Mechanism of Palladium Catalyzed Reaction Involving C-H bond activation

STUDY PROJECT

Submitted in partial fulfillment of the requirements of
CHEM F266 Study Project

By

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CERTIFICATE

This is to certify that the report entitled, "Mechanism of palladium-catalyzed reactions involving C-H bond activation" and submitted by Suchisattam Saran ID No. 2017B2A70585P in fulfillment of the requirements of CHEM F266 Study Project embodies the work done by him under my supervision.

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ABSTRACT

Palladium also referred by atomic symbol “Pd” has atomic number 46 and atomic weight “106.42”. Palladium belongs to group 10 and period 5 of the periodic table. It is a rare metal discovered in 1803 by English chemist William Hyde Wollaston and has lustrous silvery-white appearance. Palladium is present in 6 prominent isotopes namely palladium-102, palladium-104, palladium-105, palladium-106, palladium-108, and palladium-110 with 1.02%, 11.14%, 22.33%, 27.33%, 26.46% and 11.72% as relative abundances. Palladium being most abundant platinum metals at an abundance of 0.015 part per million and because of its property absorbing more than 900 times its own volume of hydrogen at suitable conditions makes it an important catalyst for organic reactions. Palladium has a melting point of 1554.9℃ (2,830.8 °F) and a boiling point of 2963℃ (5,365 °F) and a variable oxidation state +2, +4 makes its claim for catalyst predominant. Ability of Pd catalysts to be fine-tuned by several reaction conditions such as temperature, solvents, ligands, bases and other additives makes its catalysis well rounded. Moreover, to complement Pd catalyst have high tolerance of various functional groups, providing high regiospecificity and stereospecificity evading the need for introduction of protective Functional Groups. This multifaceted catalyst is known for Carbon bond forming reactions namely C-C, C-O, C-N and C-F i.e Heck coupling, Suzuki coupling, Stille coupling, Hiyama coupling, Sonogashira coupling, Negishi coupling, Buchwald-Hartwig amination, to name a few reactions. In this report there will discussions on proposed mechanisms for few Pd catalyzed reactions involving C-H bond activation.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Prof. Dr. Anil Kumar for providing me with the opportunity to pursue this project under him, introducing me to the exciting and novel field of Mechanistic Study of Palladium Catalyzed C-H bond activation and helping me expand my knowledge in this domain. I would like to thank him for his invaluable guidance and assistance, which helped me navigate the difficulties faced during this project successfully.

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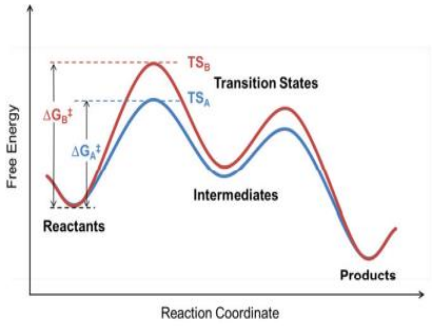
COMPUTATIONAL EXPLORATION OF PD-CATALYZED C-H BOND ACTIVATION REACTIONS

INTRODUCTION

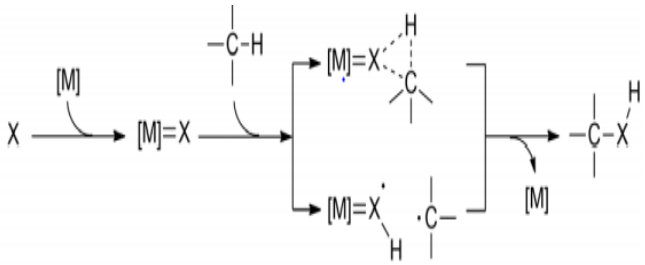
The discovery of more flexible and complex organic systems, difficulty in studying the formation such organic compounds has highlighted the need for rapid development of computational methods and use of computer power. B3YLP method (B3lyp is a functional, that includes exact exchange and GGA corrections in addition to LDA electron-electron and electron-nuclei energy. The weights of the parts were fit to reproduce geometry of a test suite of small molecules) was discovered as one of the ways for detecting transition states as well as it explored mechanism hence a need for a better method was realized leading to discovery of M06 (Global hybrid functional with 27% HF exchange. Intended for main group thermochemistry and non-covalent interactions, transition metal thermochemistry and organometallics) which certainly proved to be valuable especially for studying the energetics of organometallic reactions. In systems where dispersions played an important role M06 or B3YLP-D3 were used for geometric optimization as well as energy evaluations. Catalysts decrease the activation energy of the reaction complementing the selectivity of the reaction. Among the various transition metal catalysis palladium-catalyzed C-H bond functionalization has been termed to be the one with outmost importance. Majorly in all the reactions involving C-H bond activations at monomeric Pd(II) center, major transitions include for either Pd(II)/Pd(0) or Pd(II)/Pd(IV) catalytic cycles.



