Invention of Synthetic Reactions Based on σ−Bond Activation

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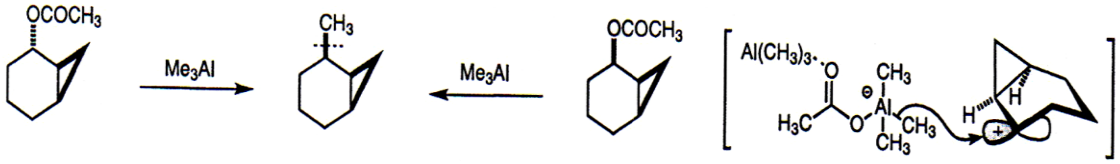
Abstract:
Many more reactions are reported that involves both carbanionic and carbocationic species. The reaction of allylic acetate with trialkylaluminum, R_3Al, whereby an allylic cation and alanate are produced and the alanate delivers an alkyl anion to the allylic cationic center. The reaction of organoaluminums is well-documented, I am convinced this new point of view, or philosophy, is essential for devising and developing novel synthetic reactions. We have observed that the reaction of trimethylaluminum with diastereometric cyclopropylmethyltype acetates provides the same product, endo-methylated norcarane, and have shown that the reaction1 proceeds via a common cyclopropylmethyl-type carbocationic intermediate (Scheme 1).

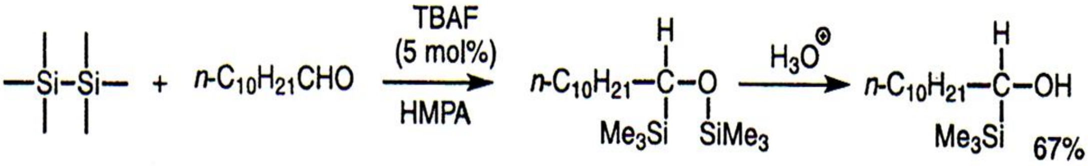
Keywords: Diastereometric, Carbocation, Disilane stereoselectivity, Chromatograpic separation.



Scheme 1.

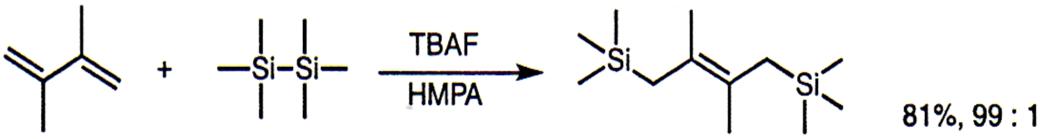
Organosilicon Reagent/Fluoride Ion

It would be fascinating if both the cationic and anionic species were generated by the cleavage of element–element bonds. I pictured a reaction scheme in which disilane and a fluoride ion produce a silyl anion and fluorosilane, with the fluorosilane behaving similar to an electrophilic silyl cation. I found that when hexamethyldisilane and tetrabutylammonium fluoride (TBAF) are mixed in hexamethylphosophric triamide (HMPA) in the presence of an aldehyde, carbonyl attack of the trimethylsilyl anion occurs, followed by O-trimethylsilylation. After aqueous workup, we obtained an α-silyl alcohol, demonstrating that the designed reaction2 works well. Heterolysis of an element–element bond is conceptually rewarding and is closely related to the recently established activation of molecular hydrogen by a frustrated base pair (Scheme 2)



Scheme 2.

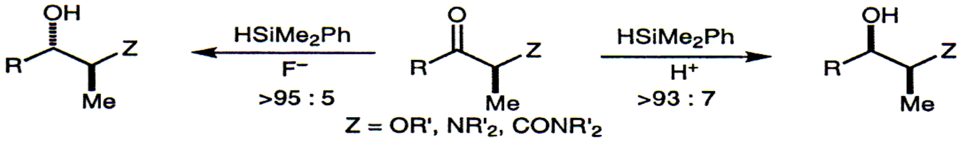
For example, 2,3-dimethyl-1,3-butadiene is converted to (E)-1,4-bis(trimethylsilyl)-2,3-dimethyl-2-butene.[2] Product formation is believed to involve a trimethylsilyl anion which undergoes single electron transfer (SET) to butadiene to give a trimethylsilyl radical and a butadiene radical anion. Coupling of these at the terminal carbon should give a TMSCH2-substituted allylic anion, which attacks hexamethyldisilane to give the product and a silyl anion. In HMPA, SET should readily occur from a naked (i.e., in the absence of a metal counter-ion) hard silyl anion. Regardless, you may consider the net transformation as an insertion of butadiene between the Si-Si σ-bond of hexamethyldisilanes (Scheme 3)



