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ARTICLE TYPE

Catalytic procedures for multicomponent synthesis of imidazoles: selectivity control during the competitive formation of tri- and tetra-substituted imidazoles

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The catalytic potential of different fluoroboric acid derived catalyst systems viz; aq HBF_4, solid supported HBF_4, metal tetrafluoroborates (inorganic salts), solid supported metal tetrafluoroborates, and tetraflouroborate based ionic liquids (organic salts) were investigated for three component reaction (3-MCR) of 1,2-diketone, aldehyde, and ammonium salts to form 2,4,5-trisubstituted imidazole and four component reaction (4-MCR) involving 1,2-diketone, aldehyde, amine and ammonium acetate to form 1,2,4,5-tetrasubstituted imidazole. The HBF_4-SiO_2 was found to be the stand alone catalyst for both the 3-MCR and 4-MCR processes. The next effective catalysts are $LiBF_4$ and $Zn(BF_4)_2$ to form 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles via the 3-MCR and 4-MCR, respectively. This is the first report on the unaddressed issue of competitive formation of 2,4,5-trisubstituted imidazole during the 4-MCR involving 1,2-diketone, aldehyde, amine and ammonium acetate and highlights the influence of the catalyst systems in controlling the selective formation of tetra substituted imidazole. The metal salt of weak protic acids drive selectivity towards tetra substituted imidazole in the order tetrafluoroborates > perchlorates > triflates). The catalytic potency of tetrafluoroborates in the order $Zn(BF_4)_2$ > $Co(BF_4)_2$ > $AgBF_4$ ≈ $Fe(BF_4)_2$ > $NaBF_4$ ≈ $LiBF_4$ ≈ $Cu(BF_4)_2$. The developed protocols worked well for different diketones, various aryl, heteroaryl, and alkyl aldehydes and in the case of the preparation of 1,2,4,5-tetrasubstituted imidazoles different amines can be used. The effectiveness of different ammonium salts as nitrogen source has been investigated and ammonium acetate is proved to be the best. The HBF_4-SiO_2 is recyclable for five consecutive uses without significant loss of catalytic activity.

Introduction

Multicomponent reactions (MCRs) enjoy an outstanding status in organic and medicinal chemistry for high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel and fulfil some of the objectives of ideal synthesis.[1]

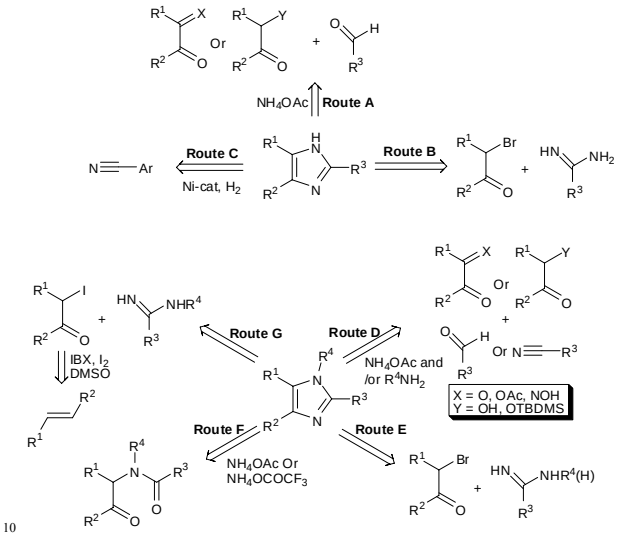
The heterocyclic scaffolds comprising of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles are present in compounds possessing versatile pharmacological action such as anti-inflammatory agents,[2] CSBP kinase inhibitor,[3] anti-bacterial agents,[4] glucagon receptor antagonists,[5] p38 MAP kinase inhibitors,[6] modulators of Pgp-mediated multidrug resistance,[7] ligands of the Src SH_2 protein,[8] antitumor agents,[9] inhibitors of mammalian 15-LOX,[10] CB1 cannabinoid receptor antagonists,[11] and inhibitors of B-Raf kinase.[12] These have generated interest to synthetic organic/medicinal chemists to develop synthetic methodologies for the construction of these heterocyclic scaffolds and the various strategies are summarised in Scheme 1.

