A quick and flexible synthetic approach to enureas (alkenyl ureas) via the Pd-catalyzed C–N coupling reaction of alkenyl tosylates, alkenyl mesylates and alkenyl nonaflates and their Bioassay.
1. Introduction

The study and expansion of novel and broad transition metal catalyzed methods for organic synthesis stay put at the midpoint of modern day organic chemistry since they allow scientists working in areas as varied as the entirely synthesis of natural products to analogues of front compounds for drug discovery. Among them, palladium catalyzed cross-coupling signifies a flexible etiquette in organic synthesis for the construction of carbon-Nitrogen bonds. Aryl halides, of course, are the mainly frequently used as electrophiles in these reactions. The development of alkenyl electrophiles in coupling reactions have not been as much of widespread. In verity, alkenyl halides are not generally available. Even though, some of them are commercially accessible. In scrutiny of the charisma of using catalytic synthesis, it is important to inflate the scope of alkenyl electrophiles. Alkenyl triflates are prepared from quite pricey triflating agent and less stable to hydrolysis than other alkenyl sulfonates. However, alkenyl tosylates and mesylates are more easily handled, highly stable, crystalline solids and readily prepared from less expensive and commercial available TsCl and MsCl respectively. Thus they are also more striking than triflates in the application of palladium catalyzed C-N coupling reaction. However, nonaflates are also a striking option, which can be readily prepared easily from nonaflyl fluoride (NfF) which is a commercially available, cheap, industrial product. Nonaflates are stable to storage and also more stable toward hydrolysis during synthesis. Nonaflates have parallel or faintly better reactivities to metal-catalyzed cross-coupling reactions.

Enureas comprise the core structure of many functional materials and biologically active molecules. The development of proficient methods for their synthesis has been a vigorous spot of research for many years. In the conventional route of synthesis, enureas are prepared by reaction of imines with isocyanates. Imines are classically synthesized via the addition of amines and carbonyl compounds. Main problem to exorcise the liberated water with related reaction still remain. Azeotropic distillation is unique technique to eliminate the liberated water. Lewis acid catalysts, molecular sieves, dehydrating solvents have also been revealed to eradicate water as well as make possible nucleophilic attack on the carbonyl compound. Thus, reaction suffers from high temperatures, lengthened periods of time, moisture receptive reagents or high outlay. Furthermore, isocyanates are highly toxic, unstable and characteristically entail the use of phosgene for their synthesis. Other routes are also to be had for the synthesis of enureas. But, they have partial scope. As to the
catalytic reaction of arylation and heteroarylation of ureas, this is of considerable worth for organic synthesis. In this circumstance, crucial advances of Pd-catalyzed reaction have arisen for \( N \)-arylation and \( N \)-heteroarylation of urea. \(^{12}\) These integral reported outcomes incited us to explore the application of the Pd-catalyzed C-N coupling reaction. So, we preferred the new and alternate way of synthesizing enureas via palladium catalyzed C–N coupling of alkenyl tosylates or mesylates and alkenyl nonaflates with a variety of ureas. However to the best of our acquaintance, Palladium catalyzed C-N coupling reactions between alkenyl tosylates or mesylates and alkenyl nonaflates with weak nucleophilic coupling partners various type of ureas have never been reported.

2. Plan of work

\( N \)-Aryl- and \( N \)-heteroaryl-substituted ureas are familiar pharmacophores in a diversity of biologically active targets and their efficient synthesis is of vast significance \(^{13,14}\), mainly to medicinal chemists \(^{15-18}\). Regrettably, this standard method for their synthesis involve numerous deficiencies: most notably, in low reaction yields resulting from instability of the isocyanates and disproportionation leading to symmetrical ureas. To evade these issues, numerous methods have been developed to allow in situ generation of the isocyanates from different precursors, such as carbamates,\(^ {19}\) carboxylic acids,\(^ {20}\) hydroxamic acids,\(^ {21}\) or acetoacetanilide \(^ {22}\). However, none of these procedures provide general and efficient syntheses for the preparation of \( N \)-aryl or \( N \)-heteroaryl ureas.