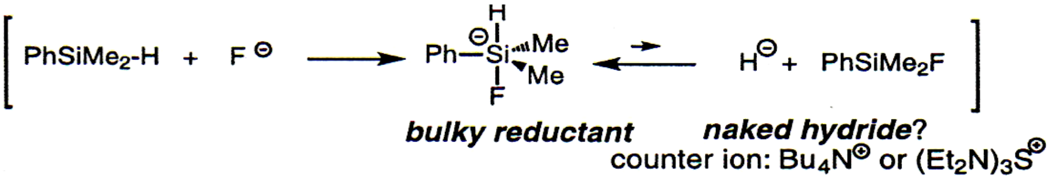
Scheme 3.

I set about generalizing the basic concept of organosilicon compound/fluoride ion-based reaction to generate metal-free (naked) anionic species, and found that halomethyl(trimethyl)silanes and trifluorovinyl(trimethyl) silane undergo an addition reaction[3] with aldehydes, even at room temperature, upon treatment with tris(dimethylamino) sulfur difluoro(trimethyl)silicate (TASF) in HMPA or THF. This finding is remarkable given that halomethyllithiums and trifluorovinyllithium are both unstable organometallic species and were thought only to be generated at extremely low temperatures. Thus, the idea that removal of a metal counter-ion from carbenoids (i.e., organometals with a leaving group on the α-carbon) to generate naked carbanionic species with a leaving group on the α-carbon led to the discovery of useful synthetic reactions that can be conducted at ambient temperature. I further extended the concept of organosilicon reagents/fluoride ion-based reaction to hydrosilane/fluoride ion in the hope of generating a naked hydride. I carried out reactions of α-chiral ketones with dimethylphenylsilane/fluoride ion and observed threo-selective reduction.[3] We expected that a pentacoordinate hydrosilicate should be sufficiently bulky to stereoselectively reduce ketone carbonyls according to the Felkin-Ahn model transition state.

It is reasonable to assume that hydrido and electronegative fluoro groups in trigonal bipyramidal pentacoordinate silicate should be both apical, and organic substituents locating at equatorial positions. Since the bond angles of H–Si–organic groups in the trigonal bipyramide are 90°, the pentacoordiante hydride is likely bulkier than tetrahedral (109.5°) borohydrides. Consequently, carbonyl groups are reduced with a high level of stereoselectivity. In any event, we failed to produce a naked hydride (Scheme 4, 5).4



Scheme 4.

