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Novel Carbazole-based N-Heterocyclic Carbene Ligands for Accessing Synthetically Relevant Stilbenes via Pd-Catalyzed Coupling Processes

Tejpalsingh Ramsingh Girase,[a] and Anant R. Kapdi*[a]

Abstract: A series of new carbazole-based N-heterocyclic carbene ligands have been synthesized via a simple and facile synthetic route. Subsequent employment of the Pd/carbazole-based NHC catalytic system was found to be effective in efficiently catalyzing Heck reaction providing substituted stilbene derivatives in good yields. Several bioactive stilbenes such as pterostilbene, pinosylvin, trimethoxy resveratrol and resveratrol were synthesized in good yields with a 10 mmol scale-up also performed for trimethoxy resveratrol. The synthetic application was also extended by performing a double tandem chemoselective Heck reaction followed by Miyaura borylation in a one-pot procedure to provide a single step access to the synthetically useful stilbenyl boronate esters. Similarly, a unique triple tandem protocol involving chemoselective Heck reaction/Miyaura borylation/Suzuki-Miyaura coupling reaction sequence was performed for the one-pot modification of biologically relevant molecules.

Introduction

Functionalized stilbene derivatives are an important class of compounds with a wide variety of biological and pharmacological activity[1]. These are naturally occurring compounds mainly found in plants (phytoalexins), for instance pinosylvin, resveratrol (commercial drug molecule), trimethoxy-resveratrol (3M-Res), piceatannol, pterostilbene having extensive biological activity ranging from anticancer, anti-oxidants, neuroprotective, anti-diabetic, antifungal, anti-inflammatory, anti-cardiac, antibacterial to antimalarial activity[1,2] (fig 1). Besides these applications, stilbenoids with borane functionalized derivatives also have exhibited enormous applications in synthesis such as coupling reactions, OLEDs, chemo-sensing, material science and are of pharmacological importance[3]. It is therefore mandatory to investigate the possibility of developing a synthetically elegant protocol for the synthesis of these molecules. Brown, Matteson, Suzuki, and Miyaura have made revolutionary contributions towards new types of organoboron compounds, and have developed ways to synthesize them and such an exploration has found considerable synthetic potential[4]. In recent years, synthesis of organoboron compounds has been accomplished by the employment of transition-metal-catalyzed[5] reactions to overcome the barrier of the traditional synthetic methods such as lithiation,[6] reaction with Grignard reagent[7].

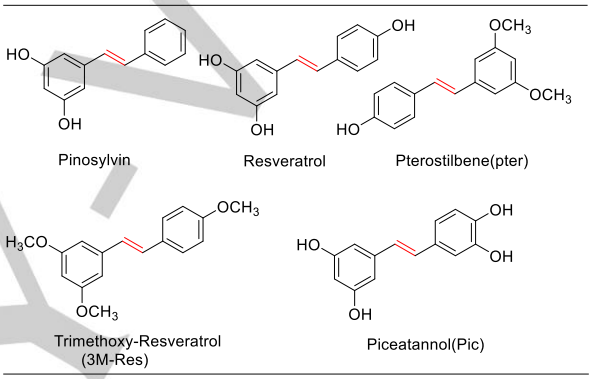

Figure 1: Examples of naturally occurring bioactive stilbenes.

Amongst the transition metals, palladium has its own pivotal role in organic synthesis from a past few decades with exceptional (remarkable) functional group tolerance, milder reaction conditions and its ability to activate a wide variety of bonds such as C–X (Cl. Br, I, OTs), C–H, C–B, C–Sn.[8] The potential of palladium towards catalyzing most difficult organic synthetic reactions immensely increases in combination with electron-rich ligand such as phosphine, *N*-heterocyclic carbenes, which have better ability to co-ordinate to metal. This property increases the electron density at palladium center so as it can activate the toughest bond[9]. From this perspective synthesis and development of electron-rich ligands is of tremendous interest to researchers due to their activating property. This fulfillment of ligand has been accomplished by the phosphines and NHC's ligand, due to which researchers are attracted towards the synthesis of new ligand system based on phosphine and NHCs. Phosphines are electron-rich ligands providing an opportunity to fine tune the steric and electronic properties promoted its dominance over the other ligand system, but their sensitivity towards the moisture and oxygen, storage and handling difficulties restricted their applicability in catalytic processes[9,10]. However, NHCs overcome the problems associated with phosphines ligand, while their strong sigma electron donating ability permits the efficient activation of an inert bond.[11] NHCs have provided greater modular flexibility over steric, electronic properties and ease of synthesis. Because of these qualities NHCs have been extensively exploited by many research groups such as Kuhn, Hermann, Nolan, Organ[8-10] etc.