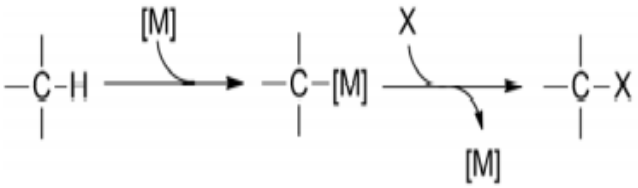
As stated by Eyring equation and Arrhenius rate law, for rate determining step a decrease in ΔG‡ by 1.36 kcal/mol leads to an increase in rate of the reaction by 10 times, hence a reduction in ΔG‡ by 2.72 kcal/mol would lead to an increase in rate of reaction 100 times which can be seen in the above figure.

C-H BOND ACTIVATION MECHANISMS

There are 2 types of mechanisms through which C-H bond functionalization takes place namely Inner Sphere Mechanism and Outer Sphere Mechanism.



Outer Sphere Mechanism



Inner Sphere Mechanism

OXIDATIVE ADDITION

This process may lead to either Pd(0)/Pd(II) or Pd(II)/Pd(IV) transition. Pd(0) to Pd(II) conversion is a process in which oxidation involves the breaking of C-H bond and formation of C-Pd and Pd-H bonds in the transition structure which leads to formal increase of the oxidation state of Palladium (0 to 2 i.e., 2 units). Pd(II) would lead to formation of Pd(IV) intermediate hence making it unfavorable due to steric factors. Studies involving cyclocarbopalladation-Stille coupling using Pd(PPh3)4 as catalyst confirmed the same, hence suggested occurrence of Pd(IV) intermediate as unfavorable.

SIGMA BOND METATHESIS AND 1,2-ADDITION

In organometallic chemistry sigma bond metathesis is referred as chemical reaction in which metal-ligand sigma bond undergoes exchange of parts i.e., metathesis with some other reagent. The main reason for this reaction being so much importance is generally hydrocarbons are unreactive substrates. Some sigma-bond metatheses are facile. In this mechanism the oxidation of metal does not undergo any change.

1,2-Addition reaction is referred as an addition of the M = X to a C-H bond via $2\sigma + 2\pi$ type mode, this involves cleavage of one C-H σ-bond and one π bond of M = X, followed by formation of two σ-bonds.

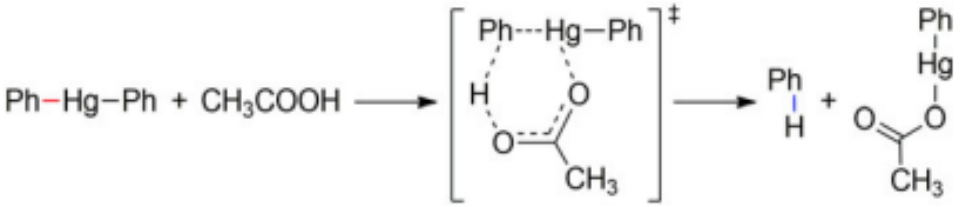
ELECTROPHILIC AROMATIC SUBSTITUTION

An organic reaction which leads to an atom attached to an aromatic system (usually hydrogen) being replaced by an electrophile is referred as SEAr (Electrophilic aromatic substitution).

As shown in the figure above SEAr mechanism involves a Wheland intermediate if followed by deprotonation and aromatization it would lead to generation of complex with Pd-C bond. Various experimental results have shown that dicationic palladium complex leads to facile C-H bond activation of arylureas with aryl iodides, arylboronic acids, and acrylates at room temperature.

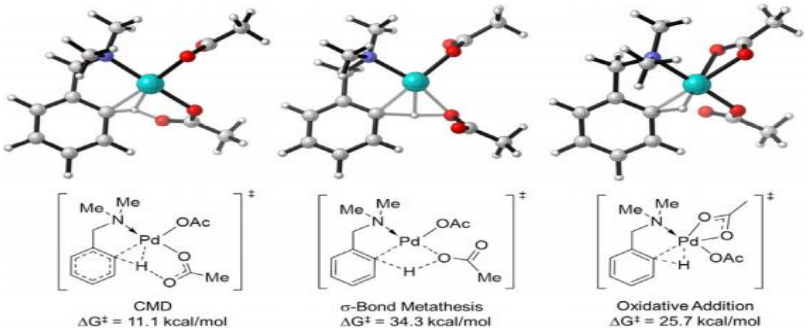
CONCERTED METALATION-DEPROTONATION (CMD)

The concerted metalation-deprotonation is a mechanism to predict relative reactivity and regioselectivity for various arenes spanning the entire spectrum of known palladium-catalyzed direct arylation coupling partners.



As shown in the figure above the process of acetolysis of diphenylmercury is the reverse reaction of C-H bond activation. Simultaneous C-H bond cleavage and a C-Hg bond formation mechanism was suggested by kinetic data. Furthermore DFT (Density Functional Theory) was used for C-H bond activation among benzene and methane. C-H bond activation by Pd(η2 -O2CH)2 was found out to be heterolytic cleavage whereas C-H bond activation by Pd(PH3)2 was found to be homolytic cleavage.