The 2,4,5-trisubstituted imidazoles are generally synthesized by the reaction of a 1,2-diketone, α-hydroxy/acetoxy/silyloxyketone or 1,2-ketomonoxime with an aldehyde and ammonium acetate (Route A, Scheme 1) (i) in HOAc under reflux[2-4,6a,6c,7,9,12,13] or under microwave/ultrasonic/classical heating in presence or absence of catalyst[14] or under pressure using continuous flow micro reactor under superheating condition,[15] (ii) in the presence of Lewis acid catalysts (Route B),[16] and (iii) Ni-catalysed cyclotrimerisation (with expulsion of NH_3) of aromatic nitriles under pressure (60-120 psi) and high temperature (180-230 °C) hydrogenation condition for prolonged period (48 h) (Route C, Scheme 1).[17]

The reported synthesis of 1,2,4,5-trisubstituted imidazoles involve reaction of a 1,2-diketone, α-hydroxy/acetoxy/silyloxyketone or 1,2-ketomonoxime, an aldehyde, an amine and ammonium acetate (Route D, Scheme 1) carried out by (i) microwave irradiation in the presence of silica gel/zeolite HY or silica gel-$NaHSO_4$,[18] (ii) heating under reflux in suitable solvents or under neat condition at 140 ºC in the presence of catalysts.[14l,19]

The alternative approaches are the reaction of *α*-bromoketone with substituted amidine[10,11] (Route E) for syntheses of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles or the cyclocondensation of *N*-alkyl-α-acetamidoketone/alcohol with

ammonium acetate in HOAc or with ammonium trifluoroacetate (as solvent) under reflux[20] for preparing 1,2,4,5-tetrasubstituted imidazoles (Route F). Recently synthesis of 1,2,4,5-tetrasubstituted imidazoles has been achieved from alkenes via a two-step ketoiodonation/cyclisation strategy (Route G).[21] The 2,4,5-risubstituted imidazoles may also be prepared following multistep process from imidazole-based vicinal bromostannanes sequentially performing Stille and Suzuki coupling reactions.[22]

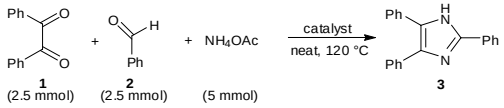


Scheme 1. Synthetic strategies for construction 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole scaffolds.

Most of these synthetic methods suffer from one or more drawbacks, such as laborious and complex work-up and purification procedure, generation of significant amounts of waste materials, strong acidic conditions, occurrence of side reactions, low yields, use of expensive and moisture sensitive reagents/catalysts, special efforts for the preparation of the starting materials,[6a,21,22] the use of auxiliary reagents,[2b,3,6a,21] and special apparatus/reactor.[15,17] These, necessitates the improvement of the tried and tested methodologies for new catalytic procedure to enrich the medicinal chemists' toolbox[23] for convenient synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles keeping in view the timely need of generating new chemical entities for newer therapeutic applications.[24] We report herein fluoroboric acid derived catalytic systems for a convenient and effective synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles following 3-MCR and 4-MCR processes, respectively, addressing the unattended issue on competitive formation of these heterocycles.

Results and Discussion

In search for an effective catalyst, we considered the 3-MCR of benzil (**1**), benzaldehyde (**2**), and NH_4OAc to form 2,4,5-triphenylimidazole (**3**) as the model reaction (Scheme 2). Since the reaction has been anticipated to proceed through electrophilic activation of the carbonyl substrates, to accelerate the imine formation with NH_4OAc,[25] we visualized that a suitable metal Lewis acid that could function as a more effective electrophilic activation agent would offer a more convenient way to from the heterocyclic framework.



Scheme 2. Synthesis of 2,4,5-trisubstituted imidazole **3** via 3-MCR.

Initially we realised that as metal salt of a strong protic acid should be strong Lewis acid, metal triflates could be ideal for the purpose as TfOH is the strongest protic acid (H_0 = -14.1)[26] However, metal triflates are prone to liberate TfOH[27] and necessitate the use of solvent, excess of reagent, and additives or sub zero temperature to minimize/avoid side reactions.[28] Although $HNTf_2$ is a weaker Brønsted acid than TfOH[29] and ligand exchange is usually not observed during organic transformation performed in the presence of metal triflimides,[30] the high cost and lack of commercial availability do not make metal triflimides popular. The metal perchlorates[31] appear to be the next best effective electrophilic activation agent but often form strong adduct with amines that could be detrimental to the catalytic efficiency for reactions involving amine.[31k] The milder Lewis acid property of metal tetrafluoroborates, as HBF_4 is a weaker Brønsted acid, brought our attention to HBF_4 derived catalyst systems as metal tetrafluoroborates are known to catalyze various organic reactions.[32] Hence, the model reaction (Scheme 2) was performed under the catalytic influence of various metal tetrafluoroborates. The best result was obtained with $LiBF_4$ affording **3** in 90% yield after 20 min. The other metal tetrafluoroborates gave lesser yields in longer time (table 1) with the relative catalytic potential following the order $Cu(BF_4)_2$ > $Fe(BF_4)_2 \approx Zn(BF_4)_2 > Co(BF_4)_2 \approx AgBF_4 > NaBF_4$. The use of tetrafluoroborate containing ionic liquids (ILs) (organic salts of HBF_4) e.g., $[bmim][BF_4]$[33] and $[NHC][BF_4]$[34] afforded inferior yields. Poor conversion to **3** was observed in the absence of catalyst (entry 11, table 1).