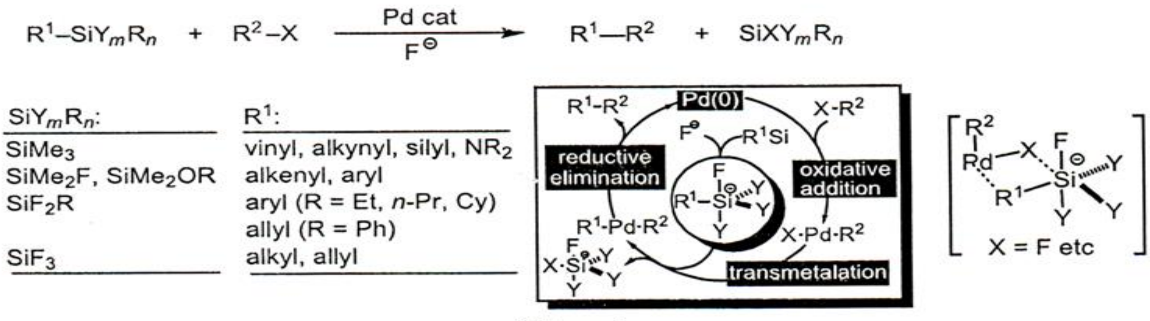


Scheme 5

Cross-Coupling Reaction with Organosilicon Compounds

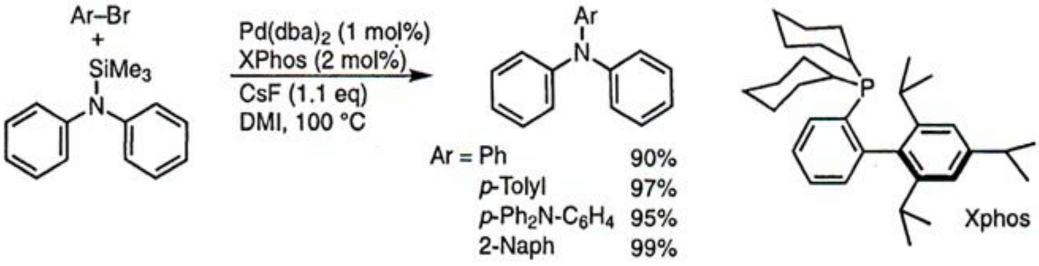
I next envisaged what would happen if a transition metal catalyst was present in the organosilicon/fluoride ion system. Is the organic group on silicon successfully transferred to the transition metal, or does the fluoride ion simply attack the transition metal center to give metal fluoride and lose catalytic activity? To find out, mixed Pd(II) complex, TASF as a fluoride source, trimethylvinylsilane and 1-iodonaphthalene in HMPA, and isolated 1-vinylnaphthalene in a nearly quantitative yield.[5] His findings demonstrate that our working hypothesis was correct; this new silicon-based cross-coupling reaction was later named Hiyama Coupling. The TASF fluoride source may be replaced with TBAF or KF.

To our surprise, KOH could also activate the C–Si bond. However, attempts to extend this approach to substituted vinylsilanes were unsuccessful. This limitation was overcome by introducing a fluorine or alkoxy group on silicon: this effectively extended the scope of the cross-coupling reaction and demonstrated that a heteroatom on silicon assists formation of pentacoordiate silicates, an essential species for successful reaction. A theoretical study6 and our intuition both suggested a four-membered cyclic transition state for the transmetalation from Si to Pd. Fluoride is believed to play a key role in the transmetalation. The following scheme summarizes the siliconbased cross-coupling reaction (Scheme 6)



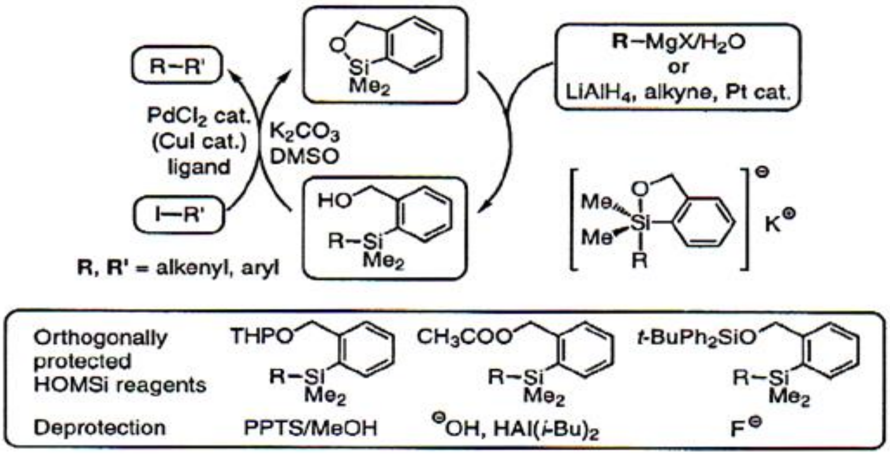
Scheme 6.

Halosilanes and alkoxysilanes are sensitive to moisture and are thus incompatible with chromatographic purification, so cross-coupling with these organosilicon reagents is less accessible compared to Suzuki-Miyaura coupling. It is showed that one organic group on tetraorganosilanes can be in situ converted to a halo- or alkoxy group by the action of a fluoride ion. We recently found that C–N coupling7 is conveniently achieved with trimethylsilylamines and allows easy synthesis of triarylamines which display a characteristic reactivity profile different from that obtained using Hartwig– Buchwald coupling (Scheme 7).



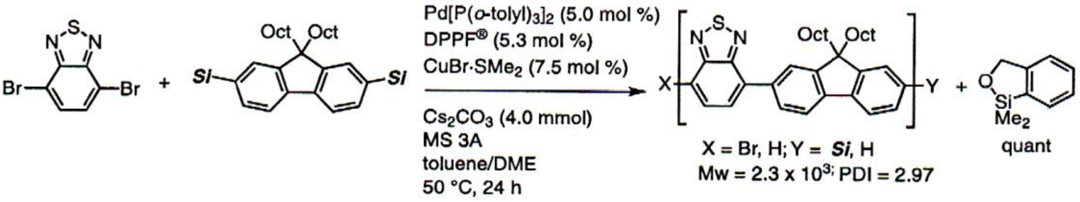
Scheme 7.