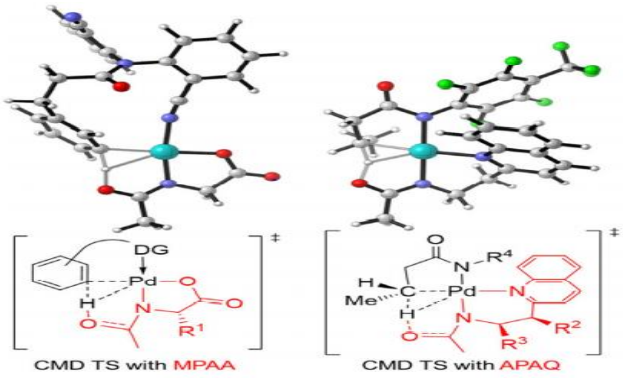
CLASSICAL CMD WITH ACETATE AS THE INTERNAL BASE



Ortho-palladation was performed on N,N dimethylbenzylamine (DMBA-H) and its detailed mechanism was studied. CMD mechanism was predicted to be the most accessible pathway for acetate assisted C-H bond activations as it has the lowest ΔG‡ for the reaction. Mechanism proposed was chelating amine directing group (DG) assisting the ortho-C-H bond by Pd(II) with two η1-coordination acetate ligands followed by the acetate ligand is the trans position acting as internal base.

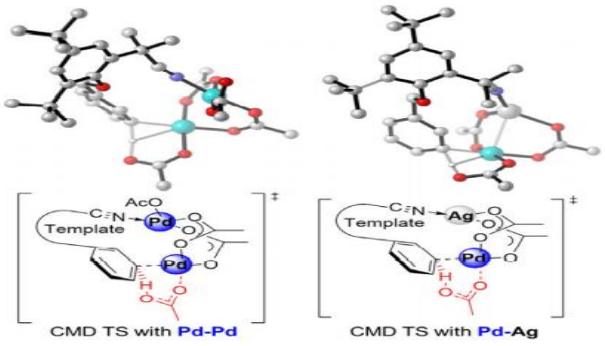
CMD WITH AMIDATE O AS THE INTERNAL BASE

There are 2 ligands namely MPAA (monoprotected amino acid) and APAQ (acetyl-protected aminoethyl quinoline) which use amidate O as the internal base for CMD reaction both the ligands participate in Pd(II) catalyzed C-H bond activation. In CMD with MPAA, Pd(II) center is coordinated by O of the carboxylate group and N of the amide group whereas the amidate O acts as the intramolecular base for deprotonation. In CMD with APAQ, the Pd(II) center is coordinated by N of the quinoline group as well as amidate group whereas amidate O acts as an internal base for deprotonation. The figure below shows the transition state of CMD with MPAA and APAQ.



CMD MECHANISM IN BIMETALLIC SYSTEMS

Discovery of meta-C-H bond activation of toluene derivatives being controlled by the nitrile-containing templates was done by Yu group. DFT calculations performed by Wu, Houk, and coworkers suggested that more Pd CMD mechanism being unfavorable as result of its orthoselectivity, in contrary to the meta selectivity shown by the experiments. Dimeric Pd and heterodimeric Pd-Ag CMD mechanisms were found out to be more favorable as it showed metaselectivity. The following figure shows CMD with dimeric Pd and heterodimeric Pd transition states.



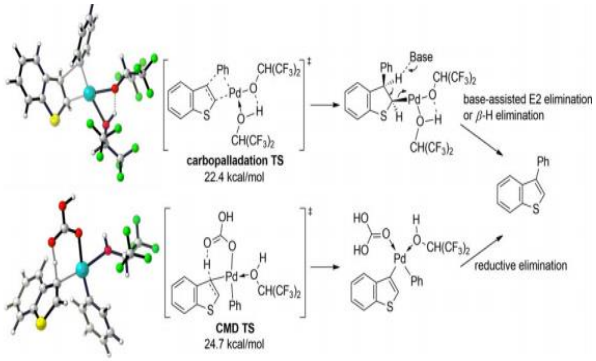
C-H BOND ACTIVATION AT PALLADIUM(IV) CENTER

CMD mechanism generally occurs at a Pd(II) center and does not change the oxidation state of palladium center. In contrary, occurrence of C-H bond activations at Pd(IV) center are relatively rare. As reported by Sanford group only 4,4-di-tert-butylbipyridine and tris(2-

pyridyl)methane (Py3CH) ligands support C-H bond activations at Pd(IV) center.

CARBOMETALLATION AND ELIMINATION

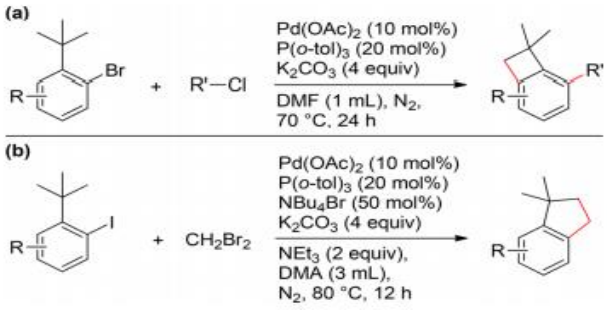
β-arylation of benzo[b]thiophenes catalyzed by Pd(II) was proposed by Larrosa group, anti-β-hydride elimination or base-assisted E2 elimination followed process of carbopalladation. This proposal was confirmed by DFT as well KIE calculations. Following figure shows that ΔG‡ for carbometallation and elimination is lower hence suggesting this pathway for reaction to occur.