Table 1. The 3-MCR of **1**, **2**, and NH_4OAc to form **3** in the presence of HBF_4 derived catalyst systems.[a]

Entry	Catalyst	Time (min)	Yield (%)[b,c]
1	$NaBF_4$	60	70
2	$AgBF_4$	60	75
3	$Cu(BF_4)_2$	45	85
4	$Zn(BF_4)_2$	45	80
5	$Co(BF_4)_2$	45	76
6	$Fe(BF_4)_2$	45	80
7	$LiBF_4$	20	90
8	$[bmim][BF_4]$	45	65
9	$[NHC][BF_4]$	45	58
10	HBF_4 (aq 50 %)	60	70
11	none	300	16

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) in the presence of the catalyst (10 mol %) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS.

However, the use of HBF_4 (aq 50%) gave **3** in 70% yield after 1 h (entry 10, table 1). This encouraged us to investigate whether the catalytic potency of HBF_4 could be enhanced on a solid surface. There has been increasing awareness on the use of solid acids and chemical processes on solid surfaces[35] and the inherited advantages of heterogonous catalyst system[36] for sustainable chemistry development. These and our interest/experience on the use of solid supported protic acid as catalyst in various organic

transformations[37] prompted us to perform the model reaction using HBF_4 immobilised on various solid supports such as chromatographic silica gel with different mesh size as well as neutral, acidic, and basic alumina (table 2). Excellent result was obtained with HBF_4 adsorbed on chromatographic silica gel (230-400 mesh) (herein referred as HBF_4-SiO_2) affording 92% yield of **3** in 15 min. As a mater of fact, HBF_4-SiO_2[38] turned out to be the most efficient catalyst system for this 3-MCR process and even was superior to the metal tetrafluoroborates.

Table 2. Catalytic potential of HBF_4 adsorbed on various solid surface for the synthesis of **3** via the 3-MCR of **1**, **2**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%)[b,c]
1	HBF_4-SiO_2 (230-400)	15	92
2	HBF_4-SiO_2 (100-200)	45	80
3	HBF_4-SiO_2 (100-200)	15	52
4	HBF_4-SiO_2 (60-120)	60	78
5	HBF_4-SiO_2 (60-120)	15	40
6	HBF_4- acidic Al_2O_3	30	75
7	HBF_4- acidic Al_2O_3	15	41
8	HBF_4- basic Al_2O_3	25	80
9	HBF_4- basic Al_2O_3	15	32
10	HBF_4- neutral Al_2O_3	30	37
11	SiO_2 (230-400)	300	42
12	SiO_2 (230-400)	15	nil
13	SiO_2 (100-200)	5 h	40
14	SiO_2 (100-200)	15	nil
15	SiO_2 (60-120)	5 h	38
16	SiO_2 (60-120)	15	nil
17	Acidic Al_2O_3	5 h	26
18	Acidic Al_2O_3	15	nil
19	Basic Al_2O_3	5 h	25
20	Basic Al_2O_3	15	nil
21	Neutral Al_2O_3	5 h	26
22	Neutral Al_2O_3	15	nil
23	K10	5 h	68
24	K10	15	34
25	KSF	5 h	66
26	KSF	15	30
27	Zeolite type Y	45	65
28	Zeolite type Y	15	22
29	Zeolite K/L	60	54
30	Zeolite K/L	15	16
31	Zeolite ZSM 5	60	53
32	Zeolite ZSM 5	15	18
33	Zeolite Na/Fau	50	55
34	Zeolite Na/Fau	15	16
35	Zeolite NH4-Y	30	53
36	Zeolite NH4-Y	15	21
37	Amberlyst 33	60	58
38	Amberlyst 33	15	23
39	none	5 h	16

[a] The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) in the presence of the catalyst (10 mol %) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS.

As often the support material itself exhibit catalytic efficiency for various organic reactions[39] we also performed the model reactions involving **1** (1 equiv), **2** (1 equiv) and **3** (2 equiv) (Scheme 2) in the presence of solid supports (various silica gel and alumina) and other heterogeneous catalysts e.g., clays, zeolites, and amberlites (table 2). However, poor yield was obtained in each case indicating the role of HBF_4 in catalyzing the reaction.

As the immobilisation of HBF_4 on silica (230-400 mesh) drastically increased its catalytic efficiency we next explored the influence of the solid support (230-400 mesh silica gel) on the catalytic potential of the metal tetrafluoroborates (table 3). However, no significant improvement of catalytic efficiency was observed indicating the fact that the silica surface exhibits some specific effect on HBF_4 perhaps in increasing its Brønsted acidity.

