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Multicomponent and one-pot synthesis of trisubstituted pyridines through a Pd-catalyzed cross-coupling/cross-coupling/cycloaddition sequence

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Abstract

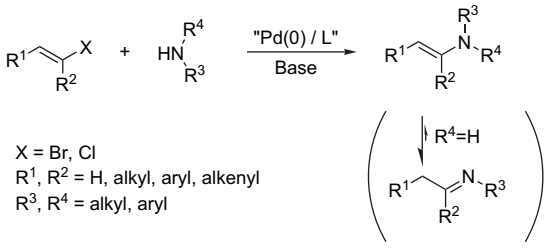
Trisubstituted pyridines are regioselectively synthesized through multicomponent and one-pot processes promoted by a bifunctional Pd-catalyst. The process involves formation of an enamine by Pd-catalyzed amination of an alkenyl bromide, formation of a 2-aza-1,3-butadiene by Pd-catalyzed cross-coupling of a trimethylsilylimine with an alkenyl bromide, and Lewis acid catalyzed cycloaddition between the enamine and the azadiene.

1. Introduction

The construction of complex molecules through multicomponent reactions (MCR) constitutes a very attractive strategy in organic synthesis.[1] In a multicomponent reaction three or more reactants are involved in a cascade of bond-forming individual steps to provide a complex molecule without isolation of intermediates or modification of the reaction conditions. Attractive features of MCRs are simplicity of operation, reduction of isolation and purification steps, and minimization of costs, time, energy, solvents, and waste production. Moreover, by employing an array of diverse reagents, molecular diversity is efficiently generated. In fact, MCRs have been extensively employed in combinatorial and parallel diversity oriented synthesis.

Most of the early examples of multicomponent reactions are based either on condensation[2] or isocyanide[3] chemistry. However, in the recent years, new methodologies have appeared, which rely on transition metal catalyzed and in particular Pd-catalyzed processes.[4] In this context, multicomponent processes in which the same catalyst promotes more than one elementary reaction (a multifunctional catalyst)[5] are particularly appealing, since catalyst economy must be added to the aforementioned list of advantages of MCRs.

In recent years we have been investigating the cross-coupling reactions between amines and alkenyl halides.[6] This transformation, which is inspired by the well-known Buchwald–Hartwig amination of aryl halides,[7] gives rise to the corresponding enamines and imines with very high yields.[8] Moreover, catalytic conditions have been developed that allow for the preparation of the corresponding coupling products from alkenyl bromides, chlorides,[9] and triflates.[10] This methodology has been applied for the preparation of simple enamines and imines, and also of 1- and 2-amino-1,3-butadienes,[11] versatile intermediates in organic synthesis through [4+2] cycloadditions (Scheme 1).



Scheme 1. Pd-catalyzed alkenyl amination for the synthesis of enamines and imines.

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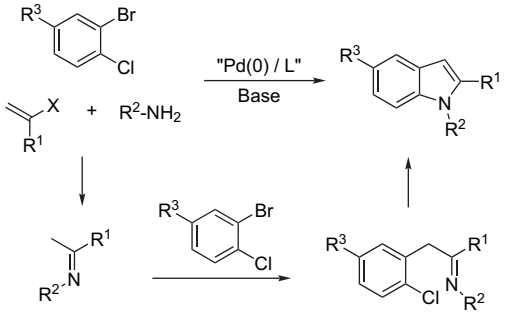
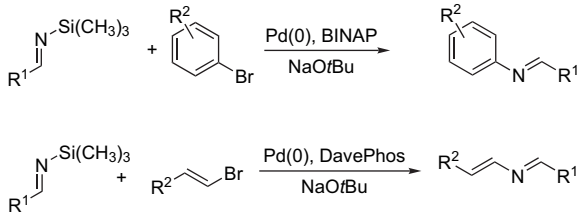
Taking advantage of the versatility and stability of currently available Pd-catalysts, we have designed various strategies in which alkenyl amination processes are included in cascade sequences leading to indoles.[12,13] In these domino processes, the same Pd-based catalytic system promotes two and even three independent coupling reactions. For instance, in Scheme 2 is presented a three-component synthesis of indoles in which the same Pd-catalyst promotes three independent coupling reactions: alkenyl amination, α-arylation of the imine formed, and intramolecular aryl amination.



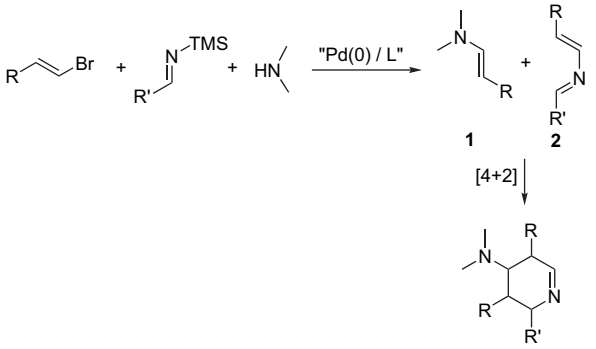
Scheme 2. Multicomponent synthesis of indoles promoted by a *multifunctional* Pd-catalyst.

Continuing with our work on Pd-catalyzed C–N bond forming reactions, we have also introduced *N*-trimethylsilylaldimines as coupling partners for C–N bond forming cross-couplings. In this way, the silylimines became a synthetic equivalent of the unstable NH-aldimines in cross-coupling reactions, and can be also employed as an alternative to introduce a protected NH_2 group in an aromatic molecule. The coupling reaction can be conducted with aryl and alkenyl halides. Noteworthy, the reaction with alkenyl halides furnishes 2-aza-1,3-butadienes, interesting intermediates in [4+2] cycloadditions (Scheme 3).



Scheme 3. Synthesis of aldimines and 2-aza-1,3-butadienes by cross-coupling reaction of silylimines with aryl and alkenyl halides, respectively.

