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Recent Advances in carbon-carbon development via carbon-Hydrogen Activation

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Abstract— Carbon-hydrogen bond activation is a burgeoning area of organometallic chemistry with the potential to provide a wealth of improved protocols in synthetic organic chemistry. However, today a lot of challenges stay that continue to limit its synthetic utility. An analysis of some current advance in the area of carbon-carbon bond formation via direct carbon-hydrogen activation is presented. So using different synthetic method Carbon-hydrogen bond activation possible and even the attract of this new and growing field, definitely prompt raised academic and industrial attention, and improved protocols for fascinating and synthetically applicable reactions are possible to still seem.

Keywords—*Carbon-Hydrogenbondactivation,Organometallic,Carbon-carbonbond,Syntheticutility,Industrial*

I. INTRODUCTION

Organic chemists struggle to develop and build use of capable and atom economical methodology for the elaboration of advanced structures from simple and promptly getable precursors. Over the history 20 years, unbelievable strides are created within the functionalization of carbon-hydrogen bonds, arguably the foremost current "functional group" in chemical science. Direct carbon-hydrogen activation (in distinction to metal-carbenoid elicited carbon -hydrogen insertion)1d has its roots within the pioneering work of Shilov, Bercaw, Bergman, Crabtree, Murai, and goldman, chemical analysis back to the Seventies and Eighties.1 Formally, it needs insertion of a transition metal (usually metallic element, Ir, Rh or Pd) across a strong carbon -hydrogen bond (90-105 kcal/mol) to make a brand new, weaker C-Metal bond (50- eighty kcal/mol), followed by creation of a completely unique C-C bond (Scheme 1).1 A central goal within the progress of any new methodology is artificial utility, one that has, for the foremost half, eluded this field. The presence and inherent stability of carbon -hydrogen bonds makes the development of synthetically valuable processes particularly intimidating. The target of this review is to speak concerning recent advances completed within the direction of the growth of synthetically useful carbon -hydrogen activation reactions within the context of carbon-carbon bond formation. The problems of reactivity, generality, functional group tolerance, and enantioselectivity are addressed.

Research completed in chemistry department of R.K. University and Saurashtra university collaboration.

II. RELATED WORK

Carbon -hydrogen activation has been limited primarily to straightforward aryl and vinyl (sp2) carbon -hydrogen bonds. The selective activation of sp3 carbon -hydrogen bonds is understood to be each kinetically and thermodynamically unfavourable, and has typically solely been attainable with hydrocarbon solvents as substrates. It's documented, however, that carbon -hydrogen bonds adjacent to heteroatom are weaker than easy alkane series sp3 carbon -hydrogen bond. In 2001, Murai et al. took advantage of this reality, and showed that pyrrolidine and piperidine carbon -hydrogen bonds may be by selection activated by $Ru_3(CO)_{12}$ and paired to inactivated alkenes, providing mixtures of mono- and dialkylated product.2 In Murai's system, a 2-pyridyl moiety on the nitrogen is needed to direct the metal centre to the specified carbon -hydrogen bond. Despite the comparatively easy product, this work set a crucial precedent for the activation of α-heteroatom sp3 carbon -hydrogen bonds

To date, all samples of catalytic intermolecular sp3 carbon -hydrogen activation need a leading group, inherently limiting reaction relevance. To the current finish, Sames and co-employees have applied Murai's construct of α -heteroatom carbon -hydrogen bond reactivity toward the arylation of sp3

carbon -hydrogen bonds within the absence of a leading group (Table 1).3 during a current statement, they report the non- directed Ru-catalyzed carbon -hydrogen arylation of N-phenylpyrrolidine with iodobenzene, and Cs_2CO_3 in t-BuOH. Enhancements within the initial yields were obtained by removing the π-acceptor (stabilizing and deactivating) CO ligand. Once a mechanistic investigation, the authors present proof of an oxidative addition pathway to the exclusion of one involving β-hydride elimination. Preliminary exam of substrate scope

Showed that pyrrolidines substituted with phenyl, methyl, benzyl, and benzoyl practicality square measure with success arylated Though yields for these comparatively straightforward product are low, the novelty and promising property for this unexampled category of transformations has raised the bar for sp3 carbon -hydrogen activation