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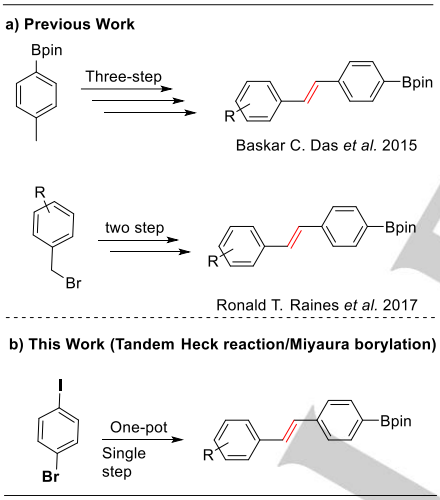
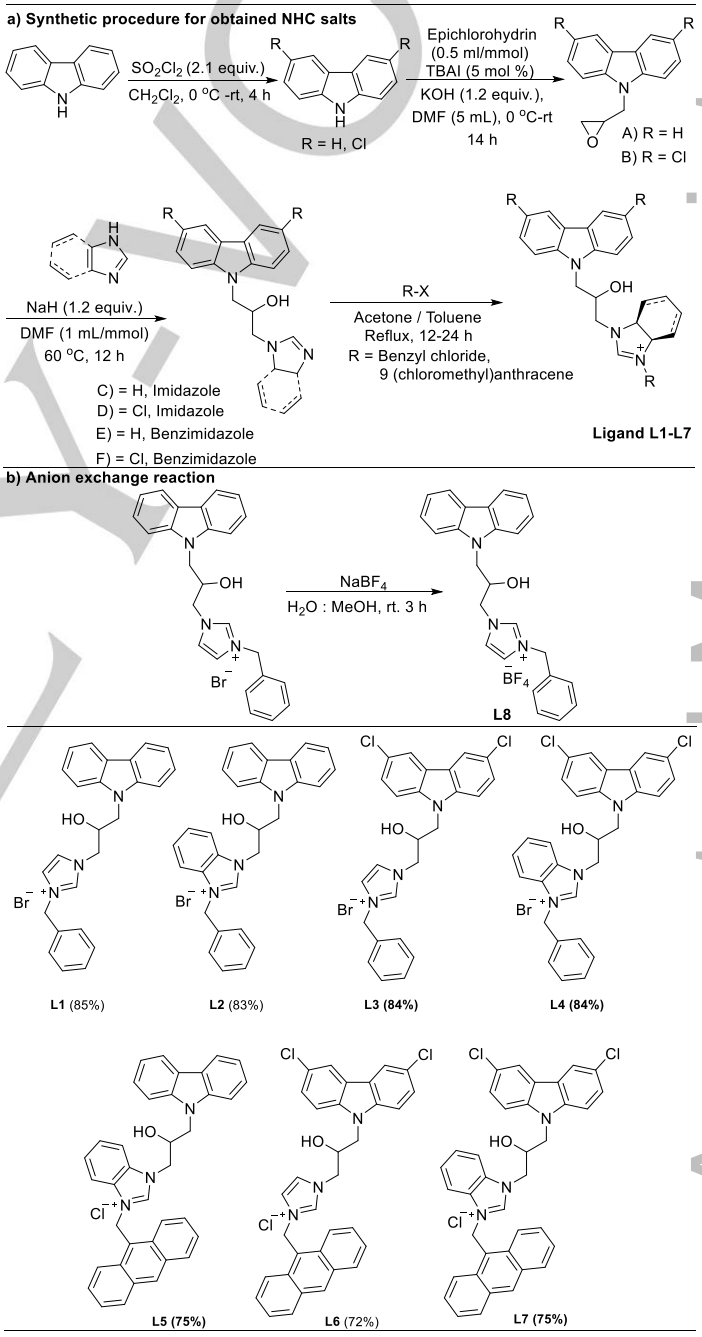
One of the areas where NHCs could play an important role would be towards the synthesis of stilbene-based boronate esters that have exhibited promising biological activity. In recent years, these substrates have been prepared by using the traditional and multistep method, for instance, Bhaskar *et al*. and Ronald *et al.* synthesized the boronate ester by transition-metal-catalyzed reaction followed by Wittig reaction[12]. But yield obtained in most of these processes was moderate and involved harsh reaction conditions, tedious work-up procedures while the multistep synthetic protocol led to a large amount of homo-coupling and deborylation. Therefore in continuation with our endevour of providing sustainable catalytic solutions[13] we report herein the synthesis and application of a series of *N*-substituted carbazole based *N*-heterocyclic carbene ligands, that can be exploited towards the synthesis of stilbene based boronate ester. For overcoming the multistep aspects and drawbacks of Wittig reaction, the synthetic protocol reported in this manuscript is synthetically elegant providing boronate esters via *in-situ* palladium-carbazole based NHC ligand-catalyzed one-pot sequential Heck reaction followed by Miyaura borylation towards the aspects of sustainable chemistry i.e., step & atom economy (scheme 1). A unique triple tandem protocol has also been accomplished providing highly functionalized nucleoside-based compounds *via* a one-pot sequential Heck reaction/Miyaura borylation/Suzuki-Miyaura coupling of 5-iodo-2'-deoxyuridine.