Table 3. Influence of the solid support (230-400 mesh silica gel) on the catalytic potential of metal tetrafluoroborates for the synthesis of **3** via the 3-MCR of **1**, **2**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%)[b,c]
1	$NaBF_4$	60	70
2	$NaBF_4$-SiO_2	60	72
3	$NaBF_4$	15	22
4	$NaBF_4$-SiO_2	15	25
5	$AgBF_4$	60	75
6	$AgBF_4$-SiO_2	60	81
7	$AgBF_4$	15	32
8	$AgBF_4$-SiO_2	15	34
9	$Cu(BF_4)_2$	45	72
10	$Cu(BF_4)_2$-SiO_2	45	75
11	$Cu(BF_4)_2$	15	35
12	$Cu(BF_4)_2$-SiO_2	15	38
13	$Zn(BF_4)_2$	45	80
14	$Zn(BF_4)_2$-SiO_2	45	82
15	$Zn(BF_4)_2$	15	35
16	$Zn(BF_4)_2$-SiO_2	15	40
17	$Co(BF_4)_2$	45	75
16	$Co(BF_4)_2$-SiO_2	45	75
19	$Co(BF_4)_2$	15	25
20	$Co(BF_4)_2$-SiO_2	15	26
21	$Fe(BF_4)_2$	45	80
22	$Fe(BF_4)_2$-SiO_2	45	82
23	$Fe(BF_4)_2$	15	35
24	$Fe(BF_4)_2$-SiO_2	15	35
25	$LiBF_4$	20	90
26	$LiBF_4$-SiO_2	20	90
27	$LiBF_4$	15	78
28	$LiBF_4$-SiO_2	15	80

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) in the presence of different catalyst system (10 mol %) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS.

Thus, two different catalyst systems derived from fluoroboric acid e.g., HBF_4–SiO_2 and $LiBF_4$ emerged out to be efficient catalysts to promote the 3-MCR of 1,2-diketone, aldehyde and NH_4OAc for a convenient synthesis of 2,4,6-trisubstituted imidazole. Further studies on the optimisation of various other reaction parameters such as the amount of the catalyst, reaction temperature, influence of the solvent and the effect of various ammonium salts as the nitrogen source.

The use of 2 mol% of HBF_4–SiO_2 and 10 mol % of $LiBF_4$ was found to be the optimal amount of the catalyst (table 4) for best results (afforded **3** in 92 % and 90 % yields after 15 and 20 min, respectively).

Table 4. Effect of amount of the catalyst during the 3-MCR of **1**, **2**, and NH_4OAc to form **3**.[a]

Entry	mol %	HBF_4–SiO_2		$LiBF_4$	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	nil	2	trace	2	trace
2	0.25	2	trace	2	trace
3	0.5	2	12	2	15
4	1.0	2	47	2	20
5	2.0	0.25	92	2	45
6	5	0.25	93	2	58
5	7.5	0.25	93	2	72

8	10	0.25	93	0.34	90
9	15	0.25	93	0.34	90

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS.

The effect of the reaction temperature was evaluated next (table 5). The best operating reaction temperature was found to be 120 °C (oil bath). An increase of the reaction temperature to 150 ºC did not show any significant increase of the yield of **3** which, however, decreased in lowering the reaction temperature to 100, 80, and 50 ºC. No significant amount of **3** was formed in carrying out the reactions at rt.

Table 5. The effect of temperature on the 3-MCR of **1**, **2**, and NH_4OAc to form **3**.[a]

Entry	Temp (°C)	HBF_4–SiO_2		$LiBF_4$	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	rt	12	trace	12	trace
2	50	12	32	12	30
3	80	12	62	12	55
4	100	12	76	12	75
5	120	0.25	92	0.34	90
6	150	0.25	92	0.34	90

[a] The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated in the presence of HBF_4–SiO_2 (2 mol %) and $LiBF_4$ (10 %) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS).

To evaluate any beneficial/detrimental effect of solvents on the HBF_4-SiO_2 and $LiBF_4$ catalysed 2,4,5-trisubstituted imidazole formation, the reactions (Scheme 2) were performed in hydrocarbon, halogenated hydrocarbon, ethereal, protic polar and aprotic polar solvents (Table 6). The yields of **3** decreased drastically indicating the detrimental effect of the solvents.

Table 6. Solvent effect on the 3-MCR of **1**, **2**, and NH_4OAc to form **3**.[a]

Entry	Solvent	HBF_4-SiO_2		$LiBF_4$	
		Yield (%)[b]	Yield (%)[c]	Yield (%)[b]	Yield (%)[c]
1	Water	5	10	trace	12
2	MeOH	48	55	42	53
3	EtOH	40	48	38	42
4	^{i}PrOH	25	24	20	25
5	^{t}BuOH	13	23	15	31
6	F_3CCH_2OH	10	25	12	32
7	MeCN	6	8	10	8
8	DCM	12	15	12	28
9	DCE	13	20	15	21
10	THF	5	9	8	12
11	Dioxane	6	9	12	9
12	PhMe	trace	trace	10	12

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was treated under reflux for 5 h in different solvent (5 mL) in the presence of the HBF_4-SiO_2 (2 mol %) and $LiBF_4$ (10 mol %). [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS).