MECHANISM OF PALLADIUM-CATALYZED ALKYLATION OF ARYL HALIDES WITH ALKYL HALIDES THROUGH C−H ACTIVATION: A COMPUTATIONAL STUDY

INTRODUCTION

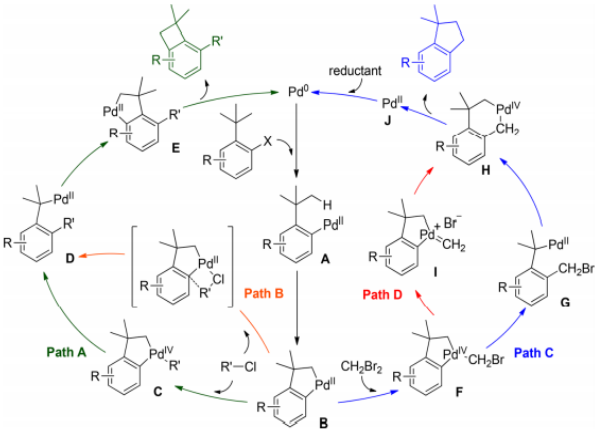
Pd catalyzed C−H activation/functionalization is a highly atom economical synthetic strategy. In an organic complex there might be several C-H bonds present having similar reactivities hence DG (Directing Group) is needed for improving the selectivity of the reaction. Functional groups such as halogens promote Pd-catalyzed C−H activation through the oxidative addition on palladium(0) complexes forming Pd−C bond, as a result it leads to C-halide bond becoming traceless by getting converted into other chemical bonds which is follows C-H activation.



[a]DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide.

Cross-coupling reaction of 2-tert-butyl-substituted aryl halides with alkyl chlorides and CH2Br2 leads to formation of orthoalkylated benzocyclobutenes and indane derivatives as shown in the above figure. Alkyl halides leads to generation of Pd(IV) intermediates, Pd(IV) complexes are generally unstable but can be generated if Pd(II) complexes are reacted with stronger oxidizing agents, an alternative to this proposed metathesis of Pd(II) intermediate with alkyl chlorides. 2 different pathways were proposed for coupling reaction with CH2Br2 one

involving reductive elimination and oxidative addition while the other proceeds via carbene intermediate. Following image shows the process of the above-mentioned reactions.

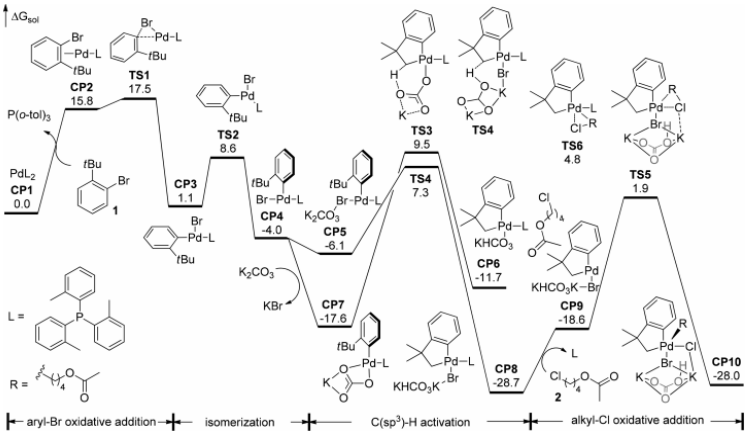


COMPUTATIONAL METHODS

Gaussian09 program was used to perform the mechanistic study. DFT method B3LYP30 and mixed basis set i.e., LANL2DZ31 with extra polarization functions for Pd (ζ(f) = 1.472), Br (ζ(d) = 0.428), and I (ζ(d) = 0.289) and 6-31G(d) for the rest of the atoms were used for conducting geometrical optimization in gas phase. Intrinsic reaction coordinate analysis was also performed. DFT method M06- L34 allied with the mixed basis set were used to calculate single-point energies. A value calculated by RT ln(Csol/Cgas) of 1.9kcal/mole was added to the Gibbs free energy of all the species as a result of change in standard state from 1 atm to 1 M at 298.15 K as a consequence of increase in concentration from 1/24.5 mol/L to 1 mol/L.