It is worth noting that the coupling reactions of alkenyl halides with secondary amines and *N*-trialkylsilylimines, which deliver enamines **1** and 2-aza-1,3-butadienes **2**, respectively, are carried out under very similar reaction conditions and employing the same catalytic system. Moreover, enamines are electron-rich olefins, while 2-aza-1,3-butadienes are expected to react as 4π-components in inverse electron demand hetero-Diels–Alder reactions.[14,15] Therefore, these systems are, in fact, complementary reagents for [4+2] cycloadditions. We wondered whether it might be possible to carry out, in a multicomponent fashion, both cross-coupling processes—promoted by the same Pd-catalyst—followed by the cycloaddition reaction (Scheme 4). This process would hopefully lead to a very convergent, regioselective, and multicomponent preparation of 2,3,5-trisubstituted pyridine derivatives,[16] a type of compounds with interesting biological activity.[17] In this paper we wish to report our progress toward this goal.

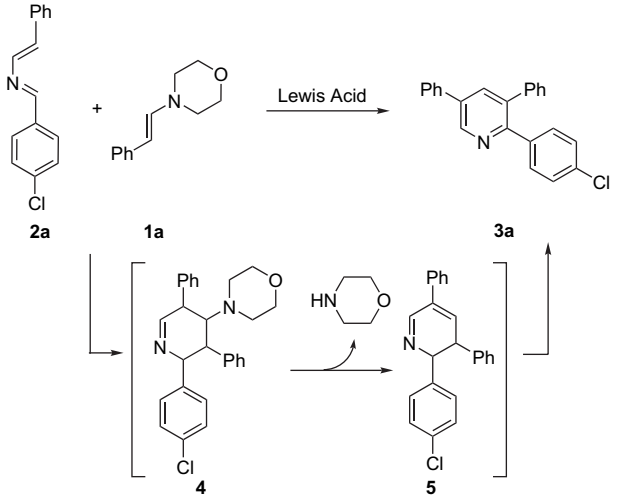


Scheme 4. Plan for a multicomponent Pd-catalyzed cross-coupling/cross-coupling/cycloaddition sequence.

2. Results and discussion

2.1. Optimization of the cycloaddition reaction

First of all we carried out a study of the proper conditions to carry out the cycloaddition reaction between the previously synthesized enamine **1a** and 2-aza-1,3-butadiene **2a** (Scheme 5).[18]



Scheme 5. Lewis acid catalyzed cycloaddition of enamine **1a** with 2-azadiene **2a**. Synthesis of pyridine **3a**.

Although some examples had been described of reactions of enamines with 2-azadienes substituted with electron-withdrawing groups,[19] to the best of our knowledge, the same type of reaction with neutral 2-azadienes had not been previously explored.[20] We found that in order to effect the cycloaddition it was necessary the presence of a catalytic amount of a Lewis acid, to enhance the reactivity of the otherwise poorly reactive 2-azadiene.

Several Lewis acids promoted the cycloaddition, and the best results were obtained employing a 20 mol % loading of $Yb(OTf)_3$ at 90 °C (Scheme 5). Under these conditions the corresponding trisubstituted pyridine **3a** was obtained with good yield. The process involves the [4+2] cycloaddition, followed by morpholine elimination, and oxidation to deliver the aromatic system. In no case could the tetrahydropyridine **4** or the dihydropyridine **5** be isolated.

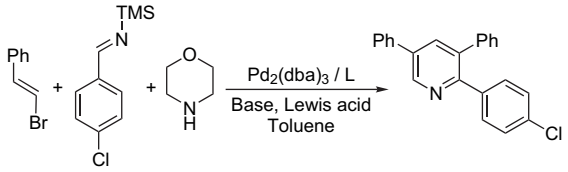
2.2. Multicomponent reactions

Once we had discovered some proper reaction conditions to effect the cycloaddition reaction, we turned our attention to the sequential multicomponent process. In a preliminary set of experiments we mixed 1 equiv of β-bromostyrene **6a**, 0.5 equiv of morpholine, and 0.5 equiv of silylimine **7a** under the cross-coupling conditions: NaO^{t}Bu as base (1.4 equiv), $Pd_2(dba)_3$ (2 mol %), and a supporting ligand for the metal (8 mol %) (Scheme 6). We employed DavePhos (2-dicyclohexylphosphino-2′-*N*,*N*-dimethylamino)biphenyl as ligand because it had been found as one of the most effective ligands in both individual cross-coupling reactions. Analysis of the reaction crude at this stage, after 10 h of reaction, showed that indeed, both coupling reactions had occurred with full conversion. As expected, no cycloaddition product was detected in the absence of an additional Lewis acid. Nevertheless, addition of 20 mol % of $Yb(OTf)_3$ to the reaction mixture at this point promoted the cycloaddition, and after additional 10 h of heating at 90 °C, the expected pyridine **3a** was obtained in a 40% overall yield.

Encouraged by this promising result, we investigated whether the transformation could be achieved in a strict multicomponent fashion, with the addition of all the reagents, including the Lewis acid, at the beginning of the reaction. To this end, a set of experiments with variation of base, reaction conditions, and amounts of reagents were conducted. Some selected results are presented in Table 1.

The amount of base has some influence on the reaction yield, and an excess has a negative effect on the overall yield (entries 1, 2). Mild bases such as Cs_2CO_3 or CsF did not promote the reaction at all (entries 6, 7). Very similar results were obtained when Sc or Yb triflates were employed as Lewis acid. Regarding the ligand, DavePhos and XPhos provided nearly identical yields. The influence of the amine in the enamine was also explored. Morpholine and *N*-methylaniline (entries 4 and 13, respectively), which would render enamines with different electronic properties, were employed in the multicomponent reactions, giving rise to very similar results. Interestingly, under these new experimental conditions, the reaction time is highly reduced, and the formation of the pyridine occurs in only 14 h at 90 °C.