The effect of the nitrogen source was evaluated in carrying out the reactions by replacing NH_4OAc with other ammonium salts (table 7) and NH_4OAc was proved to be the most effective nitrogen source.

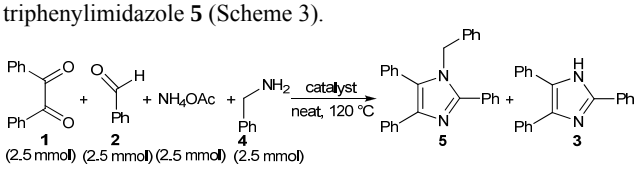
Table 7. The effect of various ammonium salts as the nitrogen source on the 3-MCR to form **3**.[a]

Entry	Nitrogen source	HBF_4-SiO_2		$LiBF_4$	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	NH_4Cl	4	nil	4	nil
2	NH_4F	4	35	4	32
3	$NH_4F{\cdot}HF$	4	41	4	40
4	NH_4HCO_3	4	40	4	35
5	$(NH_4)_2CO_3$	4	42	4	38
6	$(NH_4)_2SO_4$	4	nil	4	nil
7	NH_4SCN	4	52	4	52
8	NH_4ClO_4	4	nil	4	nil
9	$(NH_4)_2HPO_4$	4	25	4	21
10	NH_4OAc	0.25	92	0.34	90
11	HCO_2NH_4	4	55	4	48
12	$(NH_4)_4[Ce(SO_4)_4]$	4	nil	4	nil

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and **3** (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) in the presence of different ammonium salt (2 equiv) using HBF_4-SiO_2 (2 mol %) or $LiBF_4$ (10 mol %) under neat condition. [b]Yield of **3** after purification (crystallisation, aq EtOH). [c]IR, NMR and APCI-MS).

The generality of HBF_4-SiO_2 and $LiBF_4$ as catalysts for synthesis of 2,4,5-trisubstituted imidazole is demonstrated through the treatment of various aryl/heteroaryl/aliphatic aldehydes with different 1,2-diketone and ammonium acetate (Table 8). The reactions were monitored by TLC. However, the progress of the reaction can also be monitored visually. A clear melt is formed after addition of all of the components and after completion of the reaction (or maximal product formation) the reaction mixture is converted to a solid mass. Wherein the reaction mixture solidified, although complete conversion to the product did not occur, no further progress was observed in prolonging the reaction time.

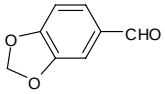
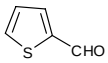
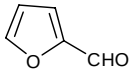
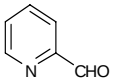
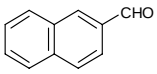
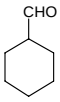
The promising results obtained in case of 3-MCR synthesis of 2,4,5-trisubstituted imidazoles encouraged to test the developed protocols for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the 4-MCR (Route D, scheme 1) by the reaction of **1** (2.5 mmol) with **2** (2.5 mmol, 1 equiv), NH4OAc (2.5 mmol, 1 equiv) and benzyl amine **4** (2.5 mmol, 1 equiv) to form 1-benzyl-2,4,5-triphenylimidazole **5** (Scheme 3).



Scheme 3. 4-MCR synthesis of 1-benzyl-2,4,5-triphenylimidazole **5**.

We were delighted with the clean formation of **5** in excellent yield (90 %) in case of the HBF_4–SiO_2 catalyzed reaction within short time intervals (10 min). However, in case of the $LiBF_4$ catalyzed reaction, we noticed the formation of 2,4,6-triphenyl imidazole **3** as side product (15% yield) in addition to desired 1-benzyl-2,4,5-triphenylimidazole **5** (45 % yield) (entry 20, table 9).

Table 8. Synthesis of 2,4,5-trisubstituted imidazoles via the 3-MCR of 1,2-diketone, aldehyde and NH_4OAc catalysed by HBF_4-SiO_2 and $LiBF_4$.[a]