It is suggested by HOMSi (dimethyl(ohydroxymethylphenyl)silane) tetraorgansilane reagents8, predicting that they would be converted to a pentacoordinate structure by intramolecular nucleophilic attack of the hydroxyl group. Protection of the hydroxyl group with a common protecting group significantly stabilizes the silicon reagents under chromatographic separation and common reaction conditions; upon deprotection, the reagents become couplingactive. After the reaction, the silicon residue is recovered as a cyclic silyl ether, which is reconverted back to the HOMSi reagent by reaction with organolithium or –magnesium reagents. Recently, direct C–H silylation of (hetero)aromatics and terminal alkenes has been demonstrated starting with a THP-protected HOMSi hydride reagent and an iridium catalyst (Scheme 8)



Scheme 8.

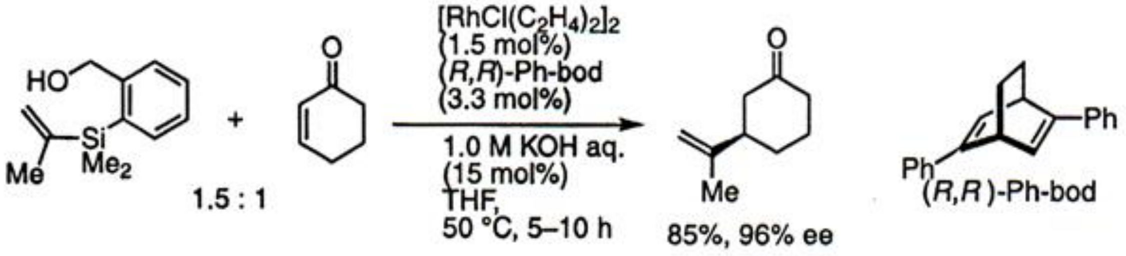
Cross-coupling reaction with HOMSi reagents has recently been applied to polymer synthesis under mild conditions. The resulting π-conjugated polymers find important applications as light-emitting and solar-cell materials (Scheme 9).[9]



Scheme 9.

Conjugate addition of HOMSi Reagents

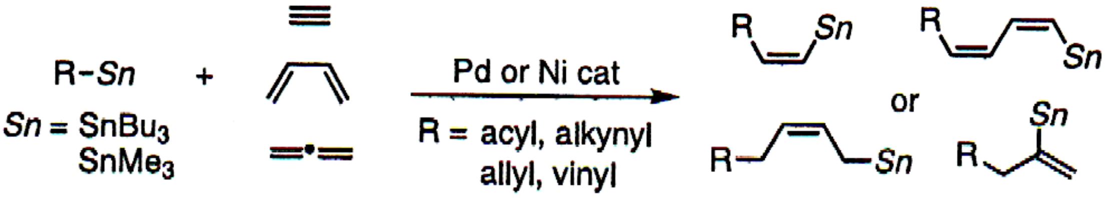
Once we discovered that transmetalation from Si to Pd is possible, we assumed that the same transformation from Si to Rh could be achieved. Indeed, Rh-catalyzed conjugate addition of organosilicon reagents had some precedents. I showed that HOMSi reagents undergo conjugate addition to enones, α,β-unsaturated esters, and amides with high enantioselection using a chiral diene ligand.10 Here again, the cogenerated cyclic silyl ether is readily recovered and converted back to the corresponding HOMSi reagent (Scheme 10).



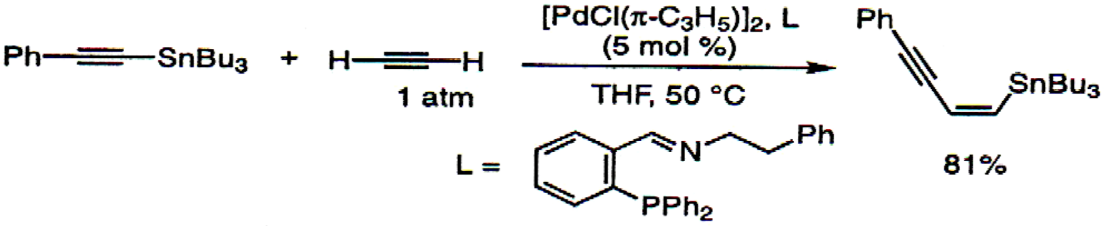
Scheme 10.