Scheme 1: a) Previous reports b) This work

Results and Discussion

At the outset of our studies, the synthesis of novel carbazole-based series of *N*-heterocyclic carbene precursors **L1, L2,L3, L4, L5, L6, L7,** and **L8** was carried out in 3 to 4 steps providing moderate to high yields of the NHC salts. The first step of synthesis of the ligands involved the chlorination of carbazole particularly in the case of ligands **L3, L4, L6,** and **L7.** In common cases, the chlorination of carbazole with N-chlorosuccinimide (NCS) suffers from selectivity issues giving multiple spots on related to the formation of mono, di and traces of tri chlorinated products that are difficult to separate by column chromatography technique. However, when sulfuryl chloride was used for the chlorination of carbazole by following the reported procedure by Jurczak and co-workers afforded 3,6-dichlorocarbazole in 72-75% yield.[14] In the second step, carbazole was deprotonated by potassium hydroxide with the resultant anion allowed to react with epichlorohydrin thus yielding the epoxide derivatized motif **A** and **B** in 75-78 % (Scheme 2)[15]. These derivatized motifs of carbazole **A** & **B** were further reacted with imidazole and benzaimidazole to furnish the corresponding products **C-F** respectively, in 70-74 % yields (scheme 2). Further, molecules **C-F** were condensed with benzyl bromide in acetone under refluxing condition for 12 h resulting into the formation of imidazolium salts **L1-L4**, respectively.



Scheme 2 : Synthesis of novel carbazole-based NHC ligands.

Similarly, when molecules **C-F** were condensed with 9-(chloromethyl) anthracene in toluene at 125 °C for 24 h provided the NHC salts **L5-L7** in moderate to excellent yields. For the assessment of the effect of change in anionic counterpart on the properties and catalytic activity of the synthesized ligands, a simple anion exchange reaction was performed on the NHC salts. The reaction was performed with ligands **L1** using sodium tetraflouroborate in methanol at room temperature resulting in the formation of a crystalline salt of NHC-tetrafluoroborate **L8** in excellent yield (Scheme 2)[16]. These imidazolium salts **(L1-L8)** were further characterized by standard spectroscopic techniques. The formation of imidazolium salts was confirmed from the ^{1}H and ^{13}C NMR spectras providing the characteristics peaks for N-CH-N as shown in Table 1. The influence of the substituent at 3,6 position of carbazole and nitrogen centre of imidazolium showed remarkable variation in ^{1}H and ^{13}C δ values. Benzyl substituent based imidazolium salts exhibit higher δ value compared to those obtained from 9-(chloromethyl) anthracene-based salts.

Table 1: NMR comparison for N-CH-N Chemical shift for NHC Ligand

Benzyl based NHC-ligand	**L1**	**L2**	**L3**	**L4**	**L8**[a]
^{1}H-δ value for N-CH-N	9.26	9.92	9.30	9.86	9.27
^{13}C- δ value for N-CH-N	140.5	143.1	139.5	143.6	140.5
9-methylanthracene based NHC-ligand		**L5**	**L6**	**L7**	
^{1}H-δ value for N-CH-N		9.00	8.99	8.91	
^{13}C-δ value for N-CH-N		141.8	139.5	140.7	

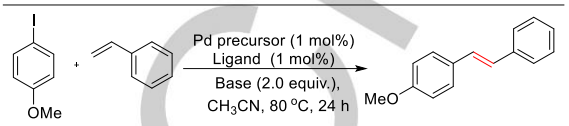
Based on the study reported by Hunuyh and co-workers[17] for the ^{13}C NMR spectroscopic determination of donor strength of NHC ligands, increase in the chemical shift observed in ^{13}C NMR for different ligands the donor capacity of the respective ligands was predicted to increase and a similar trend could be observed in the case of the carbazole-derived NHC salts **L1** to **L7**. Largest shift could be observed for ligands **L2** and **L4** suggesting better donor possibility from these ligands. Accordingly, donor strength for various ligands could be written in the following increasing order as **L4** > **L2** > **L5** > **L7** > **L1**~**L8** > **L3**~**L6**. Although, analysis of the catalytic activity would determine whether the donation capacity of ligands has any rate enhancing effect.

Application of *in-situ* generated Palladium-NHC complexes towards Heck-Borylation reaction.

a) Heck alkenylation

With the aim of developing an efficient protocol for obtaining stilbene-based boronate esters, we envisaged the analysis of the synthesized NHC salts as ligands in palladium-catalyzed Heck coupling reaction[18] of aryl iodide with styrene. Initial studies revealed, palladium precursor such as $Pd(OAc)_2$, $PdCl_2$ without the addition of activating ligands were found to be ineffective in carrying out the Heck reaction under the mentioned conditions in Table 2. Furthermore this reaction carried out with $Pd(OAc)_2$, $PdCl_2$ and $Pd_2(dba)_2$ in combination with imidazolium salts **L6**, led to the desired product in 82-83% in isolated yield at 1.0 mol% catalyst loading in 24 h (Table 2, entries no. 3, 4 & 5). Since the *in situ* generated catalytic system provided good reactivity in the Heck cross-coupling reaction, using $Pd(OAc)_2$ as the precursor, further optimization of the remaining NHC salts was carried out.