Table 1
Optimization of the reaction conditions for the multicomponent synthesis of **3a**

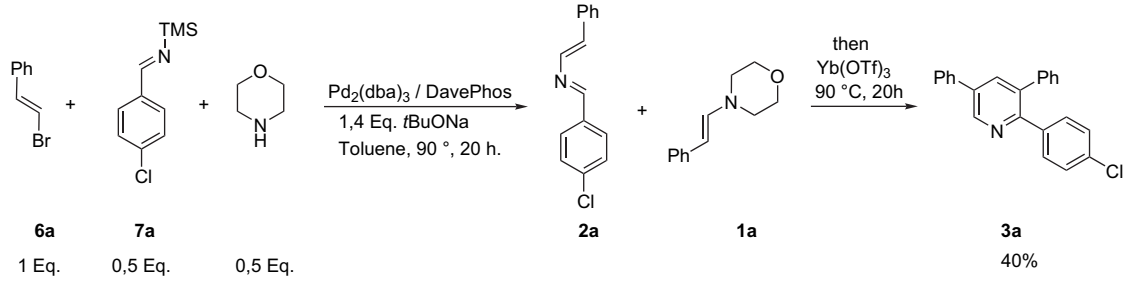


Entry	Ligand	Base[a] (equiv)	Lewis acid	*T* (°C)	Yield (%)
1	DavePhos	NaO^{t}Bu (1.4)	$Yb(OTf)_3$	90	35
2	DavePhos	NaO^{t}Bu (1.4)	$Sc(OTf)_3$	90	30
3	DavePhos	NaO^{t}Bu (1.2)	$Yb(OTf)_3$	90	40
4	DavePhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	90	50
5	DavePhos	NaO^{t}Bu (1.0)	$Yb(OTf)_3$	90	30
6	DavePhos	Cs_2CO_3 (1.1)	$Yb(OTf)_3$	90	—
7	DavePhos	CsF (1.1)	$Yb(OTf)_3$	90	—
8	XPhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	90	50
9	XPhos	NaO^{t}Bu (1.1)	$Sc(OTf)_3$	90	50
10	DavePhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	110	50
11[b]	DavePhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	90	50
12[c]	DavePhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	90	31
13[d]	DavePhos	NaO^{t}Bu (1.1)	$Yb(OTf)_3$	90	49

[a] Equivalents referred to bromostyrene.
[b] Silylimine (0.75 equiv).
[c] Silylimine (1 equiv).
[d] *N*-Methylaniline was employed instead of morpholine.

With some convenient reaction conditions for the multicomponent reaction, the scope of the process with regard of the substituents of the starting alkenyl bromide **6** and *N*-silylimine **7** was studied.

As depicted in Table 2, the trisubstituted pyridines were obtained for a variety of alkenyl bromides and imines. The reaction tolerates electron-neutral and electron-rich substituents in both aromatic rings. However, the use of a silylimine bearing an electron-withdrawing group such as the cyano did not lead to the formation of the desired pyridine, due to the low efficiency of the coupling reaction of that particular silylimine with the alkenyl bromide. We are currently working on the optimization of this reaction, and hopefully, it will enhance the

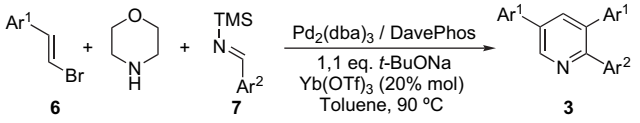


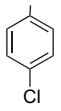
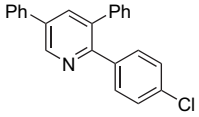
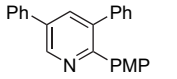
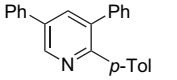
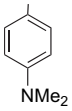
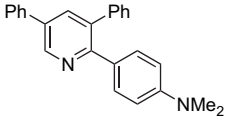
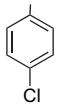
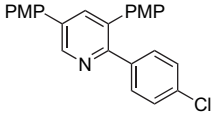
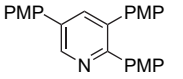
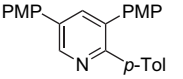
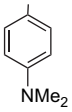
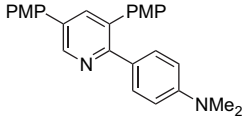
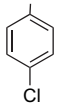
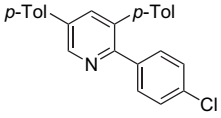
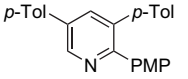
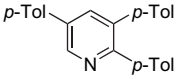
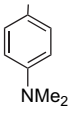
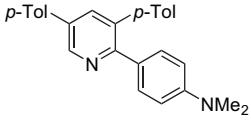
Scheme 6. Preliminary experiments on the Pd-catalyzed synthesis of pyridine **3a**.

scope of this multicomponent process. Despite this, a variety of trisubstituted pyridines can be obtained through this multicomponent reaction in a reasonable yield, taking into account all the events that have occurred in the reaction flask: (i) formation of an enamine by Pd-catalyzed alkenylation of morpholine; (ii) formation of a 2-aza-1,3-butadiene by cross-coupling reaction of the silylimine with the alkenyl bromide; note that both processes are promoted by the same catalytic system; (iii) Hetero-Diels–Alder reaction promoted by $Yb(OTf)_3$; (iv) elimination of morpholine and aromatization.

Moreover, advantages of the multicomponent process when compared to a conventional multistep synthesis can be pointed out: (i) the same Pd-catalyst is employed to promote two independent reactions; (ii) no purification of intermediates is required, which is an important fact in this particular case, since both enamines and azadienes are sensitive to humidity and are not suitable for conventional chromatographic techniques.

Table 2
Pyridines synthesized through the multicomponent reaction[a]



Compound	Ar^1	Ar^2	Pyridine **3**	Yield[b] (%)
a	Ph			48
b	Ph	PMP		55
c	Ph	*p*-Tol		57
d	Ph			61
e	PMP			60
f	PMP	PMP		55
g	PMP	*p*-Tol		58
h	PMP			54
i	*p*-Tol			54
j	*p*-Tol	PMP		53
k	*p*-Tol	*p*-Tol		54
l	*p*-Tol			62

[a] Reaction conditions: alkenyl halide **6** (1 mmol); morpholine (0.5 mmol); *N*-trimethylsilylimine **7** (0.5 mmol); $Pd_2(dba)_3$ (1 mol %); DavePhos (2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, 4 mol %); NaO^{t}Bu (1.1 mmol, 1.1 equiv); $Yb(OTf)_3$ (0.1 mmol, 0.2 equiv); toluene (4 mL).