Carbostannylation Reaction of Alkynes and Dienes

It had been examining the Migita-Kosugi-Stille coupling reaction mechanism and had evidence for a novel catalytic cycle involving oxidative addition of Pd(0) to the C–Sn bond, followed by transmetalation with organic halides. I was surprised at his proposed mechanism, and suggested that involvement of the oxidative adduct C–Pd(II)–Sn may lead to the insertion of an unsaturated C–C bond between the C–Pd or Pd–Sn bond; if this was indeed the case, then a new synthetic reaction might be realized, leading to insertion of an alkyne between the C–Sn bond. This reaction proceeded well and was named ‘transition metal-catalyzed carbostannylation’.11 Various organostannane reagents, and alkynes or dienes are applicable to the transformation. A typical example, shown below, is the addition of alkynylstannane to ethyne to give (Z)-but-3-yn-1-enyl(tributyl)stannane. This carbostannylation reaction has made various π-conjugated organostannanes accessible (Scheme 11, 12).



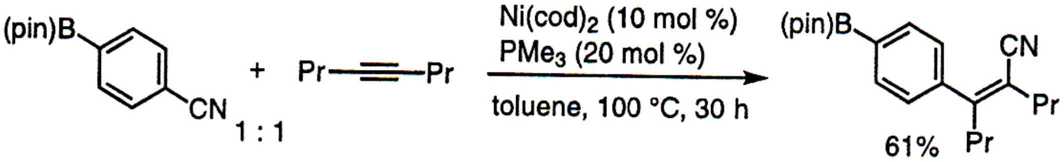
Scheme 11.



Scheme 12.

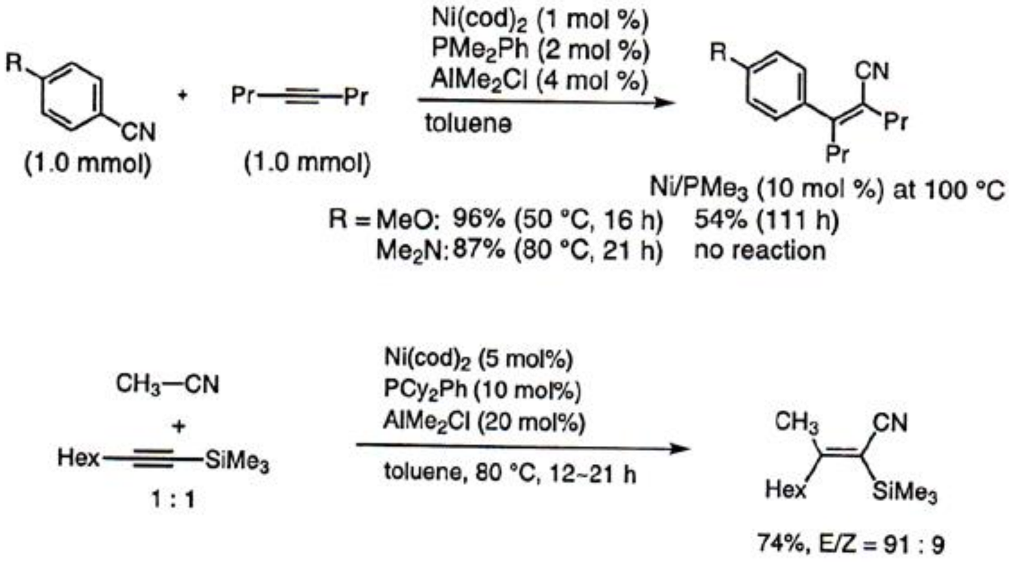
Carbocyanation Reaction of Alkynes and Alkenes

I immediately suggested examining the reaction in the presence of unsaturated substrates, as we did for the carbostannylation reaction. However, the initial protocol needed 10 mol% of Ni(0) catalyst and required a 1 or 2 days to achieve synthetically meaningful yields. Although the catalyst was lazy (the turn over number was roughly 6~7), we called the new reaction carbocyanation (Scheme 13).[11]



Scheme 13.