Figure 1 generally accepted direct carbon-hydrogen activation

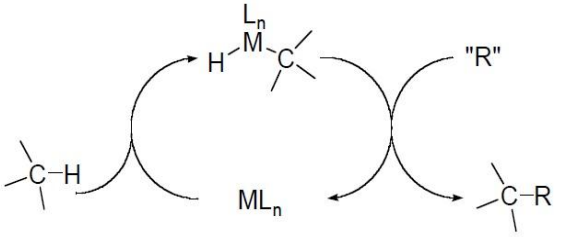

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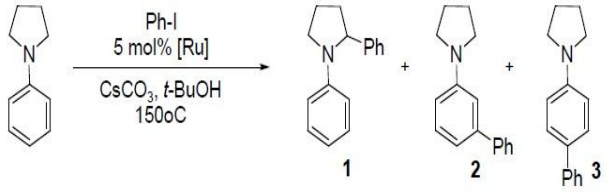
Table 1 Non-directed Sp^3 carbon-hydrogen activation



[Ru]	**1** / **2** / **3** (% yields)
$Ru(H)_2(CO)(PCy_3)_3$	32 / 6 / 4
$Ru(H_2)(H)_2(PCy_3)_3$	38 / 6 / 4
$Ru(H_2)_2(H)_2(PCy_3)_2$	40 / 7 / 4
$Ru(H_2)_2(H)_2(PCy_3)_2$ (10 mol%)	59 / 9 / 4

III. METHODOLOGY

Sames has additionally recently reportable an intramolecular CH activation of sp3 carbon–hydrogen bonds to furnish additional synthetically fascinating pyrrolidinones and indolizidinones.4 Again, harnessing the additional reactive nature of α-heteroatom carbon-hydrogen bonds, treatment of tertiary amide alkenes with $[Ir(COE)_2Cl]_2$ / IPr (Arduengo ligand) appointed the corresponding cyclized product (Figure 2). Mechanistic investigations have shown that complicated four may be a competent catalyst in stoichiometric reactions, and is thus postulated to be directly concerned within the catalytic cycle (Figure 2). The authors propose that in place generation of four positions the α-carbon -hydrogen bond for facile carbon -hydrogen activation, to furnish the group iridium-hydride (5). Olefin insertion to make six (favored over β-hydride elimination), then β-hydride elimination to seven, and eventually tautomerization provides the heterocyclic products.Despite modest yields and therefore the demand for geminal dimethyl substitution α to the amide carbonyl. Amide carbonyl, the reaction displays promising functional group tolerance, as each silyloxy- and estercontaining pyrrolidines are compatible, with prolinederived eight retentive its stereochemical integrity.

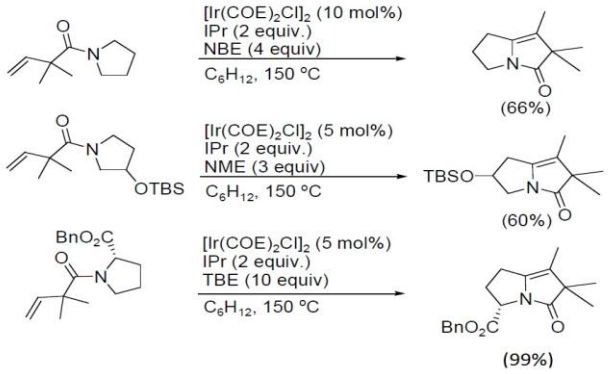


Figure 2 possibility of the intramolecular Sp^3 carbon -hydrogen activation/cyclization

The general application of carbon -hydrogen activation has been hampered by needs of either extremely specific or lowest functionality. The Sames group has created vital recent contributions toward addressing these limitations by developing a range of direct arylations of functionalized and unprotected heterocycles, the product of that are analogous to those obtained from Pd catalyzed cross coupling reactions, while not the need for a metalized aryl species. Drawing from previous precedent for carbon -hydrogen activation of azines by $Ru_3(CO)_{12}$, yet as connected catalytic carbon -hydrogen acylation reactions of nitrogen-containing heterocycles by Murai 5a and Moore,5b Sames has according the site-specific phenylation of pyridine catalyzed by a phosphido-bridged Ru compound complicated. This complicated was discovered throughout mechanistic