Table 2. Optimization of the reaction conditions for Heck reaction[a]



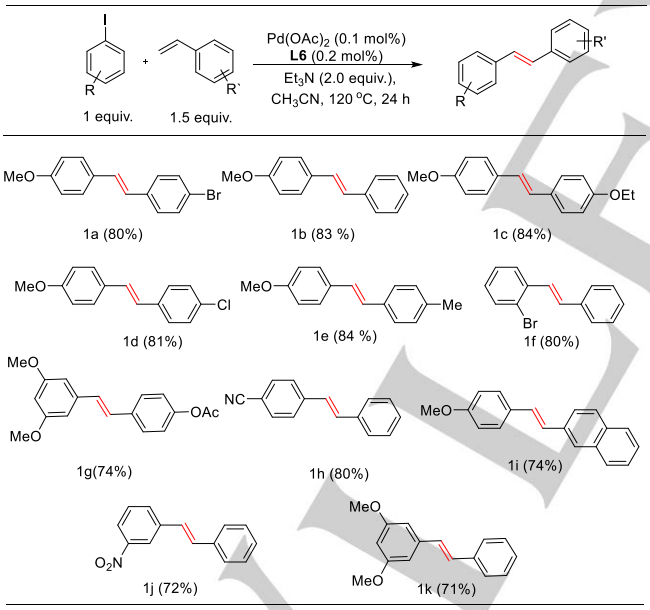
Sr.No.	Catalyst (mol %)	Ligand (mol %)	Base (2 eq.)	Yield[b] (%)
	Pd precursor screening			
1	$PdCl_2$	-	Et_3N	<5[c]
2	$Pd(OAc)_2$	-	Et_3N	<5[c]
3	$PdCl_2$	L6	Et_3N	82
4	$Pd(OAc)_2$	L6	Et_3N	83
5	$Pd_2(dba)_3$	L6	Et_3N	82
6[d]	**$Pd(OAc)_2$**	L6	**Et_3N**	**83**
	Ligand screening			
7[d]	$Pd(OAc)_2$	L1	Et_3N	82
8[d]	$Pd(OAc)_2$	L2	Et_3N	80
9[d]	$Pd(OAc)_2$	L3	Et_3N	82
10[d]	$Pd(OAc)_2$	L4	Et_3N	80
11[d]	$Pd(OAc)_2$	L5	Et_3N	82
12[d]	**$Pd(OAc)_2$**	**L6**	**Et_3N**	**83**
13[d]	$Pd(OAc)_2$	L7	Et_3N	81
14[d]	$Pd(OAc)_2$	L8	Et_3N	83
15[d]	$Pd(OAc)_2$	IMes.HCl	Et_3N	59
16[d]	$Pd(OAc)_2$	IPr.HCl	Et_3N	73
	Base screening			
17[d]	**$Pd(OAc)_2$**	**L6**	**Et_3N**	**83**
18[d]	$Pd(OAc)_2$	**L6**	CH_3COOK	25
19[d]	$Pd(OAc)_2$	**L6**	K_3PO_4	80
20[d]	$Pd(OAc)_2$	**L6**	K_2CO_3	62
	Catalyst loading studies			
21	$Pd(OAc)_2$ (1.0)	**L6**	Et_3N	83
22	$Pd(OAc)_2$ (0.5)	**L6**	Et_3N	83
23	$Pd(OAc)_2$ (0.1)	**L6**	Et_3N	60
24[e]	$Pd(OAc)_2$ (0.1)	**L6**	Et_3N	71
25[f]	$Pd(OAc)_2$ (0.1)	**L6**	Et_3N	78
26[g]	**$Pd(OAc)_2$ (0.1)**	**L6**	**Et_3N**	**84**

[a]Reaction condition: aryl iodide (0.5 mmol), styrene (1 mmol), Pd precursor (1 mol%), base (2 eq.), solvent (1 mL), [b]Isolated yields using column chromatography. [c]<10% of hydrodehalogenated product observed along with only <5% product formation and rest is starting material, [d]1.5 eq. styrene used, [e]Reaction carried out at 100°C, [f]Reaction carried out at 120 °C, [g]Reaction carried out at 0.2 mol% of ligand loading.

When the reaction was carried out using different imidazolium salts **L1** to **L8** in combination with **$Pd(OAc)_2$** at 1.0 mol% loading at 1.5 equiv. of styrene in acetonitrile as solvent, leading to the desired product in 80-83% isolated yield. Since, the entries no.7

to 14 suggested that there is no appreciable change in the final output of the reaction, indicated that electronic influence of the ligand system doesn`t play any crucial role on the outcome of the reaction. Hence, from Table 2, **Pd(OAc)$_2$** in combination with ligand **L6** was chosen as the most effective catalytic system for further optimization study (ease of synthesis was also one of the factors). Commercially available NHC ligands, Imes.HCl and Ipr.HCl were also tested under the given set of conditions. Although, IPr.HCl furnished better yield of the product than its Imes.HCl counterpart, in comparison to the synthesized NHC salt L6 the catalytic activity was found to be lower. In case of base screening studies, Et_3N proved to be most effective base over CH_3COOK and K_2CO_3, but the reactivity of K_3PO_4 and Et_3N were found to be comparable, giving 80% and 83% yield of product, respectively (entries no.15, 17 Table 2). Furthermore, catalyst loading was also performed with 1.0 mol% (TON = 83), 0.5 mol% (TON = 415), and 0.1 mol% (TON = 6000) of $Pd(OAc)_2$ in combination with **L6** was investigated. Although, 0.1 mol% at 80 ^oC provided lower yield of the product, increasing the temperature to 120 ^oC resulted into competitive yield suggesting that 0.1 mol% (TON = 8400) is effective in efficiently catalyzing Heck reaction at such reduced Pd concentration.