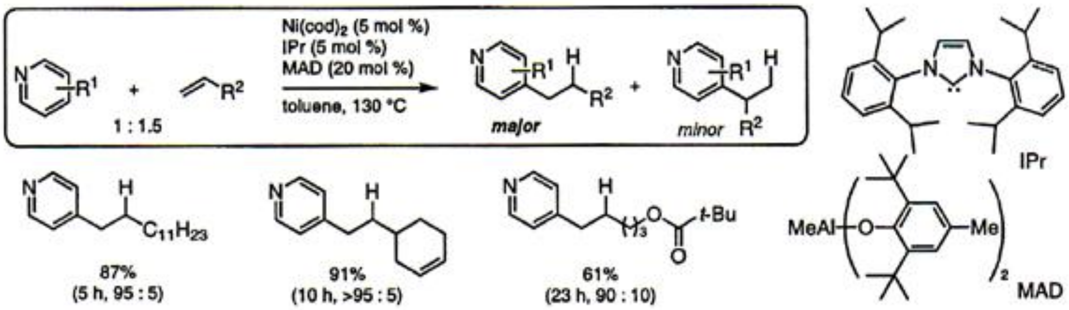
I improved the catalytic efficiency by adding a mild Lewis acid such as organoaluminum, -borane, or -zinc to make the reaction truly catalytic.[12] Under these new conditions, not only aryl cyanides, but allyl and alkenyl cyanides were also applicable, as were acetonitriles: CH_3–CN was cleaved into CH_3 and CN fragments and added to internal alkynes in a syn manner (Scheme 14)



Scheme 14.

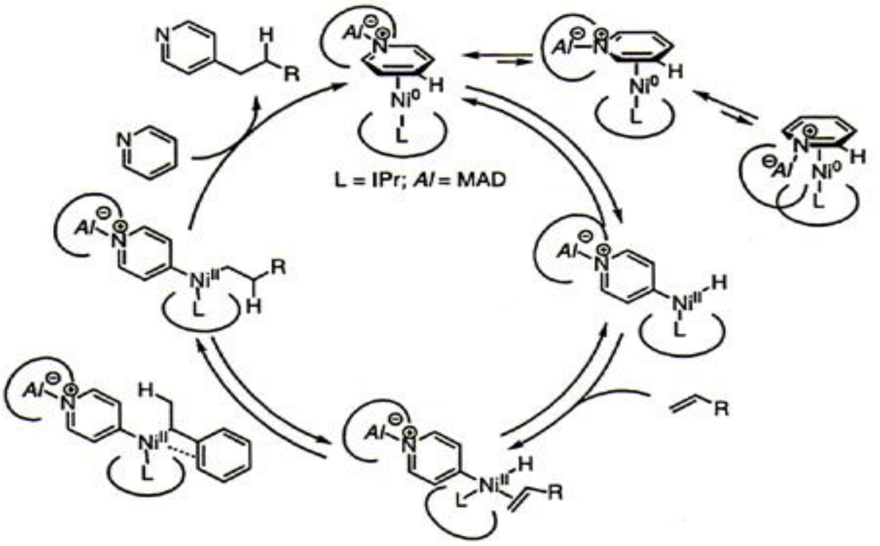
Hydro(hetero)arylation of Alkynes and Alkenes

While studying the carbocyanation of N-protected 3-cyanoindoles under the original conditions, we observed the formation of a small amount of byproduct and attributed it to C(2)–H activation followed by alkyne insertion. Tuning the protecting group and ligand resulted in C–H activation occurring uniformly with heteroaromatics and polyfluoroaromatic compounds.13 The most synthetically significant discovery was C(4)-selective normal alkylation14 of pyridines with terminal olefins using Ni(cod)2/iPr ligand and an aluminum Lewis acid MAD. Given that pyridine and its homologs are inert towards Friedel-Crafts reaction, site-selective heteroarylation with terminal olefins provides a new route to the n-alkylation of pyridines (Scheme 15).



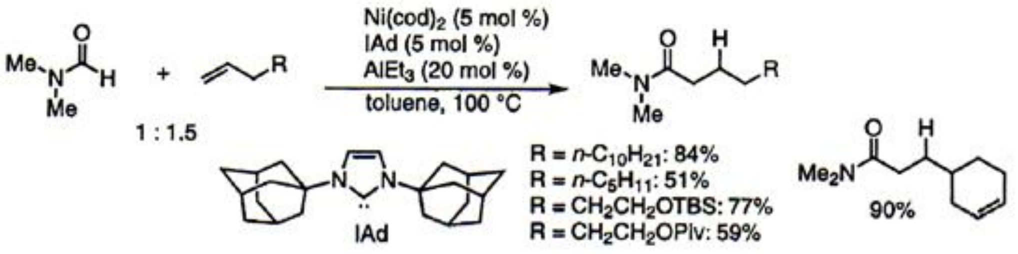
Scheme 15.