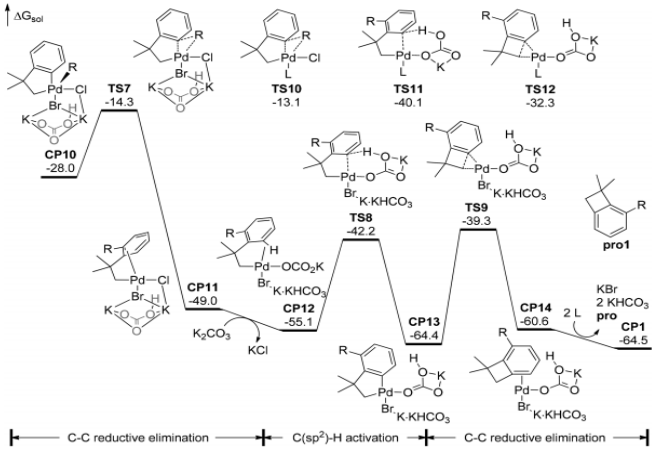
RESULTS AND DISCUSSION

MECHANISM OF ALKYLATION WITH ALKYL CHLORIDES



As shown in the above figure Pd[P(o-tol)3]2 (CP1) complex was considered as the reference state of palladium catalyst. CP1 when reacted with 1 led to bulky phosphane ligand P(o-tol)3 being released leading to formation of CP2 which on oxidative addition generated CP3 via TS1. The energy barrier for this reaction was 17.5 kcal/mol and the reaction was facile. In CP3 aryl group is trans to the phosphine ligand, making the isomer CP4 more stable. Facile Isomerization of CP3 leads to formation of CP4 via a Y shaped TS2. It was suggested oxidative addition transition state directly generated CP4 was estimated to be less stable than TS1 by only 1.5 kcal/mol. CP4 on reacting with K2CO3 generated KBr and CP7, which led to inner-sphere carbonate-assisted C(sp3)−H activation which occured via TS3. Transition state having presence of KBr i.e., TS4, was found more favored than TS3 by 2.2 kcal/mol. TS4 when compared with TS3 had longer C-H bonds and shorter O-H bonds whereas there was little or no difference in the length of Pd-C bond lengths of both the transition states. TS4 is followed by the formation of CP8 which on further reaction with alkyl halide 2 leads to formation of complex CP9 following this a C(sp3)-Cl bond cleavage occurs via a tetragonal-pyramidal

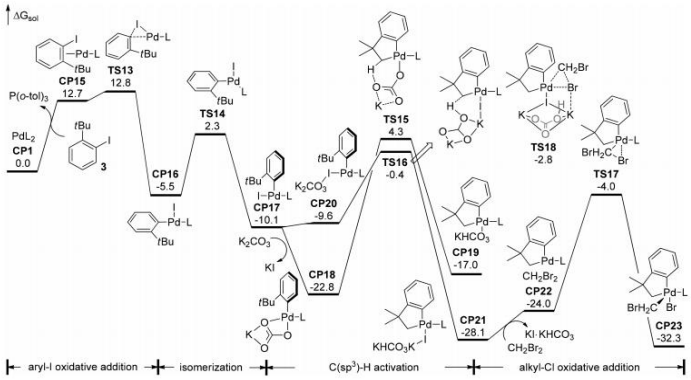
transition state i.e., TS5 which has an energy barrier of 30.6 kcal/mol. TS6 having phosphine ligand at the cis position of the aryl ligand was also considered but the experimental data suggested it being less favorable by 2.9kcal/mol. Along with pathway involving Pd(IV) intermediates, metathesis of R−Cl and Pd− Ar bonds from CP9 was also considered, but the experimental data failed to locate the corresponding transition state. Energy demand of the metathesis process was evaluated by relaxed energy surface scan and the results suggested an electronic energy increase of over 45 kcal/mol with reference to CP9. Ar-C bond reductive elimination from CP8 was also considered as a result this process also generated the final product via the following oxidative addition of R−Cl and Ar−C bonds but was kinetically less favored than the TS5 pathway by 1.5 kcal/ mol. TS5 led to formation of CP10 having relative energies closer to that of CP8.



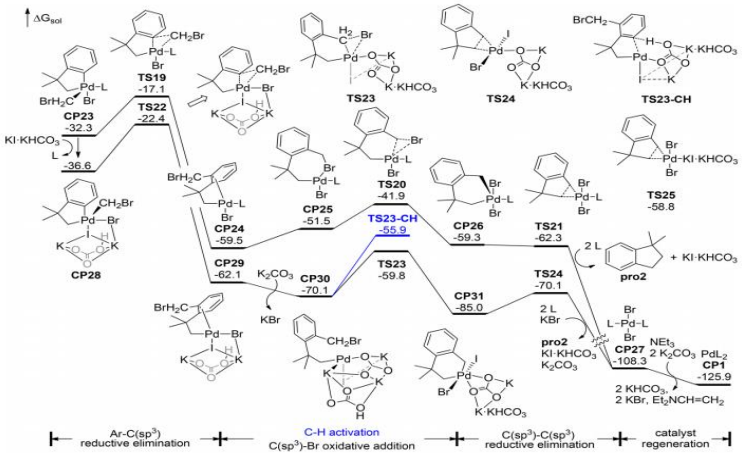
As shown in the above figure C(sp3)−C(sp2) reductive elimination occurred via TS7 and generated CP11, thereafter it underwent ligand exchange with K2CO3 and generated CP12 which led to facile C(sp2)− H bond activation via TS8 and an energy barrier of 12.9 kcal/mol was required to afford CP13. The C(sp3)−C(sp2) reductive elimination via TS9 led to the generation of strained product pro and this process required a high energy barrier of 25.1 kcal/mol. Replacement of KBr·KHCO3 with P(o-tol)3 made the above three steps (via TS10, TS11, and TS12, respectively) more kinetically difficult by 1.2, 2.1, and 7.0 kcal/mol,

respectively.