We next proceeded to utilise the optimized reaction conditions towards the synthesis of various stilbene derivatives. As summarized in scheme 3, a variety of styrene derivatives were employed as a coupling partner with 4-iodoanisole, furnishing the desired products in good to excellent yields.

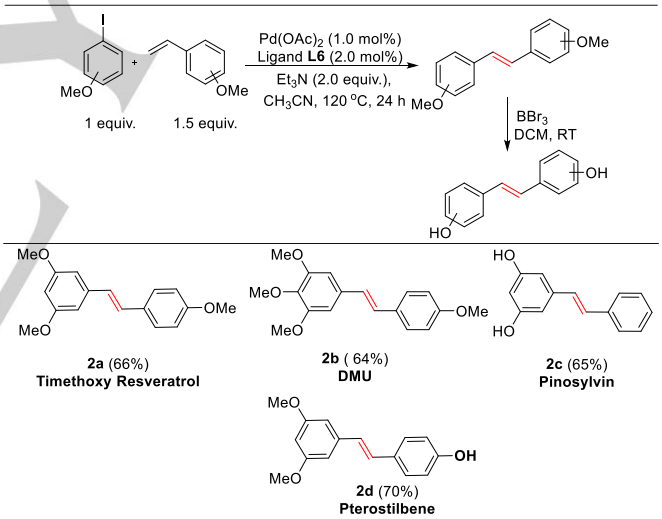


Scheme 3: Substrate scope for stilbene derivative synthesis using Heck alkenylation reaction with Pd/NHC catalytic system.

The developed protocol was found to be tolerant to the presence of electron donating, electron withdrawing and bulkier substituents, giving yields ranging from 64% to 84% except for 3-nitro styrene . The electronic effect of substituents present on the aryl iodide was also evaluated by altering the substituent such as CN, Br, and NO_2 with no appreciable difference in catalytic activity observed (Scheme 3). Uniqueness of the developed protocol is highlighted *via* the excellent chemoselectivity observed for the activation of C–I bond in preference to C–Br bond in examples such as **1a** and **1f**. Such a strategy could prove to be potentially useful towards the development of tandem catalytic protocols and will be discussed in further sections.

b) Application of Heck reaction towards the Synthesis of drug molecule.

Stilbene derivatives are an important class of compounds with wide occurrence in natural sources having potential biological applications such as cytotoxicity, anti-obesity, antioxidant[19]. The developed Heck coupling protocol was therefore expanded towards the synthesis of some naturally occurring and pharmaceutically important stilbene derivatives such as pterostilbene, pinosylvin, trimethoxy-resveratrol, and DMU providing the respective product in yields ranging from 64% to 70% in two steps involving palladium-catalyzed Heck coupling followed by demethylation using BBr_3 in CH_2Cl_2 (Scheme 4). Most of the catalytic systems described in literature suffer from higher catalyst loadings and temperature in excess of 100 °C.[18] In this regards, the Pd/NHC catalytic system presented in this manuscript allows the synthesis of stilbene derivatives in good to excellent yields at lower catalyst loading and at relatively lower temperature.



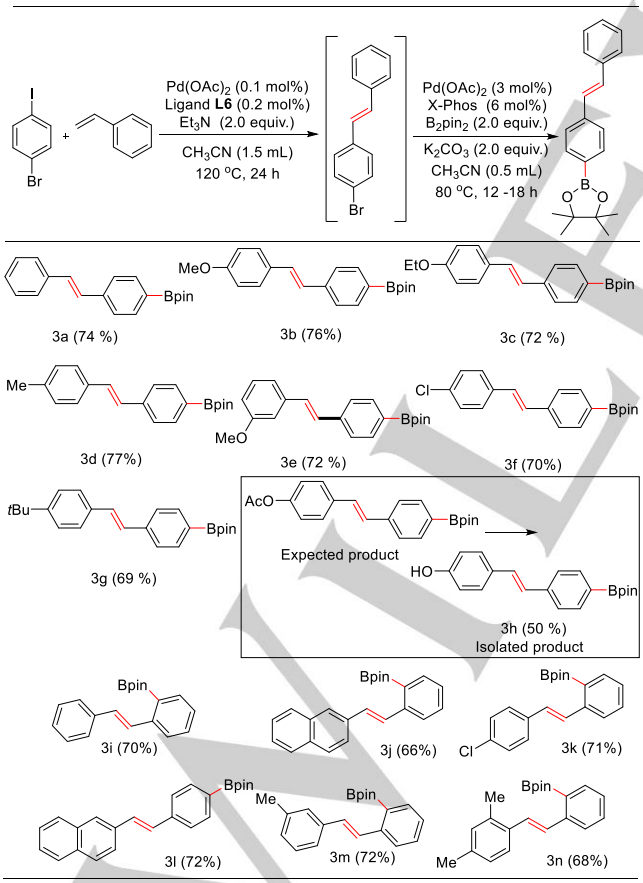
Scheme 4 : Synthesis of bio-active stilbene derivatives.