Entry	1,2-Diketone	Aldehyde	Method A		Method B	
			Time (min)	Yield (%)[b,c]	Time (min)	Yield (%)[b,c]
1	$R^1 = R^2 =$ Ph	$R^3 = R^4 = R^5 = R^6 = H$	15	92	20	90
2	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 =$ OMe	22	90	20	88
3	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 = NMe_2$	26	91	25	90
4	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 =$ Cl	15	96	12	90
5	$R^1 = R^2 =$ Ph	$R^3 =$ Br; $R^4 = R^5 = R^6 = H$	17	95	15	92
6	$R^1 = R^2 =$ Ph	$R^3 = NO_2$; $R^4 = R^5 = R^6 = H$	15	95	15	89
7	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 = CF_3$	18	94	20	95
8	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 =$ CN	25	92	30	90
9	$R^1 = R^2 =$ Ph	$R^1 = R^2 = R^4 = H$; $R^5 =$ OH	25	92	25	89
10	$R^1 = R^2 =$ Ph	$R^3 = R^5 = R^6 =$ Me; $R^4 = H$	21	96	20	92
11	$R^1 = R^2 =$ 4-OMe-C_6H_4	$R^3 = R^4 = R^5 = R^6 = H$	40	81	60	85
12	$R^1 = R^2 =$ 4-Cl- C_6H_4	$R^3 = R^4 = R^5 = R^6 = H$	22	88	20	86
13	$R^1 = R^2 =$ 2-Furyl	$R^3 = R^4 = R^5 = R^6 = H$	20	90	25	85
14	$R^1 = R^2 =$ 2-Thienyl	$R^3 = R^4 = R^5 = R^6 = H$	20	90	20	88
15	$R^1 = R^2 =$ Me	$R^3 = R^4 = R^5 = R^6 = H$	30	72	40	70
16	$R^1 = R^2 =$ Ph		20	95	22	92
17	$R^1 = R^2 =$ Ph		24	95	25	90
18	$R^1 = R^2 =$ Ph		20	97	25	95
19	$R^1 = R^2 =$ Ph		35	86	30	85
20	$R^1 = R^2 =$ Ph		30	90	35	88
21	$R^1 = R^2 =$ Ph		35	85	30	85
22	$R^1 = R^2 =$ Ph		35	84	40	82

[a]**Method A:** The mixture of 1,2-diketone (2.5 mmol), aldehyde (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 °C (oil bath) in the presence of HBF_4-SiO_2 (2 mol%) under neat condition. **Method B:** The mixture of 1,2-diketone (2.5 mmol), aldehyde (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 °C (oil bath) in the presence of $LiBF_4$ (10 mol%) under neat condition. [b]The yield of the desired 2,4,5-trisubstituted imidazoles obtained after purification (recrystallization, EtOH). [c]All compounds were characterized by IR, NMR and MS (APCI).

We realised that this is the first report on the competitive formation of the tri-substituted imidazole for a multicomponent protocol designed for the formation of tetra-substituted imidazole. Therefore, we focussed on this unattended issue on the selectivity of formation of the tri- and tetra-substitute imidazoles. The catalytic potential of different metal tetrafluoroborates was assessed for the selectivity of formation of **5** and **3** (scheme 3, table 9). While in all cases the competitive formation of **3** was observed, the best selectivity (**5**:**3** = 95:5; overall yield 96%) was exhibited by $Zn(BF_4)_2$ (entry 11, table 9). We also tested the catalytic potential for the corresponding perchlorates and triflates. The study reveals that in general, the selectivity of formation of tetrasubstituted imidazole **5** is favoured in case of metal salts of weak acid (metal tetrafluoroborates) compared to metal salts of stong protic acid (metal triflates; triflic acid). The catalytic potency for **5**:**3** selectivity in favour of **5** (tetra substituted imidazole) follows the order: metal tetrafluoroborate > metal perchlorates > metal triflates. In case of metal tetrafluoroboares, the selectivity towards **5** was observed to be in the order $Zn(BF_4)_2$ > $Co(BF_4)_2$ > $AgBF_4$ ≈ $Fe(BF_4)_2$ > $NaBF_4$ ≈ $LiBF_4$ ≈ $Cu(BF_4)_2$. This clearly distinguished the advantage of tetrafluoroborates compared to the stronger Lewis acids perchlorates and triflates and justified our rational of choosing the fluoroboric acid derived catalyst systems in the initial catalyst selection process (table 1).

Table 9. The catalytic potential of metal tetrafluoroborates, perclhorates, and triflates for the **5**:**3** selectivity during the 4-MCR of **1**, **2**, **4**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%) Overall[b]	**5**[c]	**3**[c]	Selectivity (**5**:**3**)[d]
1	HBF_4–SiO_2	10	95	95	00	100:00
2	$NaBF_4$	60	68	45	15	75:25
3	$NaClO_4$	60	65	35	23	60:40
4	NaOTf	60	68	34	28	55:45
5	$AgBF_4$	60	74	56	14	80:20
6	$AgClO_4$	60	78	42	30	58:42
7	AgOTf	60	82	41	33	55:45
8	$Cu(BF_4)_2$	45	85	54	21	72:28
9	$Cu(ClO_4)_2$	45	88	48	32	60:40
10	$Cu(OTf)_2$	45	90	43	39	52:48
11	$Zn(BF_4)_2$	15	96	89	15	95:05
12	$Zn(ClO_4)_2$	15	85	56	22	72:28
13	$Zn(OTf)_2$	15	88	40	40	50:50
14	$Co(BF_4)_2$	40	78	58	10	85:15
15	$Co(ClO_4)_2$	40	80	46	25	65:35
16	$Co(OTf)_2$	40	81	42	28	60:40
17	$Fe(BF_4)_2$	45	79	54	14	79:21
18	$Fe(ClO_4)_2$	45	82	53	21	72:28
19	$Fe(OTf)_2$	45	85	49	27	65:35
20	$LiBF_4$	30	68	45	15	75:25
21	$LiClO_4$	30	65	34	22	60:40
22	LiOTf	30	68	30	25	55:45

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv), **4** (2.5 mmol, 1 equiv), and NH_4OAc (2.5 mmol, 1 equiv), was heated at 120 ºC (oil bath) under solvent free condition in the presence of different catalyst (10 mol %). [b]Yield after crystallisation (aq EtOH) of the isolated crude product. [c]Isolated yield of **5** and **3** after chromatographic purification. [d]Based on the isolated and purified yields of **5** and **3**.