investigations into the catalytic role of $Ru_3(CO)_{12}$ during this reaction.6

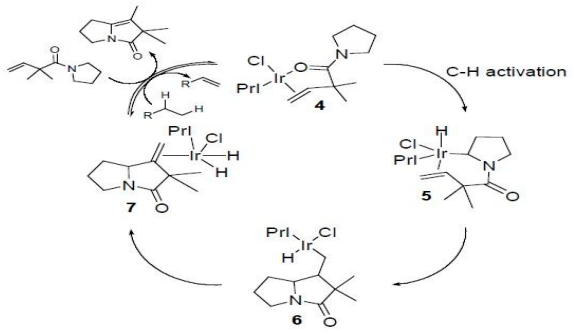


Figure 3 proposed mechanism

This easy transformation is a model for carbon -hydrogen arylation of electron-deficient heteroaromatics,that are indispensable pharmaceutical motifs. In 1998, Nomura and co-workers first reportable the intermolecular arylation of easy azoles.7 The Sames cluster has extended this system, creating it extremely useful cluster tolerant. They need obtained spectacular results with regard to C-2 arylation of protected indoles8a and unprotected (NH) azoles8b (Table 2) employing $Pd(OAc)_2$, PPh_3, and an suitably chosen base. This technique tolerates variation of both the heterocyclic (including electron-donating, electron-withdrawing, and Lewis basic functionality), in addition as comparable variation of the aryl halide. Further, Sames shows that either of 2 carbon -hydrogen bonds in base is by selection activated (Table two, entries seven and 8), affording C-2 arylated products within the absence of CuI, and C-4 arylated product within the presence of CuI. Though a proper catalytic cycle or clarification isn't provided, this unambiguously selective reactivity opens the door for future mechanistic work. The Sanford group has recently expanded the ability to functionalize carbon -hydrogen bonds in Lewis basic heterocycles. By drawing from a mechanistic analogy to previously published work,[9] they have developed a facile and high-yielding arylation of various coordinating heterocycles by treatment with $[Ar_2\ I]BF_4$ in the presence of 5 mol% $Pd(OAc)_2$ (Table 3).[10] The reaction efficiently arylates pyridines, quinolines, pyrrolidinones, and oxazolidinones, with functional group tolerance of amides, enolizable ketones, aldehydes, and benzylic hydrogens. Further, activated arenes are not required for efficient catalysis, as both electron-rich and electron-poor substrates are readily arylated.

Table 2 Representative examples of the carbon -hydrogen arylation of heterocycles

[a]base=CsOAc for entries 1-4 and MgO for entries 5-9.
[b]2 equiv, CuI added. [c]0.2 equiv, CuI added.

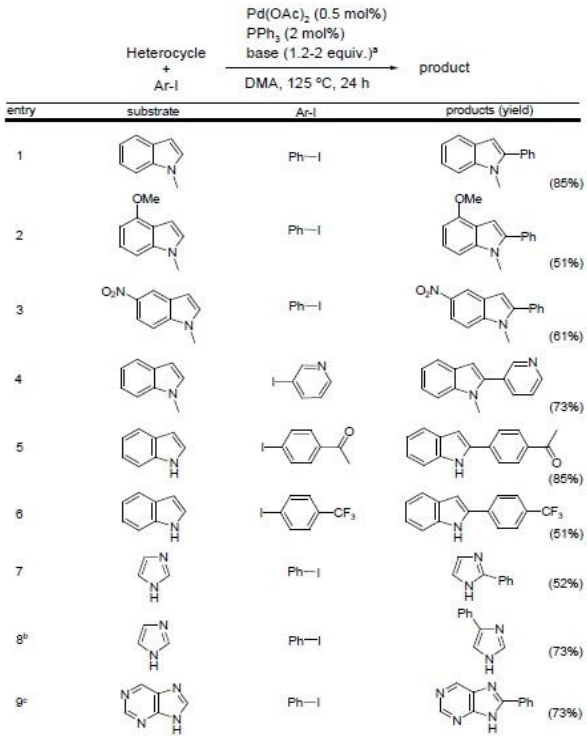
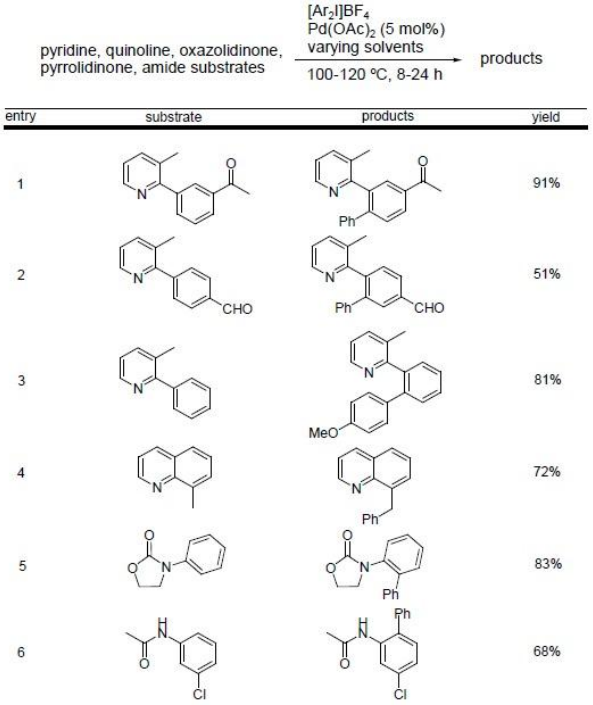