c) Tandem One-Pot Sequential Protocol: Synthesis of Stilbene-boronate esters

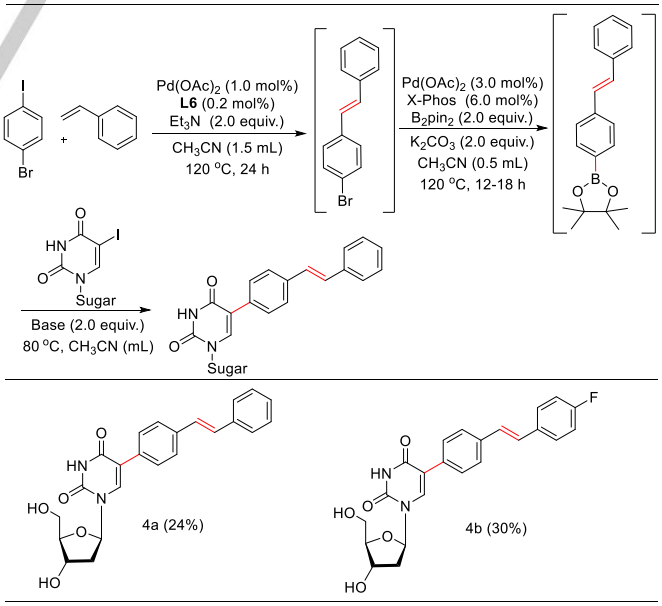
Taking into consideration the potential applications of stilbene-based derivatives in synthesis and medicinal chemistry, we envisaged that the modification of stilbene derivatives would help further enhance the synthetic utility of these molecules. With this is in mind, we proceeded with our investigation towards the development of a sustainable protocol for synthesizing stilbene-based boronate esters (also called as the analogue of polyphenol). The chemoselective Heck coupling involving the preferential activation of C–I bond over C–Br could now be envisaged as an important strategy for the installation of the

boronate ester via the subsequent activation of C–Br bond under the Miyaura borylation conditions[5a]. Such a procedure could help circumvent the problems associated with multi-step synthesis followed by Bhaskar and Ronald in a recent report.[11]
Tandem catalytic reactions in the recent years have emerged as an important tool providing a sustainable solution for the formation of multiple C–C or C–X bonds in a one-pot procedure.[20] Such a synthetic strategy provides multiple advantages over the challenging multi-step synthesis including low solvent usage, better yields and removal of tedious isolation procedures. For the incorporation of the boronate ester in a tandem catalytic procedure could therefore be made possible by combining the chemoselective Heck coupling with Miyaura borylation. Screening of reaction conditions for the installation of boronate ester on the stilbene moiety using bispinacaloto boron (1.5eq.) was performed in a tandem fashion with Heck reaction (See supporting information for screening studies). It was observed that for the activation of C–Br bond on the stilbene structural motif as a part of the boronate ester installation, catalytically more active system (combination of $Pd(OAc)_2$ with X-Phos and K_2CO_3 as the base) provided optimum results.

Scheme 5. One-pot sequential chemoselective Heck/Miyaura borylation tandem protocol for the synthesis of stilbene-based boronate esters.



The final optimized conditions for the one-pot tandem therefore involved the first step catalyzed by $Pd(OAc)_2$ (0.1 mol%) in combination with ligand **L6** (0.2 mol%) and Et_3N (2 equiv.) as base in acetonitrile at 120 °C, while for the Miyaura borylation step a catalyst combination of $Pd(OAc)_2$ (3.0 mol%) and X-phos (6.0 mol%) with K_2CO_3 (2 equiv.) as base at 80 °C was found to offer the desired product in good to excellent yield. We next explored this active catalytic system towards the synthesis of various stilbene-based boronate esters. Performance of this catalytic system investigated towards the substrate containing ethoxy, methoxy, ^{t}butyl, chloro, methyl functional groups at para and meta position of aromatic ring furnished the desired product in 50% to 76% in yields (Scheme 5). The presence of a labile acetoxy group, however was found to dissociate under the given set of conditions, although providing the stilbene-boronate product in decent yield (**3h**, Scheme 5). Several other substituted boronate esters with different aryl and naphthyl units were thus prepared (**3i-n**, Scheme 5).
Successful demonstration of the tandem one-pot procedure for the installation of boronate ester provided us with the required impetus to explore the possiblity of extending this methodology towards the modification of nucleosides[21]. Limitations on the part of the basic set of nucleosides in terms of poor absorbance values and low applicability has allowed researchers to explore the possibility of modifying nucleosides using a wide variety of synthetic methods including transition metal-catalyzed coupling processes.[22] In recent years, tandem catalytic processes has emerged as a promising alternative to multi-step synthesis for obtained highly derivatized nucleosides with promising biological activity.[23] To this perspective, we envisaged the installation of stilbene derivative on the nucleoside backbone to create a library of modified nucleosides with improved biological and photophyscial activities.[24]

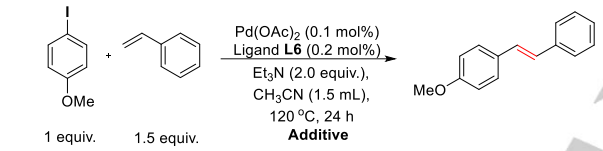


Scheme 6: Triple Tandem Heck/Miyaura borylation/Suzuki-Miyuara reaction.

