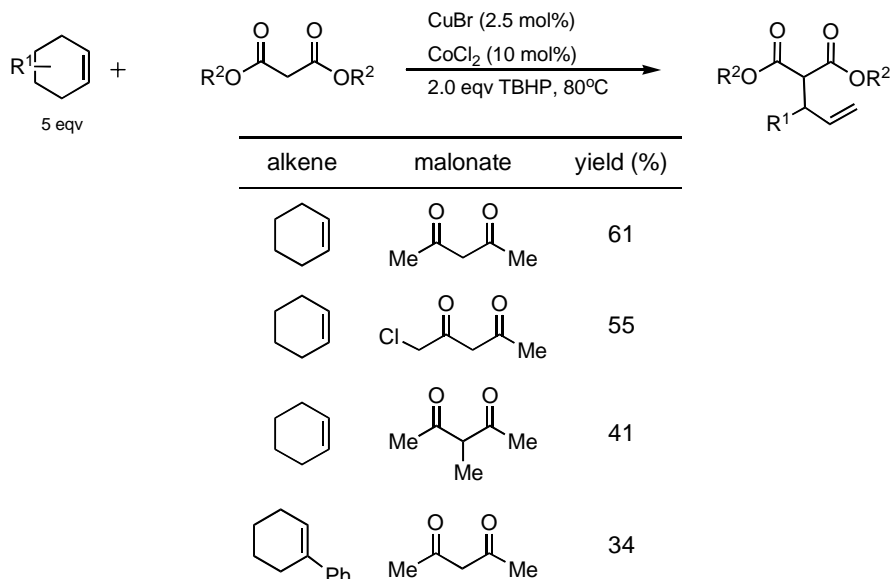
The direct sp^3 - sp^3 , C-C, bond-forming strategy, also involves the use of allylic C-H bonds. Activation of allylic C-H bonds through formation of π -allyl complexes lends itself to effective C-C bond forming strategies.¹⁸ Li demonstrated the use of a cobalt- and copper-catalyzed reaction of cyclic olefins with 1,3-diketones to afford the allylically substituted product in good yields directly from two sp^3 C-H bonds (Table 10).¹⁹

SUMMARY

Good progress has been made toward the selective formation of sp^3 - sp^3 carbon-carbon bonds. The nickel and palladium chemistry reported by Fu demonstrates the state of the art in selectivity and reactivity using activated nucleophiles and electrophiles. The Nesighi-type systems developed by Fu demonstrates great functional group tolerance, is high yielding, and effective asymmetric induction has been observed when using secondary alkyl halides. The use of sp^3 hybridized C-H bonds as unactivated precursors for sp^3 - sp^3 carbon-carbon bond formation has also been achieved. The advantages of these

methods are higher atom economy, shortened synthetic routes, more economical feedstock, and the potential of milder chemical reactions than conventional synthetic methods.¹⁸

Table 10. Coupling Next to an Olefin with Malonate



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