The observed regioselectivity is understood insofar as (1) the bulky MAD is coordinated by the pyridine nitrogen, (2) Ni-Ipr interacts with the pyridine ring π-electrons, (3) steric repulsion between the metal centers causes Ni to locate far from the nitrogen and interact at C(4), (4) Ni(0) is oxidatively added to C(4)–H, (5) hydronickelation of the terminal olefins occurs, and (6) quick reductive elimination is caused by the two bulky ligands. Accordingly, the bulkiness of the Ni ligands and the aluminum metal are key to selective alkylation (Scheme 16).



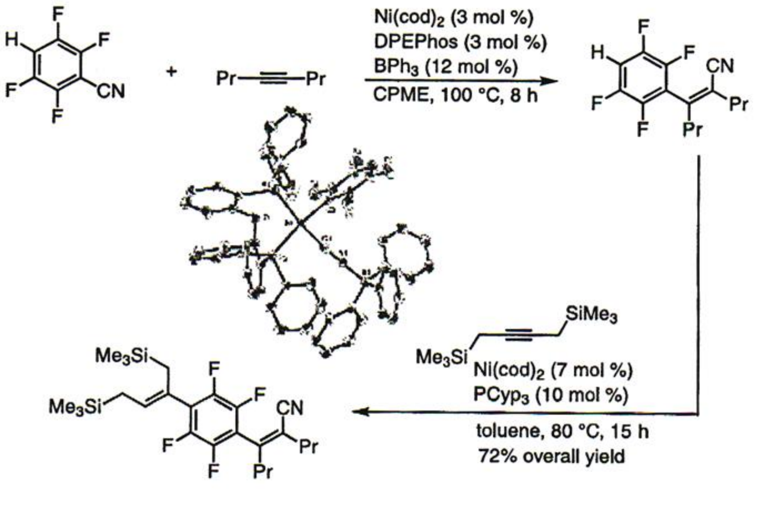
Scheme 16.

The concept of Ni(0)/Lewis acid is applicable to N,Ndimethylformamide (DMF), whose formyl C–H bond oxidatively adds to Ni(0). The resulting Ni–H bond undergoes regioselective addition to terminal olefins, then subsequent reductive elimination to produce alkanamide under one-carbon homologation of olefin (Scheme 17).[15]



Scheme 17.

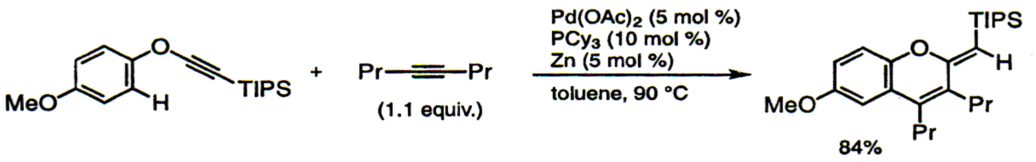
Polyfluorobenzenes undergo C–H activation by Ni(0) in the absence of a Lewis acid; it is possible that the most electrophilic position is activated to effect hydroarylation.[16] Accordingly, polyfluorobenzonitriles first undergo carbocyanation and then hydroarylation of the internal alkynes to give extensively π-conjugated polyfluorobenzenes.[17] The structure of the oxidative adduct of the C–CN bond to Ni(0) can be unambiguously determined by X-ray crystallography (Scheme 18)



Scheme 18.

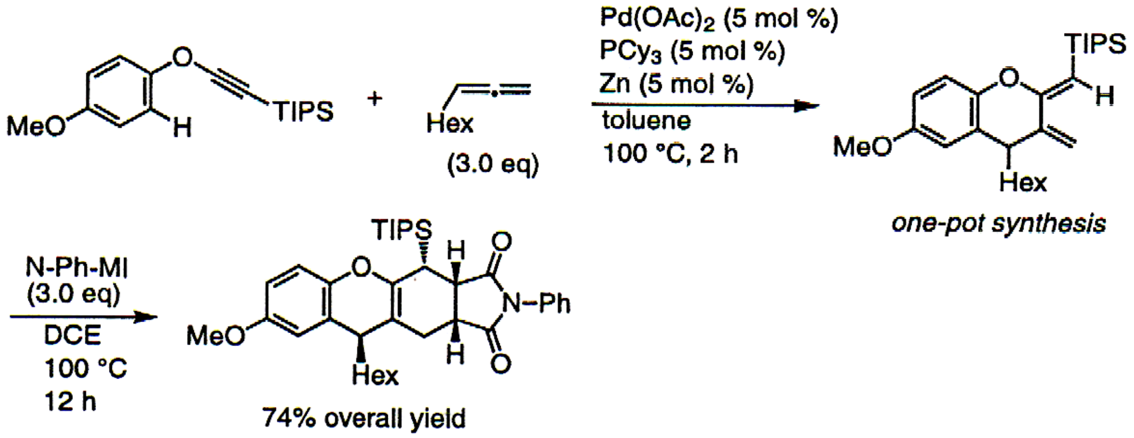
ortho-C–H Activation of Phenyl Silylethynyl Ethers and Cromane Ring Formation with Alkynes