The recent progress in arylation of amide has opened a new synthetic route. The Pd-catalyzed arylation of amide inspired to investigate a new significant method for arylation of urea. Although a significant number of cross-coupling methodologies have been developed for \( N \)-arylation of amide, few have been applied to the \( N \)-arylation of ureas.

Monodentate biaryl phosphine having a methyl group ortho to the phosphorus generates a more stable catalysts for the amidation of aryl chlorides and aryl sulfonates by anticipation of formation of the \( k^2 \)-amidate complexes which is deleterious to the efficacy of a catalyst for this transformation. The utilization of this ligand allows a variety of aryl and heteroaryl chlorides with various amides to be coupled in high yield. \(^ {23}\) (Scheme-1)
The palladium-catalyzed amidation of acyclic secondary amides and related nucleophiles with aryl nonaflates, triflates, and chlorides have been developed. This method has been extended for easy variation of the aromatic component in tertiary aryl amides. A novel biaryl phosphine JackiePhos ligand with P-bound 3,5-(bis)trifluoromethylphenyl groups was established to be exclusively effectual for C-N bond formation. Insertion of molecular sieves in the reaction mixture enhanced the yields by restraining the formation of phenols and related side products.

The significance of (1) a methoxy group on the aromatic carbon of the “top ring” ortho to the phosphorus and (2) two highly electron-withdrawing P-bound 3,5-(bis)trifluoromethylphenyl groups have been exposed for the systematic variation of ligand. Considerable feature of the ligand were revealed through synthetic, mechanistic, and computational studies. Computational studies propose the electron-deficient scenery of the ligand is imperative in making easy amide binding to the LPd(II)(Ph)(X) intermediate.

(Scheme 1)
Aryl mesylates 7 are attractive substrates because their use is more atom-economical than that of aryl tosylates. Additionally, they are less expensive and more stable than aryl triflates. Brett Fors et al. 25 have developed a catalyst, based on a biarylphosphine t-Bu-Brettphos for the Pd-catalyzed cross-coupling reactions of amides and aryl mesylates. This system was proved effectively for an array of aryl and heteroaryl mesylates to be transformed into the corresponding N-aryl amides 9 in moderate to admirable yield. 25 (Scheme-3)

\[
\begin{array}{c}
\text{R= Me, CF}_3, \text{OMe, NMe}_2, \text{CO}_2\text{Et etc.} \\
\text{R}^\prime = \text{various substituted phenyl and heteroaryl}
\end{array}
\]

Palladium catalyzed formation of enamides 12 via the formal cross-coupling reaction between amide nucleophile 11 and unactivated vinyl triflates and tosylates electrophile 10. These approach reactions capably promote the coupling and afford better yields with catalyst system caused from Pd$_2$(dba)$_3$ and biphenyl ligands. 26 Scheme 4

\[
\begin{array}{c}
\text{R} = \text{Et, Ph, allyl, Pyridyl} \\
\text{R}^\prime = \text{t-Bu, Me}
\end{array}
\]

A. Klapars et al. 27 have developed a method for stereoselective Pd-catalyzed C-N coupling of enol tosylates 13 and amides 14. Ligand and catalyst screening exposed dipf and Pd$_2$(dba)$_3$ as the most general ligand and catalyst respectively for this transformation. This procedure is relevant to enol tosylates bearing an aryl substituent or an electron withdrawing group in the β-position of the double bond. A considerable degree of steric hindrance is
tolerated in the enol tosylate provides a convenient method for the synthesis of functionalized tri substituted and tetra substituted enamides 15. 27 (Scheme 5)

Scheme 5

An efficient Pd-catalyzed amidation of nonaflates appeared in 2005. These was developed using the soluble amine bases MTBD and Xantphos as ligand resulted in good to excellent yields (91-92%) in short reaction time. Additionally, the use of a soluble, weak amine base is favorable in preserving the homogeneity of the reaction mixture for extra efficient heating and stirring. The reaction was performed under microwave condition with Pd$_2$(dba)$_3$ as catalyst.28 (Scheme-6)