An unprecedented triple tandem one-pot sequential protocol involving a chemoselective Heck reaction/Miyaura borylation/Suzuki-Miyuara cross-coupling sequence was investigated (Scheme 6). Keeping this in mind, we successfully performed the triple tandem protocol albeit in poor yields.

Mechanistic studies :

The given catalytic system was found to be most effective towards the Heck cross coupling reaction, but it is also important to investigate the pathway of reaction i.e. whether homogeneous or heterogeneous pathways.[24] To investigate the possiblity of either of the pathways operating under the given set of conditions, we performed the mercury drop test and CS_2 poisoning tests, which are considered as highly reliable tools for the inspection of the type catalytic pathways[26]. Hg drop and CS_2 tests were both found to inhibit the catalytic activity bringing about a drastic reduction in the product yield to 5% & 9%, respectively (Scheme 7). These results suggest the possibility that the catalytic reaction could be following a heterogeneous pathway with the formation of NHC-stabilized Pd-nanoparticles, that are known to be active species in catalytic reactions[27]. One of the reason for the formation of Pd nanoparticles would be the size of the NHC ligand that would prefer to dissociate under the catalytic conditions which would help enhance the reactivity of the developed catalytic system.



Additive	Yield (%)
Hg test	5
CS_2 test	9
-	84

Scheme 7: Catalyst poisoning study for the presence of heterogeneous or nanoparticular pathway.

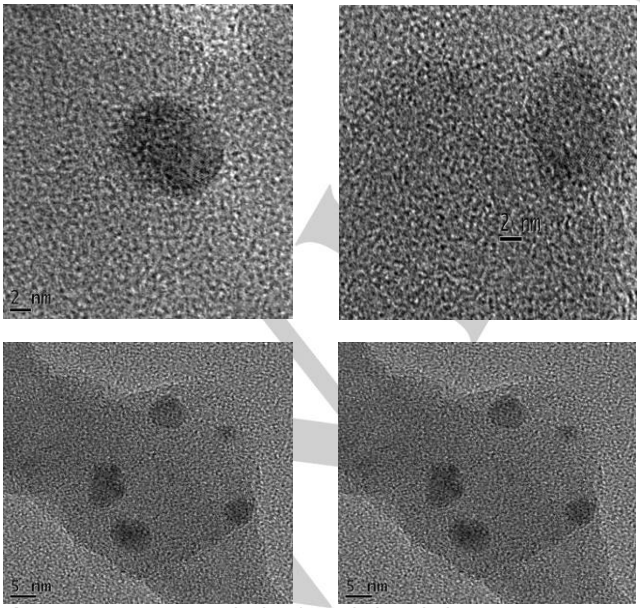
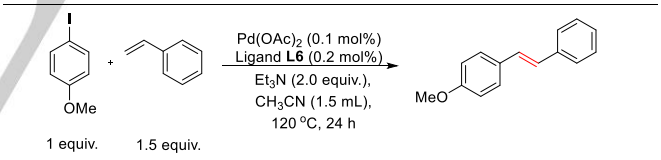


Figure 2: HR-TEM analysis of catalytic solution.

Furthermore, to ascertain the involvement of Pd nanoparticles the catalytic solution was directly subjected to HR-TEM (high resolution transmission electron microscope) analysis. This was performed by subjecting the catalytic solution or reaction mass to HR-TEM analysis after completion of reaction between iodoanisole and styrene (Scheme 7) by simple deposition of the reaction mass on carbon coated Cu grid. Presence of Pd nanoparticles were found to be present in the reaction mass with sizes ranging from 2 nm to 5 nm.

To ascertain the role of NHC ligand in catalytic system and to investigate whether it co-ordinates to Pd nanoparticle or first is preceeded by complexation to form an *in-situ* Pd-NHC complex that could later undergo degradation to form NHC-stabilized nanoparticles, we analyzed the reaction mass (containing $Pd(OAc)_2$ and NHC ligand L6) on HRMS. HRMS analysis provided further evidence of a possible formation of $Pd(NHC)_2$ at m/z = 1206.1676 while other peaks corresponding to $[Pd(NHC)_2Na_2]^{2+}$ at m/z = 1252.1699 and $[Pd(NHC)_2ClNa_2]^{2+}$at m/z = 1287.0914, respectively were also detected (Figure 3). The possible formation of the nanopartcles could therefore be taking place under the catalytic conditions and to verify this assumption we envisaged to carry out recycling studies of the catalytic material, which could be isolated at the end of the first catalytic reaction.

Recycling studies were performed by the isolation of the catalytic material at the end of the first parent cycle, subsequently adding new batch of substrate for continuing the studies (Scheme 8). It was observed that the recycling ability of the isolated material was limited as possible aggregation of the NHC-stabilized nanoparticles might be happening leading to reduced catalytic activity even after the first recycle.