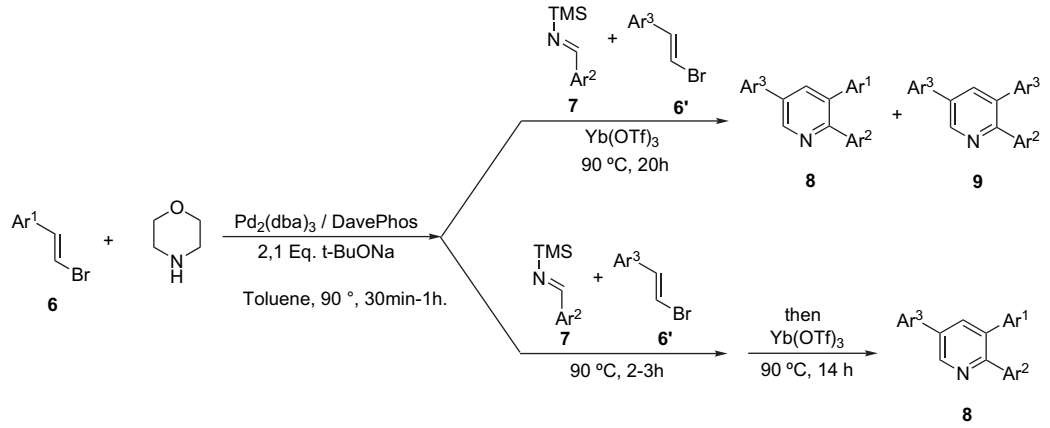
[b] Isolated yields after column chromatography or recrystallization. PMP= *p*-MeO-C_6H_4.

2.3. One-pot reactions: synthesis of pyridines with three different substituents

An important limitation of the present strategy is that the pyridines **3** obtained feature the same substituent Ar^1 at positions 3 and 5, since both are coming from the same alkenyl bromide **6**. To increase the versatility of this multicomponent reaction we decided to investigate a different approach that might circumvent this limitation by employing two different alkenyl halides.

We carried out some preliminary experiments employing two different alkenyl halides (bromides and chlorides) under the same conditions presented above, but a mixture of pyridines with scrambled substituents was always obtained. For this reason we decided to explore a sequential addition of reagents, that hopefully would allow for the preparation of the differently substituted pyridines.

To this end, the right sequence for the addition of reagents should be found. We observed that after the formation of the enamine by coupling reaction of an alkenyl halide with morpholine, which takes place very fast, the Pd retains its catalytic activity, and by addition of a second alkenyl halide and the silylimine, the second coupling reaction occurs efficiently. Poor results were obtained when the sequence of coupling processes was reversed. These preliminary experiments allowed us to design a *one-pot* procedure for the preparation of the trisubstituted pyridines. First of all, $Pd_2(dba)_3$, DavePhos, and NaO^{t}Bu are mixed in toluene and heated at 90 °C. Then, the first alkenyl halide **6** is added, after 1 min, by the morpholine. After the proper reaction time (0.5–1 h as monitored by GC/MS) a solution containing the second alkenyl halide **6′** and the silylimine is added. Finally, once the second alkenyl halide has been consumed as monitored by GC/MS, $Yb(OTf)_3$ is added to the reaction mixture and heating is continued for additional 14 h (Scheme 7). It is important to wait until the second alkenyl halide **6′** has been consumed before adding the Lewis acid. If $Yb(OTf)_3$ is added at the same time as the silylimine **7** and the second alkenyl halide **6′**, the expected pyridine **8** is obtained together with a smaller amount of pyridine **9**. The formation of **9** can be explained considering that during the formation of **8** a molecule of morpholine is



Scheme 7. One-pot synthesis of trisubstituted pyridines **8** with three different substituents.

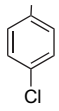
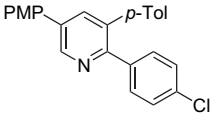
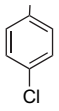
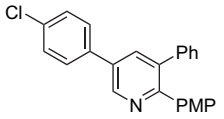
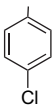
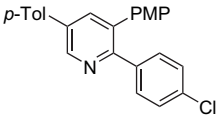
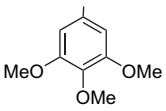
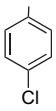
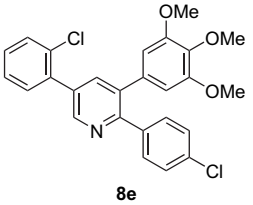
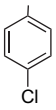
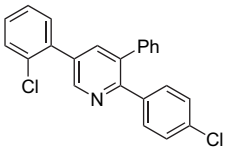
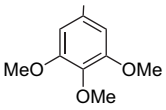
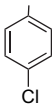
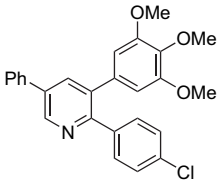
released, which could react with the second alkenyl halide **6′**, and participate in an undesired cycloaddition (Scheme 7). Nevertheless, employing the optimized protocol described above, the trisubstituted pyridines are obtained with comparable yields than those obtained in the multicomponent reaction discussed previously (Table 3).

The one-pot reaction features similar characteristics to the multicomponent process. Electron-neutral and electron-rich substituents are tolerated on every substituent. Moreover, *o*-substitution in the aromatic ring is also compatible with the reaction. Additionally, the presence of a chlorine atom in the aromatic ring is particularly interesting, since it could be easily substituted employing cross-coupling techniques in order to increase the structural diversity of pyridines. The examples presented in Table 3 establish the one-pot procedure presented herein as a viable and efficient route to the preparation of 2,3,5-trisubstituted pyridines with three different substituents. Although the scope of the reaction is still limited, we are currently working on the optimization of the independent steps to increase the functional group tolerance of these reactions.