Microwave-assisted, palladium catalyzed C–N coupling reaction with activated cycloalkenyl nonaflates 19 and enolizable heterocycles 20 utilizing a catalytic system employing Pd(OAc)$_2$/Xantphos or Pd(OAc)$_2$/dppp and Cs$_2$CO$_3$ as a base were originated to be effectual in dynamic the reactions to completion. This reaction optimization afforded good to excellent yields of the coupled products (22 examples, 25–90%) in short reaction time (30–
60 min). Under most favorable conditions, cycloalkenyl nonaflates were established to be an efficient option to analogous triflates in C–N coupling protocol due to their improved constancy beneath the reaction conditions. The use of tetrabutyl ammonium bromide (Bu4NBr) as an additive in these transformations proved to be effective and resulted in better yields of the coupled products, but the corresponding cycloalkenyl bromides did not give promising yield due to the prolonged exposure of bromo intermediate under thermal conditions which resulted in its degradation. For substrates bearing electron withdrawing groups, longer reaction times (1 h compared to 45 min) were required and low yields of the coupled products were obtained. The electron withdrawing groups reduces the nucleophilicity of the nitrogen thereby making the reactions very sluggish.29 (Scheme 7)

![Scheme 7](image)

The upward a well-organized and selective Pd-mediated C–N coupling reactions of 3-bromocoumarins 22 with various nucleophiles including amides, sulfonamides and amines using palladium acetate as a catalyst, Xantphos as a ligand and Cs2CO3 as a base have been succeeded. Under this synthetic approach, a series of 3-(N-substituted) aminocoumarin derivatives 24 was obtained in satisfactorily good yields and isolation of the products was straightforwardly achieved by column chromatography.30 (Scheme-8)
S. Messaoudi et al. have synthesized a series of 3-(N-substituted)-aminoquinolin-2(1H)-ones via palladium-catalyzed C–N coupling reaction starting from 3-bromoquinolin-2-(1H)-ones with various nucleophiles including amides, sulfonamides, amines, carbamates and ureas. The synthetic route developed involves catalytic system containing palladium acetate as a catalyst, Xantphos as a ligand and Cs₂CO₃ as a base. On the whole, these reactions take place rapidly and proceed in good to excellent yield. (Scheme-9)
A general, practical and efficient method for the preparation of asymmetrically ureas has been developed by using the combination of a novel nonproprietary bipyrazole ligand (bippyhos) with Pd$_2$dba$_3$. This method offers a relatively inexpensive, effective catalyst system with high reactivity that enables the coupling of aryl, benzyl, and aliphatic ureas with not only aryl bromides but also aryl and heteroaryl chlorides.$^{32}$ (Scheme-10)
TRPV1 receptor antagonist 33 have been developed by a concise, robust and scalable synthesis. In which key step involves a novel palladium-catalyzed coupling reaction between 4-chloro-1-methylindazole 31 and substituted benzyl urea 32 with readily available nonpropriety bippyphos as the ligand as well as high yielding. (Scheme-11)

Beletskaya et al. reported the pd catalyzed C-N coupling reaction of Bromo carbazolone 34 with imidazolidin-2-one 35 and 6-bromoindole 37 with urea 38 in the presence of Pd$_2$dba$_3$, 3,5-(CF$_3$)$_2$Xantphos Cs$_2$CO$_3$ in dioxane at 100°C. Use of 3,5-(CF$_3$)$_2$Xantphos afforded 71% and 91% yield respectively, while Xantphos ligand afforded reduced yield. (Scheme-12 & 13)
3. Results and discussion

Part-1

Pd-catalyzed C–N coupling reaction of alkenyl tosylates and alkenyl mesylates with ureas.