MECHANISM OF ALKYLATION WITH CH2BR2



As shown in the above figure alkylation reaction 3 with CH2Br2 proceeds via oxidative addition of the aryl−I bond (TS13) followed by isomerization (TS14), then C(sp3)−H activation (TS16), and oxidative addition of the alkyl−Br bond (TS17) which are similar to steps of coupling in 1 and 2 of Mechanism of Alkylation with Alkyl Chlorides. TS16 being more stable as compared to TS15 because of absence of KI. TS18 is less favored than that via TS17 by 1.2 kcal/mol as in oxidation addition of alkyl-Br bond salt seemed to be of a lesser importance. K-Br dissociated energy is lesser as compared to K-Cl dissociation energy by 13kcal/mol. Direct Ar−C reductive elimination from CP21 was also investigated but it was found out to be less favored than TS17 (might be due to weak C-Br bond).

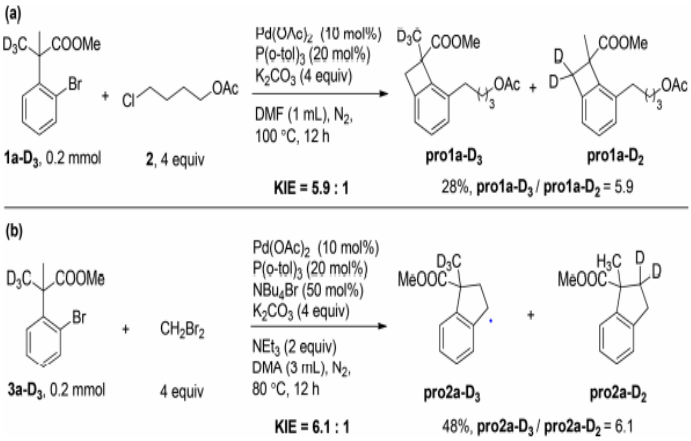


As shown in the figure above Pd(IV) complex CP23 led to direct reductive elimination via TS19 which helped is CP24 formation. Ligand exchange at CP23 with KI· KHCO3 generates CP28 which leads to a reduction in overall energy barrier by 5.3 kcal/mol for the irreversible reduction elimination via TS22. Palladium carbene complexes formation from CP22 is found to be highly endergonic and have relative energies higher than TS22 by over 30 kcal/mol. Availability of one reactive benzylic C−Br bond after TS19 and TS22 thus leads to fast oxidative addition of the C−Br bond could via TS20 and TS23. The salt presence via TS23 leads to an elementary energy barrier of 10.3 kcal/mol with reference to CP30 which is lower than the elementary energy barrier from CP24 to TS20 by 7.3 kcal/mol. TS23-CH was kinetically slower than the C−Br bond oxidative addition via TS23 by 3.9 kcal/mol. TS21 had a lower elementary energy barrier when compared to those via TS24 and TS25. In conclusion it was found that overall energy barrier of the pathway with salt participation via TS22, TS23, and TS24 was 14.9 kcal/mol from CP31 to TS24 whereas the pathway with no salt participation via TS19, TS20 and TS21 was 17.6 kcal/mol from CP24 to TS20. The indane product pro2 was generated because of C(sp3)− C(sp3) reductive elimination stage along with formation of a PdBr2Ln complex. Calculations found out that the direct elimination from CP27 to generate Br2 and CP1 was highly endergonic i.e., by 58.9 kcal/ mol, and as a result this possibility was excluded.

RATIONALE OF PRIMARY KIE EFFECT

KIE effects are generally used to determine reaction mechanisms by rate determining step and transition states and which are commonly measured with the help of NMR to detect isotope location or GC/MS to detect mass changes. C−H bond cleavage was proposed to be the rate-determining step in the two types of alkylation reactions, whereas in contrast to this proposal, with the help of calculations it was found out that the oxidative addition of alkyl halide 2 (via

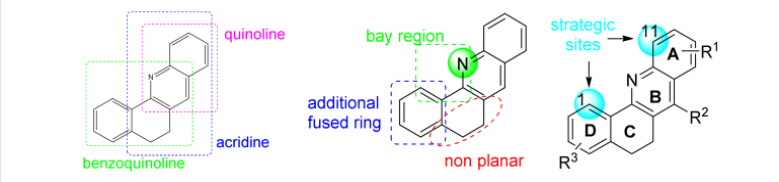
TS5) was kinetically slower than the C−H bond cleavage (via TS4) in the alkylation with alkyl halides. Similarly, in the alkylation with CH2Br2, the oxidative addition of CH2Br2 (via TS17) was found to be slower than the C−H activation (via TS16) and the catalyst regeneration, respectively. Thus, to conclude oxidative addition and catalyst regeneration were proposed to be the possible rate determining steps. The KIE study for the stated proposal is shown in the figure below.