3. Conclusion

In summary, we have presented herein novel multicomponent and one-pot methodologies for the regioselective

Table 3
Pyridines **8** prepared by the one-pot procedure[a]

Ar[1]	Ar[2]	Ar[3]	Pyridine **8**	Yield[b] (%)	Ar[1]	Ar[2]	Ar[3]	Pyridine **8**	Yield[b] (%)
p-Tol	PMP		 **8a**	51	Ph	PMP		 **8d**	52
PMP		*p*-Tol	 **8b**	56				 **8e**	47
Ph			 **8c**	49			Ph	 **8f**	51

[a] Reaction conditions: alkenyl halide **6** (1 mmol); morpholine (1 mmol); *N*-trimethylsilylimine **7** (1.2 mmol); alkenyl halide **6′** (1 mmol); $Pd_2(dba)_3$ (2 mol %); DavePhos (2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, 8 mol %); NaO′Bu (2.1 mmol, 2.1 equiv); $Yb(OTf)_3$ (0.2 mmol, 0.2 equiv); toluene (3 mL).
[b] Isolated yields after column chromatography or recrystallization. PMP=*p*-MeO-C_6H_4.

synthesis of trisubstituted pyridines through processes, which involve (i) formation of an enamine by cross-coupling of an alkenyl halide with an amine; (ii) formation of a 2-azadiene by cross-coupling of a silylimine with an alkenyl halide; (iii) Lewis acid catalyzed aza-Diels–Alder cycloaddition; (iv) aromatization. These procedures present all the advantages associated with multicomponent processes, such as easy generation of molecular diversity, reduction of time, solvents, and waste, no need for purification of intermediates, and additionally, catalyst economy, since the same Pd-based catalytic system is employed to promote two independent transformations.

4. Experimental section

4.1. General

All reactions were carried out under nitrogen atmosphere in a RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas-tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. NMR spectra were recorded at 400 or 300 MHz for ^{1}H and 100.6 or 75.45 MHz for ^{13}C, with tetramethylsilane as internal standard for ^{1}H and the residual solvent signals as standard for ^{13}C. Chemical shifts are given in parts per million. Mass spectra were obtained by EI or electrospray ionization (ESI). $Pd_2(dba)_3$ was purchased from Strem Chemical co. and used without further purification. All phosphine ligands used are commercially available from Strem or Aldrich and were used without further purification. Commercial NaO^{t}Bu was lyophilized and stored under nitrogen. Non-commercial *N*-trialkylsilylimines were prepared according to literature procedures.[21]

4.1.1. General procedure for the multicomponent synthesis of pyridines **3**

A carousel reaction tube under nitrogen atmosphere was charged with $Pd_2(dba)_3$ (0.01 mmol, 1 mol %), DavePhos (0.04 mmol, 4 mol %), NaO^{t}Bu (1.1 mmol), and toluene (1 mL). After 1 min of stirring, morpholine (0.5 mmol), the bromoalkene **6** (1 mmol), the silylimine **7** (0.6 mmol) and $Yb(OTf)_3$ (0.1 mmol, 20 mol %) were added sequentially while stirring, separated by 1 min intervals. Finally an additional 1 mL of toluene was added. The mixture was heated at 90 °C for 14 h. Once the reaction has been completed, the mixture is allowed to reach rt, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ solution. The aqueous phase is extracted with EtOAc (2×5 mL) and the combined organic layers are dried over Na_2SO_4 and concentrated under reduced pressure. The pyridines are purified by flash chromatography.

4.1.1.1. 2-(4-Chlorophenyl)-3,5-diphenylpyridine ***3a***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 164 mg of white solid were obtained (48%), recrystallized from diethyl ether. Mp=173.3–174.5 °C. IR (KBr): ν 1429, 1090, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.26–7.22 (m, 4H), 7.38–7.32 (m, 5H), 7.53–7.43 (m, 3H), 7.69–7.63 (m, 2H), 7.93 (d, J=2.3 Hz, 1H), 8.93 (d, J=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=127 (2CH), 127.4 (–CH), 128.0 (2CH), 128.2 (CH), 128.5 (2CH), 129.0 (2CH), 129.4 (2CH), 131.1 (2CH), 133.8 (C), 135.1 (C), 135.8 (C), 136.9 (CH), 137.8 (C), 138.1 (C), 139.4 (C), 146.6 (CH), 154.4 (C). MS(EI): 343 (23), 342 (47), 431 (68), 340 (100). HRMS calcd for $C_{23}H_{15}ClN$ (M–H): 341.0893; found: 340.0884.

4.1.1.2. 2-(4-Methoxyphenyl)-3,5-diphenylpyridine ***3b***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 186 mg of white solid were obtained (55%), recrystallized from diethyl ether. Mp=179.6–181.0 °C. IR (KBr): ν 1429, 1243, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.79 (s, 3H, OCH_3), 6.80 (d, J=8.8 Hz, 2H), 7.44–7.29 (m, 8H), 7.50 (t, J=7.5 Hz, 2H), 7.69–7.66 (m, 2H), 7.90 (d, J=2.3 Hz, 1H), 8.92 (d, J=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=55.0 (OCH_3), 113.2 (2CH), 126.9 (2CH), 127.1 (CH), 127.9 (CH), 128.3 (2CH), 128.9 (2CH), 129.4 (2CH), 131.1 (2CH), 132.0 (C), 134.4 (C), 135.4 (C), 136.8 (CH), 137.7 (C), 140.1 (C), 146.4 (CH), 155.3 (C), 159.3 (C). MS(EI): 337 (82), 336 (100). HRMS calcd for $C_{24}H_{18}NO$ (M–H): 336.1383; found: 336.1382.