Tosylates and mesylates are fewer effectual than triflates towards the cross coupling reaction, chiefly due to their virtual dullness toward oxidative addition by palladium complexes.\textsuperscript{35} Apposite ligand preference is renowned to have a considerable impact on the effect of reactions. Recently, synthetic chemists have been astonishingly skilled at devising effective ligands for exact bond constructions under palladium catalysis and the extension of these reactions to tosylates and mesylates couplings is exceedingly remarkable. In last decades, the mainly active ligands such as electron-rich biarylphosphines, CM-phos or ferrocenyl phosphines of the Josiphos family are required for Pd catalyzed C–N coupling of tosylates and mesylates. To our knowledge, however, there are few examples of P, N-ligands that were reported to be highly effective in the Pd-promoted catalytic reactions.\textsuperscript{36} Among them, ferrocene-based phosphine–triazine ligands revealed admirable activity. These ligands are extremely modular, willingly accessible and steady towards oxygen and moisture. The preface of the extra heterocyclic N-donor atoms into P, N-ligands is decidedly beneficial to get better activity of the catalytic reaction.\textsuperscript{36a, 36c} We then deduced that these ligands may also be effectual for the Pd catalyzed C–N coupling reaction of alkenyl tosylates or mesylates with a variety of ureas. To mediate this type of C–N bond formation reaction, high effective catalyst system based on ferrocene-based phosphine–triazine Ligand L (Figure 1) has been developed to carry out reaction in anticipation of better yield.
An effort to investigate the optimize condition for the synthesis of enureas, none activated and sterically hindered alkenyl tosylate 41 and phenyl urea 42 were originally designated as the model substrates. A series of ligands, palladium sources, bases and solvents were screened for viability of coupling approach. The highest yield was achieved by utilizing ferrocene-based phosphine–triazine Ligand L. All other ligands convinced moderate or lower yields. (Table 1) The upshot of different Pd sources on the reaction was inspected. Pd$_2$(dba)$_3$ was accredited as preeminent for our coupling reaction. (Table 2) Frequently used bases were also screened for viability of coupling approach. The highest yield was consummated by making use of K$_2$CO$_3$. (Table 3) In addition, different solvent systems were also evaluated. Toluene was initiated to be advanced to other solvents. (Table 4)

![Scheme 14](image)

**Table 1.** Screening of ligands$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xphos</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Sphos</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Ruphos</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Dppf</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>Xantphos</td>
<td>49</td>
</tr>
</tbody>
</table>
6 DPEphos 35
7 Josiphos 78
8 Ligand L 93
(ferrocene based triazine ligand)

\[ \text{a} \text{ Pd}_2(\text{dba})_3: 1.6 \text{ mol \%}, \text{ Ligand: 5 mol \%}, \text{ Phenyl Urea: 1.0 mmol, alkenyl tosylate: 1.0 mmol, K}_2\text{CO}_3: 1.4 \text{ mmol, toluene: 5 ml per mmol, bIsolated yields.} \]

**Table 2.** Screening of the Pd-Catalysts\( ^{\text{a}} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Yield( ^{\text{b}} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(_2)(dba)_3</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)(_2)</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dpdpf)Cl(_2)</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>Pd(Ph(_3)P)(_2)Cl(_2)</td>
<td>33</td>
</tr>
</tbody>
</table>

\[ \text{a} \text{ Pd: 1.6 mol \%}, \text{ ligand L: 5 mol \%}, \text{ Phenyl Urea: alkenyl tosylate:1.0 mmol, K}_2\text{CO}_3: 1.4 \text{ mmol, toluene: 5 ml per mmol, bIsolated yields.} \]

**Table 3.** Screening of bases\( ^{\text{a}} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield( ^{\text{b}} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs(_2)CO(_3)</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>NaOtBu</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>K(_2)CO(_3)</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>K(_3)PO(_4)</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>N(C(_2)H(_5))(_3)</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ \text{a} \text{ Pd}_2(\text{dba})_3: 1.6 \text{ mol \%}, \text{ ligand L: 5 mol \%}, \text{ Phenyl Urea: 1.0 mmol, alkenyl tosylate:1.0 mmol, Base: 1.4 mmol, toluene: 5 ml per mmol, bIsolated yields.} \]
Table 4. Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,4-dioxane</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>(t-BuOH)</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^a\) Pd\(_2\)(dba)\(_3\): 1.6 mol %, ligand L: 5 mol %, Phenyl Urea: 1.0 mmol, alkenyl tosylate: 1.0 mmol, K\(_2\)CO\(_3\): 1.4 mmol, solvent: 5 ml per mmol; \(^b\) Isolated yields.