PALLADIUM-CATALYZED REGIOSELECTIVE ALKOXYLATION VIA C-H BOND ACTIVATION IN THE DIHYDROBENZO[C]ACRIDINE SERIES

INTRODUCTION

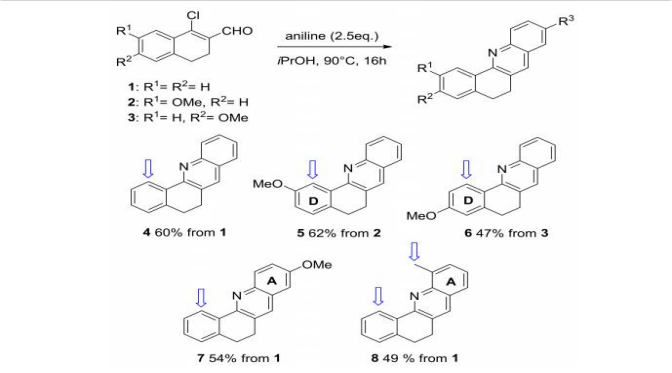
Acridines and related derivatives have an important class of aza-polycyclic compounds that attracted a considerable interest in the last century by reason of their broad range of properties and applications. Most recent applications of acridine motifs include cell imaging probes, catalysis, Organic Light-Emitting Diodes (OLEDs) and organic semiconductors. Varied application of acridine has led to (1) construction of the acridine backbone (2) selectively installing substituents (3) modulation of the substitution pattern, fusion of additional rings towards extended molecules and (4) inducing distortion from planarity by including a partially saturated fragment. 5,6-dihydrobenzo[c]acridine molecule is known to represent a mix of bicyclic quinoline and tricyclic benzo[h]quinoline or acridine scaffolds. Nitrogen atom and a peri-fused aromatic ring together is used to define an aza-bay region and presence of the non-planar ethylene bridge leads to deviation from the planarity as shown in the figure below. 2 major routes to obtain 5,6-Dihydrobenzo[h]acridine are Friedländer cyclisation between tetralone derivatives and o-aminoacetophenones and thermally induced or acid-catalyzed cyclisation of 1-halovinyl-2-carboxaldehyde derivatives and anilines.



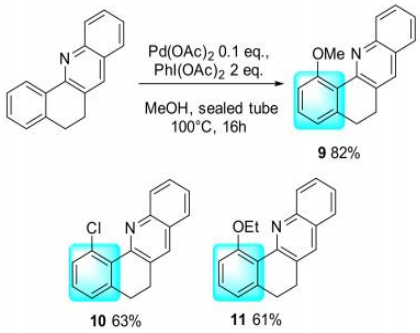
Pd- and Cu-catalyzed strategies were used for formation of C-C and C-N bonds and the formation of homocoupling products was realized using the Cu-catalyzed Ullman reaction. In the dihydro analogues, the main question was that distortion from planarity that arised due to the presence of the partially hydrogenated ring C would allow or hamper the transient palladacycle to form through C-H activation and the selective installation of substituents at position 1.

RESULTS AND DISCUSSION

Preparation of Variously Substituted Acridines:

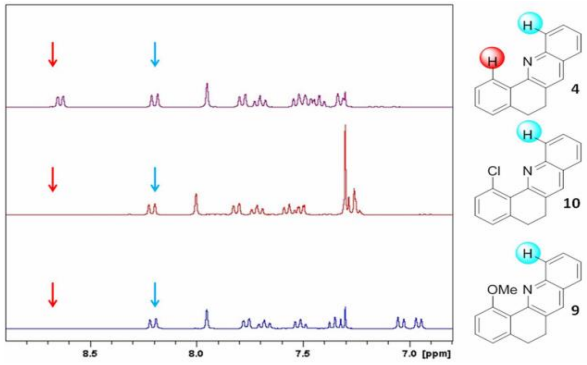


Various substituted acridines were prepared from 1-chlorovinylcarboxaldehydes 1–3. Compounds 1–3 when reacted with 2.5 eq. of aniline derivatives in iPrOH at 90 ◦C for 16 hours, yielded acridines 4 to 7 with yields ranging from 47 to 60%. Acridines 5 and 6 were substituted at ring D in the 2 and 3 positions, whereas in contrast, acridines 7 and 8, substituents are located at ring A in the 9 and 11 positions. Pd-catalyzed alkoxylation takes place in the 1 position for substrates 4 to 7 whereas acridine 8 being a more challenging substrate as it displays two potential reaction sites: the sp2 carbon atom located in the 1 position at ring D and the sp3 benzylic carbon atom located at ring A.



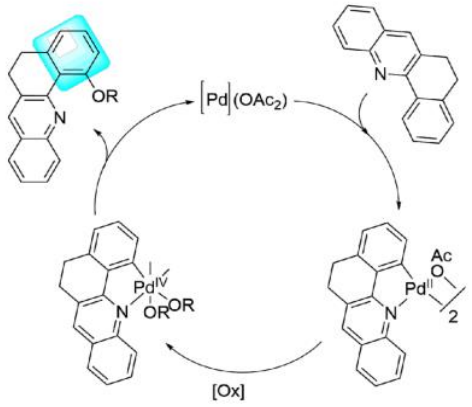
Experiments suggested Pd(OAc)2(10%) to be effective to obtain 1-methoxy-5,6-dihydrobenzo[c]acridine 9 also after testing several oxidants, PhI(OAc)2 (2 eq.) proved superior to I2 or oxone. MeOH at 100 ◦C in a sealed tube gave alkoxy acridine 9 in high yield whereas a little decrease in the temperature even to 80 ◦C led to a severe decrease of conversion. Dichloroethane (DCE)/ MeOH as the solvent led to mixtures of 1-methoxy and 1-chloro derivatives 9 and 10. Moving from MeOH to EtOH and iPrOH led to different issues. EtOH led the ethoxy analogue 11 in satisfactory 61% yield whereas in contrast iPrOH failed to react.