Table 3 Representative examples of the Sanford carbon -hydrogen arylation

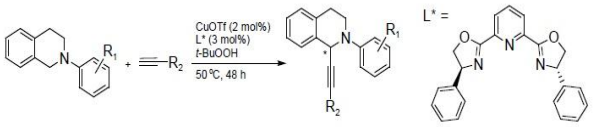


The reaction is also highly regioselective when Meta substituted substrates are employed, affording only para-arylated products (Table 3, entry 6). The key to the chemistry appears to be the unique choice of an iodine- (III) arylating agent, $[Ar_2I]BF_4$. Phenylation proceeds readily with $[Ph_2I]BF_4$, but the more sterically demanding $[Mes\text{-}I\text{-}Ar]BF_4$ is used to selectively transfer other functionalized aryls without generating a mixture of products. To probe the unique reaction mechanism, the authors conducted experiments that rule out a traditional Pd (0)/Pd (II) pathway. Rather, they propose a seldom invoked Pd(II)/Pd(IV) mechanism involving formation of a cyclometalated Pd(II) species, then oxidation to Pd(IV) mediated by iodine(III), and finally C-C bond forming reductive elimination. The possibility of electrophilic cleavage of the Pd-C bond without any change in the Pd oxidation state was also not ruled out. These results combine an interesting mechanistic problem with an important C-C bond forming reaction showing remarkable tolerance for functionality and substrate diversity.

IV. Results and Discussion

Recently, enantioselective carbon -hydrogen activation reactions have begun to emerge. In general, the harsh nature of CH activation has made stereoselectivity difficult to attain. Despite this, a few groups have begun to tackle the problem, and recent results are encouraging. In 1997, Murai et al. reported the first enantioselective intramolecular carbon -hydrogen activation reaction[11] between two olefins to afford chiral cyclopentane products, catalyzed by [RhCl(COE)2]2 and a chiral ferrocene ligand. In this pioneering work, promising ee's as high as 82% were achieved with imidazole-tethered 1,5-dienes. In 1999, the Mikami group reported an enantioselective Fujiwara-Moritani reaction,[12] in which electron-deficient cyclohexenes were coupled with benzene, catalyzed by chiral Pd(II) complexes, in up to 49% ee.