4.1.1.3. 3,5-Diphenyl-2-p-tolylpyridine ***3c***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 183 mg of pale orange solid were obtained (57%), recrystallized from diethyl ether. Mp=187.0–188.2 °C. IR (KBr): ν 1425, 780, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.34 (s, 3H, CH_3), 7.08 (d, J=8 Hz, 2H), 7.27–7.34 (m, 7H), 7.42–7.46 (m, 1H), 7.50–7.54 (m, 2H), 7.68–7.70 (d, J=8 Hz, 2H), 7.93 (d, J=2.2 Hz, 1H), 8.94 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 (CH_3), 127.1 (2CH), 127.3 (CH), 128.1 (CH), 128.4 (2CH), 128.6 (2CH), 129.1 (2CH), 129.5 (2CH), 129.8 (2CH), 134.7 (C), 135.8 (C), 136.7 (C), 137.0 (CH), 137.4 (C), 137.7 (C), 140.0 (C), 146.4 (CH), 155.7 (C). MS(EI): 321 (62), 320 (100). HRMS calcd for $C_{24}H_{18}N$ (M–H): 320.1434; found: 320.1433.

4.1.1.4. 2-(4-N,N-Dimethylaminophenyl)-3,5-diphenylpyridine ***3d***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 213 mg of yellow solid were obtained (61%), recrystallized from diethyl ether. Mp=182.6–184.4 °C. IR (KBr): ν 1607, 1426, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.98 (s, 6H, $N(CH_3)_2$), 6.63 (d, J=8.7 Hz, 2H), 7.30–7.54 (m, 10H), 7.68 (d, J=8.7 Hz, 2H), 8.00 (d, J=2.3 Hz, 1H), 8.96 (d, J=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=40.26 ($2CH_3$), 111.7 (CH), 126.9 (2CH), 127.6 (CH), 128.5 (2CH), 128.6 (2CH), 129.2 (2CH), 129.3 (2CH), 129.7 (C), 131.2 (2CH), 132.7 (C), 133.6 (CH), 135.0 (C), 137.0 (C), 144.9 (C), 150.1 (CH), 154.7 (C). MS(EI): 350 (85), 349 (100). HRMS calcd for $C_{25}H_{21}N_2$ (M–H): 349.1699; found: 349.1699.

4.1.1.5. 2-(4-Chlorophenyl)-3,5-bis-(4-methoxyphenyl)-pyridine ***3e***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 241 mg of pale orange solid were obtained (60%),

recrystallized from diethyl ether. Mp=143.5–144.5 °C. IR (KBr): ν 1512, 1245, 823 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.87 (d, J=8.7 Hz, 2H), 7.04 (d, J=8.7 Hz, 2H), 7.15 (d, J=8.7 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H), 7.36 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.86 (d, J=2.28 Hz, 1H), 8.86 (d, J=2.28 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=55.2 (OCH_3), 55.4 (OCH_3), 114.0 (2CH), 114.8 (2CH), 128.1 (2CH), 129.6 (C), 130.6 (2CH), 131.2 (2CH), 131.8 (C), 133.7 (C), 134.9 (C), 135.5 (C), 136.3 (CH), 138.5 (C), 146.0 (CH), 159.1 (C), 159.9 (C). HRMS calcd for $C_{25}H_{19}NO_2Cl$ (M–H): 400.1099; found: 400.1101.

4.1.1.6. 2,3,5-Tris-(4-methoxyphenyl)pyridine ***3f***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 217 mg of pale orange solid were obtained (55%), recrystallized from diethyl ether. Mp=133.2–135.0. IR (KBr): ν 1512, 1243, 812 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.78 (s, 3H, OCH_3), 3.80 (s, 3H, O–CH_3), 3.85 (s, 3H, OCH_3), 6.79 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 7.17 (d, J=8.8 Hz, 2H), 7.35 (m, 2H), 7.59 (m, 2H), 7.82 (d, J=2.3 Hz, 1H), 8.82 (d, J=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=57.6 (OCH_3), 57.6 (OCH_3), 57.8 (OCH_3), 115.7 (2CH), 116.2 (2CH), 116.9 (2CH), 130.53 (2CH), 132.3 (C), 133.0 (2CH), 133.5 (2CH), 134.8 (C), 134.9 (CH), 136.5 (C), 137.5 (C), 138.7 (CH), 148.2 (C), 157.2 (C), 161.2 (C), 161.6 (C), 162.1 (C). HRMS calcd for $C_{26}H_{22}NO_3$ (M–H): 396.1594; found: 396.1593.

4.1.1.7. 3,5-Bis-(4-methoxyphenyl)-2-(4-tolyl)pyridine ***3g***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 221 mg of pale orange solid were obtained (58%), recrystallized from diethyl ether. Mp=109.3–110.1 °C. IR (KBr): ν 1510, 1243, 827 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.34 (s, 3H, CH_3), 3.83 (s, 3H, O–CH_3), 3.89 (s, 3H, O–CH_3), 6.85 (d, J=8.7 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.7 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 7.62 (d, J=8.7 Hz, 2H), 7.87 (d, J=2.2 Hz, 1H), 8.87 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 (CH_3), 55.2 (–OCH_3), 55.4 (–OCH_3), 113.8 (2CH), 114.6 (2CH), 128.1 (2CH), 128.7 (2CH), 129.7 (2CH), 130.6 (2CH), 132.2 (C), 134.5 (C), 135.5 (C), 136.6 (CH), 137.6 (C), 145.5 (CH), 154.8 (C), 158.9 (C), 159.8 (C). MS(EI): 381 (85), 380 (100). HRMS calcd for $C_{26}H_{22}NO_2$ (M–H): 380.1645; found: 380.1648.

4.1.1.8. 2-(4-N,N-Dimethylaminophenyl)-3,5-bis-(4-methoxyphenyl)pyridine ***3h***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 221 mg of orange solid were obtained (54%), recrystallized from diethyl ether. Mp 115.6–117.2 °C. IR (KBr): ν 1608, 1246, 824 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.97 (s, 6H, $N(CH_3)_2$), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.61 (d, J=8.9 Hz, 2H), 6.88 (d, J=8.7 Hz, 2H), 7.04 (d, J=8.7 Hz, 2H), 7.23 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.9 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.83 (d, J=2.2 Hz, 1H), 8.8 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=40.3 ($2CH_3$), 55.2 (OCH_3), 55.4 (OCH_3), 111.6 (2CH), 113.9 (2CH), 114.5 (2CH), 128.0 (2CH), 129.7 (C), 130.5 (2CH), 130.8 (2CH), 132.7 (C), 133.6 (CH), 135.0 (C), 137.0 (C), 144.9 (C), 150.1 (CH), 154.7 (C), 158.8 (C), 159.7 (C). MS(EI): 409 (95), 410 (100). HRMS calcd for $C_{27}H_{25}N_2O_2$ (M–H): 409.1911; found: 409.1914.