Recycle	Parent cycle	1st recycle	2nd recycle
%Conversion	<99	90	50

Scheme 8: Recycling studies for Heck alkenylation reaction.

Conclusion:

In conclusion, series of novel *N*-substituted carbazole-based NHC ligands were synthesized and characterized by standard characterization technique. The investigation of the catalytic performance of synthesized ligand in combination with Pd precursor was successfully attempted towards the development of chemo-selective double tandem Heck-Borylation protocol for obtaining stilbene-based boronate esters using readily available simple starting material, 1,4-iodobromobenzene, styrene's, bispinacaloto borane in good to excellent yields. Finally, the modification of biologically important nucleosides (5-iodo-2'-deoxyuridine) was carried out by the installation of the stilbene derivatives at 5 positions of nucleoside *via* an unprecedented one-pot chemoselective Heck/Miyaura borylation/Suzuki-Miyuara triple tandem reaction sequence. Mechanistic studies

were also performed to ascertain the presence of active molecular species, which was investigated and confirmed by the catalyst poisoning tests (Hg drop, CS_2 test) along with HR-TEM analysis of the catalytic reaction mass.

Aknowledgements

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Keywords: Carbazole, N-Heterocyclic ligand, Tandem protocol, Heck-Borylation reaction

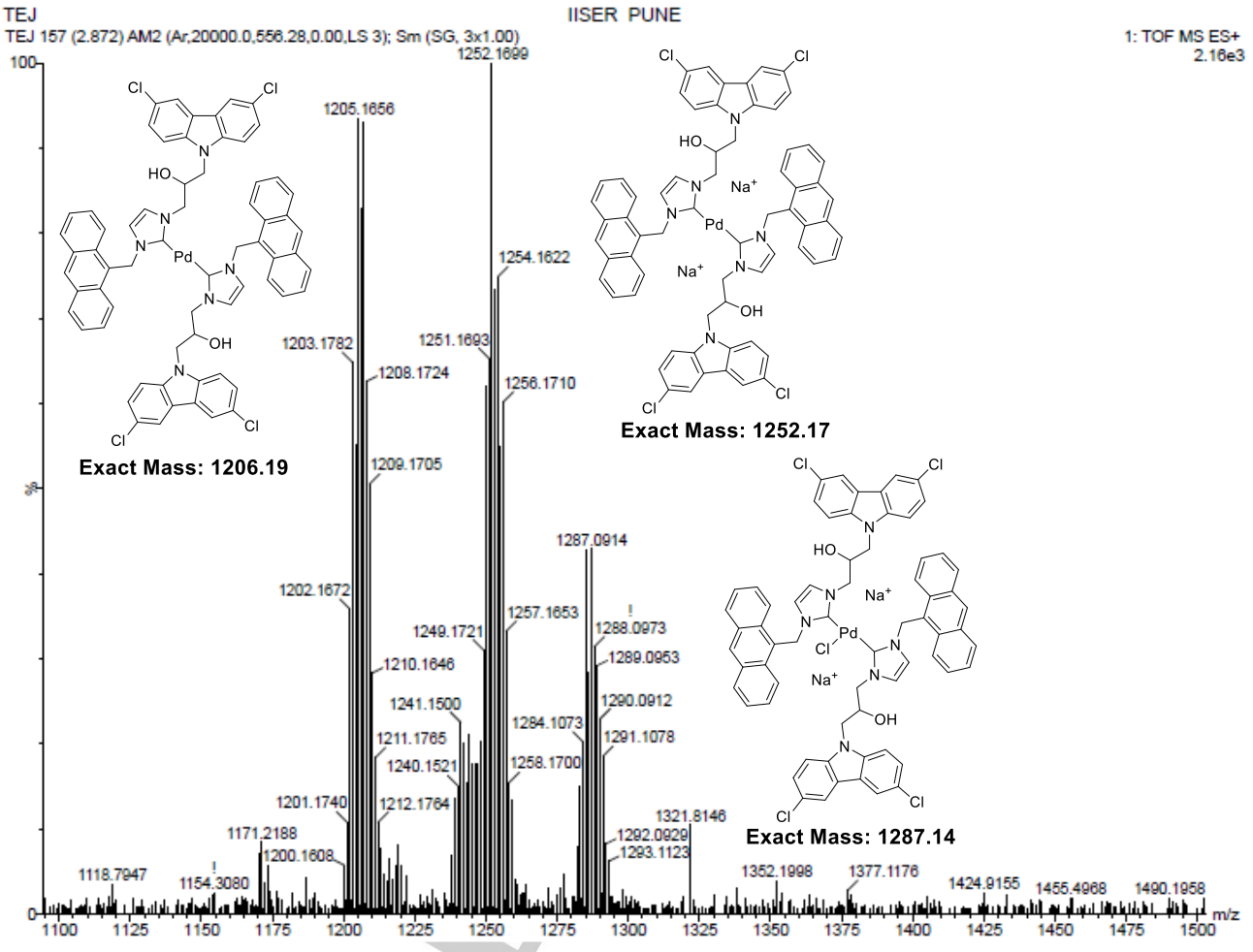

Figure 3: HRMS analysis of reaction mixture for the detection of Pd species in solution.

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