Various organic and inorganic protic acids were also used as catalyst for the 4-MCR of **1**, **2**, **4**, and NH_4OAc to determine the **5**:**3** selectivity (table 10). The best yields (90-95%) were obtained with TfOH, $HClO_4$ and HBF_4 adsorbed on silica. However the selectivity in favour of the tetrsubstituted imidazole **5** was observed with weaker protic acid HBF_4 (entry 5, table 10). In general, significant inprovement in terms of reaction time, yield and selectivity was observed in using the corresponding protic acid adsorbed on silica gel (230-400 mesh) but the influence on the catalytic potential due to adsorbtion on the solid support was more pronounced with inorganic protic acids than that of organic protic acids (except for TfOH). The non-protic/Lewis acid (e.g., $BF_3{\cdot}OEt_2$) acid was less effective although the yield and selectivity was increased on being adsorbtion on silica.

Table 10. The catalytic potential of organic and inorganic Bronsted acids as such as well as immobilised on silica gel for the **5**:**3** selectivity during the 4-MCR of **1**, **2**, **4**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%) Overall[b]	**5**[c]	**3**[c]	Selectivity (**5**:**3**)[d]
1	TfOH	60	74	38	27	58:42
2	TfOH-SiO_2	10	92	51	34	60:40
3	$HClO_4$ (aq 70 %)	60	75	45	23	66:34
4	$HClO_4$-SiO_2	10	90	66	16	80:20
5	*p*-TsOH	60	72	43	17	72:28
6	*p*-TsOH-SiO_2	10	80	57	13	82:18
7	MSA	60	75	48	16	75:25
8	MSA-SiO_2	10	78	59	11	84:16
9	TFA	60	70	47	15	76:24
10	TFA-SiO_2	10	74	52	13	80:20
11	H_2SO_4 (conc)	60	78	49	21	70:30
12	H_2SO_4-SiO_2	10	85	66	12	85:15
13	HBF_4 (aq 50 %)	60	72	57	8	88:12
14	HBF_4-SiO_2	10	95	95	00	100:00
17	BF_3-OEt_2	4 h	52	30	10	74:26
18	BF_3-SiO_2	2 h	65	50	08	85:15

[a]The mixture of **1**, **2** (2.5 mmol), **4** (2.5, 1 equiv) and NH_4OAc (2.5 mmol, 1 equiv) was heated at 120 ºC (oil bath) under solvent free condition in the presence of different catalyst (10 mol %). [b]Yield after crystallisation (aq EtOH) of the isolated crude product. [c]Isolated yield of **5** and **3** after chromatographic purification. [d]Based on the isolated and purified yields of **5** and **3**.

To examine whether the catalytic potency (in terms of yield as well as **5**:**3** selectivity) of various metal tetrafluoroborates for the 4-MCR of **1**, **2**, **4**, and NH_4OAc could imrpoved by immobilisation on silica gel (230-400 mesh), various metal tetrafluoroborates adsorbed on silica were used as the catalyst (table 11). However, only marginal improvement was observed in each case further suggesting that the adsorption on solid support has greater influence on the protic (Brönsted) acid than the corresponding metal Lewis acid.

Table 11. Comparison of the catalytic potential of metal tetrafluoroborates as such as well as immobilised on silica gel for the **5**:**3** selectivity during the 4-MCR of **1**, **2**, **4**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%) Overall[b]	**5**[c]	**3**[c]	Selectivity (**5**:**3**)[d]
1	$NaBF_4$	60	68	45	15	75:25
2	$NaBF_4$-SiO_2	60	70	48	12	80:20
3	$AgBF_4$	60	74	56	14	80:20
4	$AgBF_4$-SiO_2	60	75	60	11	85:15
5	$Cu(BF_4)_2$	45	85	54	21	72:28
6	$Cu(BF_4)_2$-SiO_2	45	84	60	15	80:20
7	$Zn(BF_4)_2$	15	96	89	5	95:05
8	$Zn(BF_4)_2$-SiO_2	15	98	89	5	95:05
9	$Co(BF_4)_2$	40	78	58	10	85:15
10	$Co(BF_4)_2$-SiO_2	40	80	58	14	80:20
11	$Fe(BF_4)_2$	45	79	54	14	79:21
12	$Fe(BF_4)_2$-SiO_2	45	85	59	15	80:20
13	$LiBF_4$	30	68	45	15	75:25
14	$LiBF_4$-SiO_2	30	76	51	14	78:22

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv), **4** (2.5 mmol, 1 equiv), and NH_4OAc (2.5 mmol, 1 equiv), was heated at 120 ºC (oil bath) under solvent free condition in the presence of different catalyst system (10 mol %). [b]Yield after crystallisation (aq EtOH) of the isolated crude product. [c]Isolated yield of **5** and **3** after chromatographic purification. [d]Based on the isolated and purified yields of **5** and **3**.