4.1.1.9. 2-(4-Chlorophenyl)-3,5-(4-tolyl)pyridine ***3i***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 200 mg of pale yellow solid were obtained (54%), recrystallized from diethyl ether. Mp 135.8–136.6 °C. IR (KBr): ν 1437, 1013, 812 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.38 (s, 3H), 2.44 (s, 3H), 7.14 (m, 4H), 7.25 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H), 7.90 (d, J=2.2 Hz, 1H), 8.90 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 ($2CH_3$), 126.9 (2CH), 128.1 (2CH), 129.3 (2CH), 129.4 (2CH), 129.9 (2CH), 131.2 (2CH), 133.8 (C), 133.8 (C), 134.2 (C), 135.2 (C), 135.9 (C), 136.5 (C), 136.9 (C), 138.2 (C), 146.2 (CH), 154.0 (C). HRMS calcd for $C_{25}H_{20}ClN$: 369.1279; found: 369.1280.

4.1.1.10. 2-(4-Methoxyphenyl)-3,5-(4-tolyl)pyridine ***3j***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 194 mg of pale yellow solid were obtained (54%), recrystallized from diethyl ether. Mp=124.1–125.0 °C. IR (KBr): ν 1437, 1249, 817 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.38 (s, 3H), 2.43 (s, 3H), 3.81 (s, 3H), 6.81 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.50 (m, 4H), 7.57 (d, J=8.0 Hz, 2H), 7.90 (d, J=2.4 Hz, 1H), 8.89 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 ($2CH_3$), 55.2 (OCH_3), 113.4 (2CH), 126.9 (2CH), 129.2 (2CH), 129.3 (2CH), 129.8 (2CH), 131.2 (2CH), 134.4 (C), 134.5 (C), 135.7 (C), 137.1 (CH), 137.2 (C), 138.1 (C), 145.7 (CH), 154.8 (C), 159.4 (C). HRMS calcd for $C_{26}H_{23}NO$: 365.1774; found: 365.1771.

4.1.1.11. 2,3,5-Tris-(4-tolyl)pyridine ***3k***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 189 mg of pale yellow solid were obtained (54%), recrystallized from diethyl ether. Mp=122.3–123.1 °C. IR (KBr): ν 1441, 828, 815 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.38 (s, 3H), 2.39 (s, 3H), 2.45 (s, 3H), 7.10 (d, J=8.1 Hz, 2H), 7.16 (m, 4H), 7.45 (m, 4H), 7.60 (d, J=8.1 Hz, 2H), 7.90 (d, J=2.4 Hz, 1H), 8.93 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 ($2CH_3$), 21.3 (CH_3), 126.9 (2CH), 128.6 (2CH), 129.1 (2CH), 129.4 (2CH), 129.8 (2CH), 129.9 (2CH), 134.6 (C), 134.7 (C), 135.7 (C), 136.7 (CH), 137.0 (C), 137.1 (C), 137.2 (CH), 137.5 (C), 138.0 (C), 146.2 (CH), 155.5 (C). HRMS calcd for $C_{26}H_{23}N$: 349.1825; found: 349.1821.

4.1.1.12. 2-(4-N,N-Dimethylaminophenyl)-3,5-bis-(4-tolyl) pyridine ***3l***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 235 mg of orange solid was obtained (62%), recrystallized from diethyl ether. Mp=194.0–195.6 °C. IR (KBr): ν 1611, 1439, 1192, 816 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.39 (s, 3H), 2.44 (s, 3H), 2.96 (s, 6H), 6.62 (d, J=8 Hz, 2H), 7.19 (m, 4H), 7.33 (m, 4H), 7.58 (d, J=8 Hz, 2H), 7.85 (s, 1H), 8.88 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz):

δ=21.20 (CH_3), 21.23 (CH_3), 40.3 ($2CH_3$), 111.6 (2CH), 126.8 (2CH), 129.1 (2CH), 129.4 (2CH), 129.8 (2CH), 130.9 (2CH), 133.6 (C), 134.8 (C), 135.1 (C), 136.7 (C), 136.9 (CH), 137.8 (C), 137.9 (C), 146.1 (CH), 150.0 (C), 155.6 (C). HRMS calcd for $C_{27}H_{26}N_2$: 378.2091; found: 378.2098.

4.1.2. General procedure for the one-pot synthesis of pyridines ***8***

A carousel reaction tube under nitrogen atmosphere was charged with $Pd_2(dba)_3$ (0.02 mmol, 2 mol %), DavePhos (0.08 mmol, 8 mol %), NaO^{t}Bu (2.1 mmol), and toluene (2 mL). After 1 min of stirring, morpholine (1 mmol) and the first bromoalkene 6 (1 mmol) were added and the mixture was stirred at 90 °C for 1 h. The silylimine **7** (1.2 mmol) and the second bromoalkene **6′** (1 mmol) were added to the reaction mixture and stirring continued at 90 °C for 6 h or until complete disappearance of the bromoalkene (GC monitoring). Then, $Yb(OTf)_3$ (0.2 mmol, 20 mol %) was added while stirring. Finally an additional 1 mL of toluene was added. The mixture was heated at 90 °C for additional 14 h. The mixture was allowed to reach rt, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (2×5 mL) and the combined organic layers dried over Na_2SO_4 and concentrated under reduced pressure. The pyridines were purified by flash chromatography.