Optimistic by this screening outcome, concentration was curved to ascertain the extent and generalization of the process. We consequently studied the substrate scope of the reaction with diverse alkenyl tosylates with phenyl ureas by operating a feasible catalyst system based on optimized condition. The obtained results resumed in Table 5 reveals that the optimized conditions portrayed above established to be inclusive for the coupling with an array of alkenyl tosylates including cyclic and acyclic structures (entries 1-5). The catalyst system also attuned ester and N-Boc groups (entries 4, 5).

Table 5. Scope of the reaction of alkenyl tosylates with phenyl urea

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenyl Tosylate</th>
<th>Product</th>
<th>Yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}CH=CH\text{OTs})</td>
<td>(\text{Ph}CH=CH\text{CONHPh})</td>
<td>88</td>
</tr>
</tbody>
</table>
Next, the prospect in coumarin-, quinoline-, furanone- and pyronyl derived alkenyl tosylates was also explored (Table 6). The coupling reaction underwent smoothly with our standard condition at room temperature. Remarkably, aromatic ureas bearing either electron donating or electron withdrawing groups at ortho, meta, or para positions experience C-N bond formation commonly. Use of K$_2$CO$_3$ as the base in optimized condition consented to the existence of a base susceptible functional group to be well tolerated. The beneficial of K$_2$CO$_3$ that it is congenial with functional group during reaction. The coupling was instigated to be genial with aromatic ureas containing electron withdrawing groups providing in rational yields the analogous coupling products (entries 2-4, 8). While aromatic ureas bearing electron donating groups were successfully coupled and resulted into excellent yields (entries 5-7, 9). The C-N bond coupling reaction was studied for coupling of benzyl urea and result was obtained as productively (entry 10). Finally, carrying out the coupling reaction was also effective with cyclic urea as well as acyclic urea given that in slightly lower yields the correspondingly bis-heteroarylated urea products (entries 11, 12).
**Table 6** Scope of the reaction of tosloxycoumarin, tosloxyquinolinone, tosloxypyranone and tosloxyfuranone with different ureas

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyronyl tosylate</th>
<th>Urea</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Pyronyl tosylate" /></td>
<td><img src="image2" alt="Urea" /></td>
<td><img src="image3" alt="Product" /></td>
<td>3f 91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Pyronyl tosylate" /></td>
<td><img src="image5" alt="Urea" /></td>
<td><img src="image6" alt="Product" /></td>
<td>3g 82</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Pyronyl tosylate" /></td>
<td><img src="image8" alt="Urea" /></td>
<td><img src="image9" alt="Product" /></td>
<td>3h 85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Pyronyl tosylate" /></td>
<td><img src="image11" alt="Urea" /></td>
<td><img src="image12" alt="Product" /></td>
<td>3i 80</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Pyronyl tosylate" /></td>
<td><img src="image14" alt="Urea" /></td>
<td><img src="image15" alt="Product" /></td>
<td>3j 94</td>
</tr>
</tbody>
</table>
The substrate scope was further expanded to impression of the process and the couplings of an array of structurally varied alkenyl mesylates with different ureas were studied. The results summarized in Table 7 exhibits that the corresponding desired products were achieved in moderate to better yields (entries 1-7). The catalyst system reserved linger together the chloro group (entry 5). The catalyst system was also competent to couple of benzene sulfanyl urea (entry 7).

Table 7. Scope of the reaction of alkenyl mesylates with different ureas

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenyl Mesylate</th>
<th>Urea</th>
<th>Product</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MsO</td>
<td>NH₂</td>
<td>3r</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Boc</td>
<td>NH₂</td>
<td>3s</td>
<td>93</td>
</tr>
</tbody>
</table>
Reaction condition: \( \text{Pd}_2(\text{dba})_3 \): 1.6 mol %, Ligand L: 5 mol %, Phenyl Urea: 1.0 mmol, alkenyl mesylate: 1.0 mmol, \( \text{K}_2\text{CO}_3 \): 1.4 mmol, toluene: 5 ml per mmol. \(^a\) Isolated yields.