Excluding compound 5, all other acridines 4, 6–8 display characteristic chemical shifts for H(1) ranging from 8.55 to 8.70 ppm as shown in the figure below.

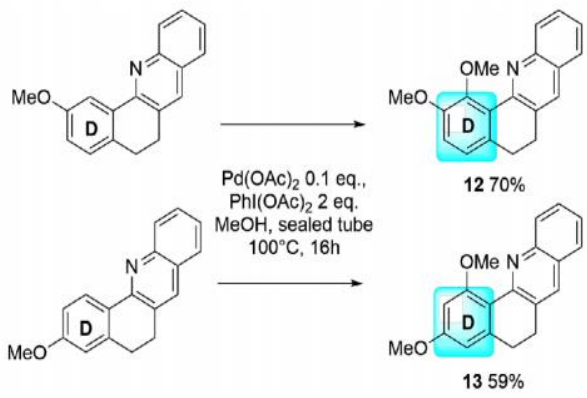


Benzo[h]quinoline would involve successively a ligand-directed C-H activation to form a cyclometallated dimer, oxidation to generate a Pd(IV) species, and a release of the product after

C-O bond-forming reductive elimination. Last step might proceed either by intramolecular C-OR bond elimination from the metal center or by attack of an external nucleophile in an “SN2-like” reaction as shown in the figure below.

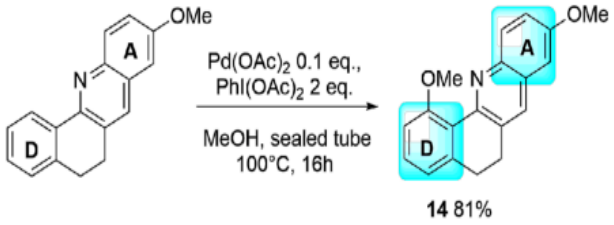


Pd(OAc)2, PhI(OAc)2, in methanol(or ethanol) at 100 ◦C led to formation of suitable conditions to promote alkoxylation in the dihydrobenzo[c]acridine series. Along with this condition in hand installing an additional methoxy group was tried though ring D already had a methoxy substituent, for preparation of 1,2- and 1,3-bismethoxy acridine motifs as shown below.



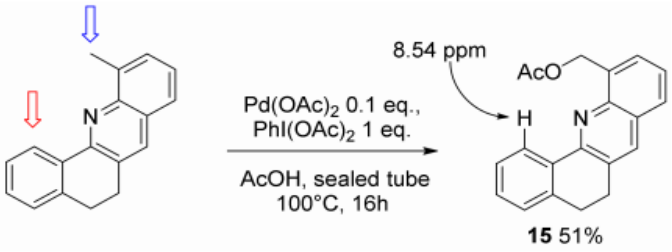
Similar catalytic conditions led to formation of bismethoxy derivative 14 with 81% yield from acridine 7 as shown in the figure below. The bismethoxy derivative displayed

complementary substitution pattern when compared with acridines 12 and 13.



14 81%

In contrary to acridine substrates 4–7, compound 8 displayed two different C-H activation sites which further led to producing a transient five-membered palladacycle through C-H activation and hence, might allow alkoxylation. Changing solvent from MeOH to AcOH along with one equivalent of PhI(OAc)2 led to isolation of acridine 15 as the major product with 51% yield as shown below.



15 51%

LEARNING OUTCOMES

Palladium as a catalyst has various application in organic as well as inorganic reactions. Although formation of Pd(IV) is unstable still in presence of strong oxidizing agents Pd(IV) complex formation is possible. Palladium catalyst is very important for regioselective and stereoselective reactions. As the complexity of compounds are increasing day by day means increasing importance of Computational Study for studying mechanisms of various reactions. Computational Study provides important insights on structures of various transition states. Combining kinetic experiments with spectroscopic characterization, such as nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, mass spectrometry (MS), and DFT computations provides insights for comprehensive mechanistic understanding of the catalytic system. New mathematics and machine learning algorithms have gained more attractions in rational design of catalyst and reaction. Sigman's study combined physical organic chemistry with modern “big data” analysis tools to develop correlations between descriptors and reactivity and selectivity.

CONCLUSION

Couplings of o-tBu-substituted aryl bromides with alkyl chlorides generate ortho-alkylated benzocyclobutene derivatives. Metathesis mechanism and carbene-involved mechanism were found to be less possible. Salts can not only act as bases to promote C−H activation but also possibly cooperate with Pd catalysts to lead to more kinetically favored pathways.

Alkoxylation occurs selectively in position 1 of the acridine platform using 10% Pd(OAc)2, PhI(OAc)2 and MeOH as the best combination of catalyst, oxidant, and solvent, respectively. Strategy allowed a selective functionalization of sp3 carbon atom located at the benzylic position of ring A.

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