4.1.2.1. 2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-3-(4-tolyl)-pyridine ***8a***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 187 mg of pale orange solid were obtained (51%), recrystallized from diethyl ether. Mp=129.3–130.8 °C. IR (KBr): ν 1515, 1606, 1243, 831 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.39 (s, 3H), 3.89 (s, 3H), 7.05 (d, J=8.4 Hz, 2H), 7.15 (m, 4H), 7.26 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H), 7.88 (d, J=2.4 Hz, 1H), 8.89 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 (CH_3), 55.4 (CH_3), 114.7 (CH), 120.2 (CH), 128.3 (CH), 129.3 (CH), 129.4 (CH), 129.5 (C), 131.2 (CH), 133.9 (C), 135.0 (C), 136.0 (CH), 136.6 (C), 136.8 (C), 137.4 (C), 138.1 (C), 145.9 (CH), 153.6 (C), 160.0 (C). HRMS calcd for $C_{25}H_{20}NOCl$: 385.1228; found: 385.1226.

4.1.2.2. 2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-(4-tolyl)-pyridine ***8b***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 216 mg of yellow solid were obtained (56%), recrystallized from diethyl ether. Mp=111.8–113.3 °C. IR (KBr): ν 1603, 1510, 1246, 815 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.44 (s, 3H), 3.84 (s, 3H), 6.87 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H), 7.90 (s, 1H), 8.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2 (CH_3), 55.3 (CH_3), 114.1 (CH), 126.7 (CH), 128.3 CH), 129.9 (CH), 130.6 (CH), 131.3 (CH), 131.7 (C), 133.9 (C), 134.2 (C), 135.4 (C), 135.8 (C), 137.0 (CH), 138.1 (C), 138.4 (C), 145.9 (CH), 153.9 (C), 159.2 (C). HRMS calcd for $C_{25}H_{20}NOCl$: 385.1228; found: 385.1222.

4.1.2.3. 2-(2-Chlorophenyl)-5-(4-chlorophenyl)-3-phenylpyridine ***8c***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 216 mg of pale yellow solid were obtained (56%). ^1H NMR ($CDCl_3$, 300 MHz): δ=7.2–7.4 (m, 13H), 7.89 (s, 1H), 8.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=127.3 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 129.6 (CH), 130.3 (CH), 131.3 (CH), 131.4 (CH), 132.8 (C), 133.8 (C), 134.1 (C), 135.4 (C), 136.4 (C), 138.2 (C), 139.3 (C), 139.5 (CH), 148.5 (CH), 154.7 (C). MS(EI): 379 (5), 378 (17), 377 (33), 376 (67), 375 (54), 374 (100). HRMS (ESI) calcd for $C_{23}H_{16}NCl_2$ (M+1): 376.0654; found: 376.0650.

4.1.2.4. 5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-3-phenylpyridine ***8d***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 193 mg of pale yellow solid were obtained (52%), recrystallized from diethyl ether. Mp 139.0–139.9 °C. IR (KBr): ν 1512, 1430, 1251, 785 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.81 (s, 3H), 6.81 (d, J=8.6 Hz, 2H), 7.25 (m, 7H), 7.37 (d, J=8.6 Hz, 2H), 7.48 (d, J=8.6 Hz, 2H), 7.87 (d, J=2.4 Hz, 1H), 8.88 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=55.2 (CH_3), 113.4 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 129.3 (CH), 129.5 (CH), 131.2 (CH), 132.0 (C), 133.3 (C), 134.3 (C), 135.7 (C), 135.9 (C), 136.9 (CH), 140.0 (C), 155.8 (C), 159.5 (C). MS(EI): 373 (26), 372 (45), 371 (91), 370 (100), 329 (13), 327 (36). HRMS (ESI) calcd for $C_{24}H_{19}NOCl$ (M+H): 372.1150; found: 372.1143.

4.1.2.5. 5-(2-Chlorophenyl)-2-(4-chlorophenyl)-3-(3,4,5-trimethoxy)pyridine ***8e***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 219 mg of yellow solid were obtained (47%), recrystallized from diethyl ether. Mp=126.4–127.2 °C. IR (KBr): ν 1584, 1409, 1241, 1128 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.68 (s, 6H), 3.87 (s, 3H), 6.42 (s, 2H), 7.27 (d, J=8.4 Hz, 2H), 7.4–7.5 (m, 5H), 7.53 (dd, J=6.6 Hz, J=1.2 Hz, 1H), 7.89 (d, J=2.4 Hz, 1H), 8.76 87 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=56.1 (CH_3), 61.0 (CH_3), 107.0 (CH), 127.3 (CH), 128.2 (CH), 129.6 (CH), 130.3 (CH), 131.1 (CH), 131.3 (CH), 132.9 (C), 133.9 (C), 134.1 (C), 134.5 (C), 135.2 (C), 136.3 (C), 137.6 (C), 138.3 (C), 139.0 (CH), 148.5 (CH), 153.2 (C), 154.7 (C). MS(EI): 469 (17), 467 (78), 465 (100), 454 (6), 452 (20), 450 (27), 151 (29). HRMS (ESI) calcd for $C_{26}H_{22}NO_3Cl_2$ (M+H): 466.0971; found: 466.0967.

4.1.2.6. 2-(4-Chlorophenyl)-3-(3,4,5-trimethoxy)-5-phenylpyridine ***8f***. Flash chromatography in (SiO_2, HxH/EtOAc, 9:1); 220 mg of yellow solid was obtained (51%), recrystallized from diethyl ether. Mp=144.7–146.3 °C. IR (KBr): ν 1583, 1408, 1237, 1127 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.71 (s, 6H), 3.89 (s, 3H), 6.44 (s, 2H), 7.2–7.5 (m, 7H), 7.68 (d, J=7.5 Hz, 2H), 7.96 (s, 1H), 8.9)s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=56.1 (CH_3), 61.0 (CH_3), 107.0 (CH), 127.2 (CH), 128.1 (CH), 128.4 (CH), 129.2 (CH), 131.1 (CH), 133.9 (C), 134.8 (C), 135.4 (C), 135.9 (C), 136.5 (CH), 137.2 (C), 137.9 (C), 138.4 (C), 146.8 (CH), 153.2 (C), 154.6 (C). MS(EI): 433 (36), 431 (100), 418 (12), 416

(32). HRMS (ESI) calcd for $C_{26}H_{23}NO_3Cl$ (M+H): 432.1361; found: 432.1354.

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