I started studying the interaction of transition metal complexes with p-methoxyphenyl TIPS-ethynyl ether in the presence of 4-octyne, with the intention of cleaving either of the ethereal C–O bonds. However, to our surprise, the orthoC–H bond was found to be selectively activated by Pd(0), allowing incorporation of 4-octyne to give 2-(TIPSmethylene) benzochromene. This reaction is attributed to nucleophilic attack of Pd(0) on the α-carbon of the ethynyloxy group to give a Pd(II) intermediate, which then oxidatively adds to the orthoC–H bond to mediate chromene annulation.18 Worthy of note is the silylethynoxy group behaved as an acceptor of Pd(0) to produce Pd(II) temporalily before oxidative addition to an orthoC–H bond. This is a new type of directing group of ortho-C–H activation (Scheme 19).



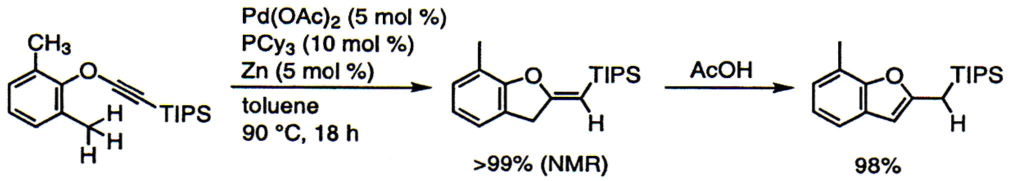
Scheme 19.

Conducting the reaction using an allene in lieu of an internal alkyne produced 2,3-bismethylenechromane.[19a] This readily underwent Diels–Alder reaction to stereoselectively provide the tetracyclic ring structure. Isocyanates also react with the same alkynyl ether to give solid benzoxazine[19b] which emits light upon UV irradiation, even in the solid state (Scheme 20).



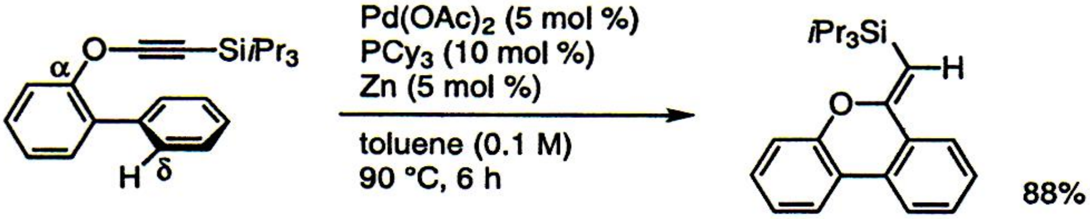
Scheme 20.

The Pd(II)/Zn catalyst promotes cyclization of 2,6-dimethylphenyl TIPS-ethynyl ether to give 2-(TIPSmethylene)dihydrobenzofuran. Thus, γ-C–H bond activation is made feasible (Scheme 21).[20]



Scheme 21.

Under similar conditions, 2-(TIPS-ethynyloxy)-2-biphenyl underwent δ-C–H activation to form an oxatricyclic product[21] which was readily converted to the 10,10-disubstituted 9-oxaphenanthrene framework, often used as potent electron carrier materials (Scheme 22).



Scheme 22.

In summary, this is the story to date of how I have invented synthetic reactions for C-C formation. I, of course, encountered problems during my research; now readers know how I analyzed the problems, how I constructed working hypotheses, and how I solved the problems. Invention of reactions described herein would suggest how it is essential to understand reaction mechanism and pay attention to relating science and technology.

Acknowledgement

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