Table 4 Representative scope of the enantioselective alkynylation

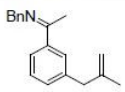
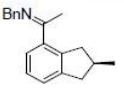
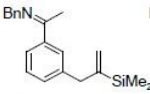
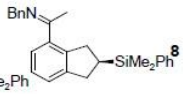
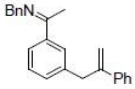
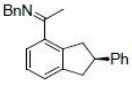
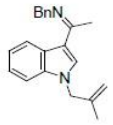
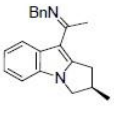
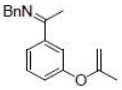
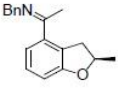


entry	R_1	R_2	yield (%)	ee (%)
1	H	Ph	67	63
2	H	4-MeOPh	65	41
3	H	4-BrPh	72	64
4	H	Hex	65	26
5	4-MeO	Ph	59	60
6	2-MeO	4-MeOPh	48	69
7	2-MeO	4-BrPh	56	74
8	2-MeO	Pyridyl	57	36

Despite straightforward substrates and modest ee's, Murai and Mikami ordered the muse for this new space of carbon hydrogen activation analysis. Recently, the Li group has developed a catalytic enantioselective alkynylation of prochiral secondary sp3 carbon -hydrogen bonds (Table 4).13 during this work, chiral Cu•pyBox complexes were found to catalyze the coupling of variably functionalized terminal alkynes with N-aryl tetrahydroisoquinolines to afford enantioenriched product analogous to those obtained from asymmetric Pictet-Spengler or imine hydrogenation reactions. Under the optimum conditions, a spread of enantioselectivities is obtained, as high as 74 ee, with moderate isolated yields. Modest variability is tolerated at the terminal alkyne position, whereas functionality on the N-aryl moiety is confined to phenyl and methoxyphenyl. Though the challenges undertaken and results obtained by the authors are spectacular, any optimization is needed for this fascinating reaction to be synthetically applicable.

Perhaps the foremost spectacular and solely really synthetically helpful enantioselective direct carbon -hydrogen activation reaction so far recently came out of the Bergman and Ellman labs. Supported precedent by Jun et al.14, they initial reportable an imine-directed intramolecular carbon -hydrogen activation/cyclization reaction catalyzed by Wilkinson's catalyst,15 providing a broad array of racemic benzo-fused carbonyl product in good yield.

Table 5 Representative scope of the asymmetric carbon -hydrogen activation/cyclization

entry	substrate	product	L*	temp (°C)	time (h)	yield (%)	ee (%)
1			**9**	50	9	94	95
2			**8**	125	0.3	91	70
3			**9**	75	3	96	90
4			**9**	125	1	90	70
5			**9**	23	23	95	96

The authors advise that the Lewis basic imine directs the catalyst to the carbon -hydrogen bond to be activated. a lot of recently, they need extended this technique by creating it enantioselective (Table 5).16 Through an extensive ligand screen, they determined that chiral phosphoramidite ligands 8 and 9 with 5 mold [RhCl(COE)2]2 with efficiency catalyzes

the enantioselective description of the reaction. Despite the unplanned correlation between substrate and optimum ligand, a range of functionalized benzylimines cyclize promptly, with ee's starting from 70 to 96. Within the planned catalytic cycle, coordination of the chiral Rh catalyst to the imine is followed by a directed carbon -hydrogen insertion of the α-aryl proton. Migratory insertion of the pendant olefine, followed by reductive elimination, then liberates enantioenriched benzo-fused product. The authors advise that the high rates are because of improved π-acceptor ability and diminished σ-donor ability of the phosphoamidite ligand relative to phosphines, whereas a extremely diastereoselective migratory insertion of the olefine into the Rh-H bond, mediate by the chiral ligand framework, is liable for the high enantioselectivities.

Discussion

Finally, artificial utility of the silylated product (Table five, entry 2) is illustrated by a stereospecific Tamao-Fleming oxidation to the corresponding secondary alcohol. Though the sphere of enantioselective carbon -hydrogen activation is comparatively new, the pioneering work of Murai and Mikami, and therefore the recent contributions of the Bergman, Ellman and Li teams, shows the potential of achieving generality and artificial relevance to the current difficult category of reactions.

V. Conclusion and Future Scope

In the past a little number of years, many teams have addressed vital aspects of carbon -hydrogen activation. As evident, new developments within the areas of reactivity, substrate scope, purposeful cluster tolerance and enantioselectivity are pushing the boundaries of carbon -hydrogen activation; but, systems of great sensible utility are simply begin to seem. The attract of this new and increasing field, definitely spur raised academic and industrial attention, and improved protocols for fascinating and synthetically applicable reactions are possible to still seem.

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