\(^a\) Reaction condition: \( \text{Pd}_2(\text{dba})_3 \): 1.6 mol %, Ligand L: 5 mol %, Phenyl Urea: 1.0 mmol, alkenyl mesylate: 1.0 mmol, \( \text{K}_2\text{CO}_3 \): 1.4 mmol, toluene: 5 ml per mmol. \(^b\) Isolated yields.
Part-2

Pd-catalyzed C–N coupling reaction of alkenyl nonaflates with ureas

Conventional methods of heating reactions require additional time, complicated, monotonous tackle, resulting in higher expenses and also environmental contamination. There is very well acknowledged that microwave heating can steer to massive rate improvement compared to conventional heating. Microwave assisted synthesis have apparent advantages such as high scale of purity, improved reproducibility, superior yields, fewer side reactions and energy saving. In recent years, microwave-assisted Pd-catalyzed C-N coupling reactions have also reported in the literature.

As a foreword investigate to optimize conditions for the synthesis of enurea, alkenyl nonaflate 44 and phenyl urea 45 were originally designated as the model substrates. (Table 8) The heating in reaction mixture is very proficient below microwave heating and the essential temperature can be attained in seconds. In the common of the reaction time, potency was retained 60 Watt and temperature in 100 °C. The temperature and potency profile for the reactions under microwave irradiation are shown in Figure 2.

Figure 2
A series of ligands, palladium sources, bases and solvents were screened under microwave irradiation for viability of coupling approach within 10 minutes (Table 8). Firstly, we had to be familiar with apposite phosphine ligand for our coupling partners. Various bulky, electron rich, bidentate phosphine ligands and sterically hindered monodentate biaryl based phosphine ligands were exploited in Pd-catalyzed C-N coupling reactions of a variety of heteroaryl halides. Based on this, eight ligands (as summarized in Figure 3) were chosen to determine the efficacy of ligand in supporting a catalytic system for this transformation.

![Ligands](image)

**Figure 3**

**Table 8.** Reaction optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$</td>
<td>Xphos</td>
<td>K$_3$PO$_4$</td>
<td>t-BuOH</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$</td>
<td>Brettphos</td>
<td>K$_3$PO$_4$</td>
<td>t-BuOH</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$</td>
<td>t-Bu-Xphos</td>
<td>K$_3$PO$_4$</td>
<td>t-BuOH</td>
<td>55</td>
</tr>
</tbody>
</table>
To make sure the effectiveness of the coupling reaction, we have prelude examined Pd-catalyzed coupling reaction underneath procedure having catalyst system one of 8 different ligands, K$_3$PO$_4$ as base in t-BuOH at 100 °C under microwave heating. The highest yield was achieved by utilizing josiphos (Entry 5). All other ligands induced lower yields while biaryl based monodentate ligand convinced moderate yields (Entries 1-4, 6-8).
In the next phase, concerning the Pd source was also inspected. Pd(OAc)$_2$ provided less effective catalyst system than Pd$_2$(dba)$_3$ (Entry 9). The proxy of Pd$_2$(dba)$_3$ by Pd(dppf)Cl$_2$ afforded moderate yield (Entry 10). In contrast, Pd(Ph$_3$P)$_2$Cl$_2$ conferred not as good as yield (Entry 11). The upshot of different bases on the reaction was scrutinized. In discrepancy, replacing K$_3$PO$_4$ by the strong base NaOrBu and Cs$_2$CO$_3$ decreased the yield radically (Entries 12, 13). When the reaction was carried out in the subsistence of K$_2$CO$_3$ as an alternative of K$_3$PO$_4$ remarkably poorer yields of 33 % were acquired correspondingly (Entry 14). Thus, K$_3$PO$_4$ was accredited as preeminent base for our coupling reaction. In addition, different solvent systems were also evaluated. Switching the solvent to other slightly polar solvent such as THF or 1, 4- dioxane or non polar solvent such as toluene, product was afforded in slightly lower yields (Entries 15, 16 and 17). However, more polar solvent such as DMF furnished mediocre results (Entry 18).

After utilizing the optimized reaction conditions, concentration was curved to ascertain the extent and the generalization of the process. The above results also verified that synthesis of enureas is potential to prepare within 10 minutes below microwave irradiation with equivalent yields. We consequently studied the substrate scope of the reaction with diverse alkenyl nonaflates with phenyl urea by operating a feasible catalyst system based on optimized condition under microwave heating (**Table 9**). The obtained results resumed in **Table 9** reveal that the optimized conditions exposed above established to be broad for the
coupling with an assortment of alkenyl nonaflates together with cyclic and acyclic structures (entries 1-6). The catalyst system also accustomed ester and N-Boc groups (entries 4, 5).

**Table 9** Scope of the reaction of alkenyl nonaflates with phenyl urea

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenyl nonaflate</th>
<th>Product</th>
<th>Yield$^b$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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Next, the prospect in coumarin-, quinoline-, furanone-, pyronyl and other alkenyl derived nonaflates was also explored (Table 10). The coupling reaction experienced slickly below microwave heating condition. Remarkably, aromatic ureas bearing either electron donating or electron withdrawing groups at ortho, meta, or para positions experience C-N bond formation commonly. Use of K$_3$PO$_4$ as the base in optimized condition consented to the existence of a base susceptible functional group to be well tolerated. The beneficial of K$_3$PO$_4$ that it is affordable with functional group during reaction. The coupling was instigated to be genial with aromatic ureas containing electron withdrawing groups providing in rational yields the analogous coupling products (Entries 2-4, 9, 13, 14). The catalyst system reserved linger together the chloro group (Entry 5). While aromatic ureas bearing electron donating groups were successfully coupled and resulted into high yields (Entries 6-8, 10). Other electron rich aromatic ureas were also reacted in dazzling yields (Entries 11-12). The C-N bond coupling reaction was studied for coupling of benzyl urea and result was obtained as productively (Entries 15). Finally, carrying out the coupling reaction was also effective with cyclic urea as well as acyclic urea given that in slightly lower yields the correspondingly bis-heteroarylated urea products (Entries 16, 17). The catalyst system was also competent to couple of benzene sulfonyl urea (Entry 18).

Table 10 Scope of the reaction of alkenyl nonaflates with different ureas$^a$

\[
\begin{align*}
R^1R^2ONf + R^3R^4HN & \xrightleftharpoons{\text{Pd}_2(\text{dba})_3, \text{Josiphos}}\text{K}_3\text{PO}_4, \text{r-BuOH} \\
& \quad 60 \text{ watt, } 100^\circ \text{C} \\
& \quad 10 \text{ min}
\end{align*}
\]
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<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
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4. Mechanism

An anticipated catalytic cycle of Pd-catalyzed C–N coupling reaction of alkenyl tosylate or mesylate with urea is portrayed in Scheme 15. The Ferrocene-based phosphine–triazine type of Ligand L stabilized catalytically active Pd$^{0}$ species. Oxidative addition of alkenyl tosylate to species I began catalytic and turned out the adduct II as a homogeneous-Pd species, which was followed by coordination of phenyl urea to species II, forming species III.
The Base subsequently abstracts a proton from coordinated phenyl urea, forming species IV, from which the cross-coupling product is achieved by reductive elimination regenerating catalyst species I.

A proposed catalytic cycle of Pd-catalyzed C–N coupling reaction of alkenyl nonaflate with urea is portrayed in Scheme 16. The ligand Josiphos stabilized catalytically active Pd$^0$ species. Oxidative addition of alkenyl nonaflate to species I commenced catalytic and turned out the adduct II as a homogeneous-Pd species, which was followed by coordination of phenyl urea to species II, forming species III. The Base afterward abstracts a proton from coordinated phenyl urea, forming species IV, from which the cross-coupling product is attained by reductive elimination regenerating catalyst species I.
5. Experimental Section

5.1 Reagents

All reactions were carried out under a nitrogen atmosphere. Air- and moisture-sensitive solvents and solutions were transferred via syringe or stainless steel cannula. All chemicals were purchased from sigma Aldrich, merck and fluka. Solvents used were of analytical grade. Anhydrous potassium carbonate was stored in a nitrogen-filled glovebox, ground and was taken out in small quantities and stored in a desiccator. Aryl ureas were prepared by known methods. Ferrocene based triazine ligand L were synthesised according to the literature method without modification. Pyronyl tosylates and mesylates were prepared from their corresponding precursors with TsCl or MsCl in the presence of triethylamine in CH$_2$Cl$_2$ according to the literature method without modifications. Other alkenyl tosylates and mesylates were prepared from their corresponding species according to the literature method without modifications. Alkeny nonaflates were prepared from their corresponding species.
according to the literature method without modifications. All reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F254 grade, Merck DC) with spots visualized by UV light. Column chromatography was performed on silica gel LC 60A (70-200 micron).

5.2 Instrumental

All compounds were characterized by 1H NMR, 13C NMR as well as elemental analysis. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. 1HNMR and 13C NMR spectra were recorded on a Bruker400 MHz model spectrometer using DMSO-d6 as a solvent and TMS as internal standard with 1H resonant frequency of 400 MHz and 13C resonant frequency of 100 MHz. The 1H NMR, 13C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me4Si). The splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; m, multiplet. Elemental analyses (C, H, N) were performed using a Heraeus CarloErba 1180 CHN analyzer (Hanau, Germany). CEM benchmate microwave reactor was used for microwave heating. The general parameters used were: closed vessel synthesis, stirring on, power 60 watt, temperature 100 °C, hold time 10 minutes, external cooling on.

5.3 General procedures coupling reactions for Pd-catalyzed couplings of alkenyl tosylates or mesylates with various ureas

To an oven dried flat-bottomed flask which was equipped with a magnetic stir bar, was charged with urea (1.0mmol), K2CO3 (1.4 mmol), ligand L (5 mol %), Pd2(dba)3 (3.3 mol %), and alkenyl tosylate or mesylate (1.0 mmol) in Toluene (5.0 ml). The reaction was sparged with nitrogen for 15 minutes, stirred and heated to 60 °C (reactions were carried out at room temerature for the coupling of tosylxycoumarin, tosylxyquinolinone, tosylxypyrane and tosylxyfuranone with different ureas) for 10 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

5.4 General procedure for Pd-catalyzed couplings of alkenyl nonaflate with various ureas by using Microwave Heating:
To a vial was charged with urea (1.0 mmol), K$_3$PO$_4$ (1.5 mmol), Josiphos (3 mol %), Pd$_2$(dba)$_3$ (1.6 mol %), and alkenyl nonaflate (1.0 mmol) sequentially. The mixture was dissolved in t-BuOH (5.0 ml) and degassed with Nitrogen over 5 min. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 60 watt and 100 °C for 10 minutes. After cooled to rt and filtered through a pad of Celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.
### 6. Characterization

#### 6.1 Physical and analytical data of compounds (3a-3x)

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6.6 Mass Spectra

MS, m/z 324.8 [M+1]: 239.8, 172.9, 171.0, 128.0, 93.1

MS, m/z 379.1 [M+1]: 222.0, 179.1, 162.0, 137.3, 94.1
7. Biological evaluation

Antimicrobial activity data of compounds (3f-3n, 3w)

The minimum inhibitory concentration (MIC) of the synthesized compound were tested against two representative Gram-positive (*Staphylococcus aureus* MTCC 96 and *Staphylococcus pyogenes* MTCC 443) and two Gram-negative (*Escherichia coli* MTCC 442 and *Pseudomonas aeruginosa* MTCC 441). Ampicillin and Chloramphenicol were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The in vitro results of the antibacterial activity of the some newly synthesized compounds are presented in Table 11. From the bioassay results it can be stated that some of the compounds displayed excellent antibacterial activity against most of the microorganisms studied. However, the antibacterial property of the each compound varies by varying structural features of aryl urea. The antimicrobial screening suggests that among the newly synthesized compounds, the compounds 3l and 3n exhibited good activities towards Gram-negative *E. coli*. Similarly, compounds 3h and 3m showed better activities against Gram- negative bacteria *P.Aeruginosa*, while good antimicrobial activities for Gram-positive bacteria were found for compounds 3k and 3j against the test microorganisms. Rest of the compounds exhibited with moderate to poor activity profile.

Table 11: Antibacterial activities in MIC

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<th>COMPOUND</th>
<th>R</th>
<th>E.COLI MTCC 442 µg/ml</th>
<th>P.AERUGINOSA MTCC 441 µg/ml</th>
<th>S.AUREUS MTCC 96 µg/ml</th>
<th>S.PYOGENUS MTCC 443 µg/ml</th>
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References