Thus, identifying the unaddressed issue on the selectivity of formation of the tri- and tetra-substituted imidazoles during the 4-MCR of a 1,2-diketone, an aldehyde, an amine and NH_4OAc inspired us to revisit the reported methods (table 12). It was revealed that all of these reported procedures led to the mixture of **5** and **3** during the 4-MCR involving **1**, **2**, **4**, and NH_4OAc. Compared to these reported catalysts the fluoroboric acid derived catalyst systems HBF_4-SiO_2 and $Zn(BF_4)_2$ afforded the best results with **5**:**3** selectivities of 100:0 and 95:5, respectively, and

with 95 and 89% yield, respectively, of the purified **5**.

Table 12. Re-assessment of reported catalyst system for competitive formation of **5** and **3** during the 4-MCR of **1**, **2**, **4**, and NH_4OAc.[a]

Entry	Catalyst	Time (min)	Yield (%) Overall[b]	**5**[c]	**3**[c]	Selectivity (**5**:**3**)[d]
1	$FeCl_3·6H_2O$	[e]	86	54	21	72:28
2	$FeCl_3·6H_2O$	10[f]	52	30	10	75:25
3	$InCl_3$	[g]	76	52	13	82:18
4	$InCl_3$	10[f]	72	44	21	68:32
5	$ZrOCl_2·8H_2O$	[h]	81	63	07	90:10
6	$ZrOCl_2·8H_2O$	10[f]	68	51	09	85:15
7	$Zn(BF_4)_2$	10	96	89	5	95:05
8	HBF_4–SiO_2	10	95	95	00	100:00

[a]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv), **4** (2.5 mmol, 1 equiv), and NH_4OAc (2.5 mmol, 1 equiv), was treated under different experimental condition in the presence of the catalyst. [b]Yield after crystallisation (aq EtOH) of the isolated crude product. [c]Isolated yield of **5** and **3** after chromatographic purification. [d]Based on the isolated and purified yields of **5** and **3**. [e]Reaction was performed following the reported procedure under ref 19c. [f]Reaction was performed using this reported catalyst under solvent free condition at 120 °C. [g]Reaction was performed following the reported procedure under ref 19f. [h]Reaction was performed following the reported procedure under ref 19g. [e]Isolated yield as reported in the corresponding literature.

Thus, for selective formation of the tetra substituted imidazoles via the 4-MCR of a 1,2-diketone, an aldehyde, an amine and NH_4OAc two new catalyst systems derived from HBF_4 have been identified: HBF_4-SiO_2 [Method C] and $Zn(BF_4)_2$ [Method D]. The application of these two catalyst systems was extended for diversified synthesis of 1,2,4,5-tetrasubstituted imidazole by the reaction of different aryl/heteroaryl/aliphatic aldehydes with 1,2-diketone, various amines and NH_4OAc (table 13).

We next investigated the reusability of HBF_4–SiO_2. The reaction of **1** (50 mmol) was carried out with (i) **2** (50 mmol, 1 equiv) and NH_4OAc (100 mmol, 2 equiv) to form the 2,4,5-trisubstituted imidazole **3** via the 3-MCR and (ii) **2** (50 mmol, 1 equiv), **4** (50 mmol, 1 equiv) and NH_4OAc (50 mmol, 1 equiv) to form the 1,2,4,5-tetrasubstituted imidazole **5** via the 4-MCR at 120 °C in the presence of HBF_4–SiO_2 (2 mol%) under neat condition. In each case, after completion of the reaction, the reaction mixture was diluted with EtOH (100 mL) and the catalyst was separated by filtration. The recovered catalyst was reactivated by heating at 80 °C for 24 h under vacuum (10 mm Hg) and reused for consecutive fresh batches of reactions without any significant decrease in product yields (tables 14 and 15).

Table 14. Catalyst recovery and reuse during the preparation of the trisubstituted imidazole **3** via the 3-MCR of **1**, **2**, and NH_4OAc.[a]

Run	Scale[b] (mmol)	HBF_4-SiO_2 Used (g)	Recovered (g)	Recovery (%)	Yield (%)[c,d]
1st	50	1.0	0.9	90	95
2nd	40	0.50	0.45	90	95
3rd	30	0.25	0.22	88	90
4th	20	0.12	0.09	75	88
5th	10	0.05	0.04	80	84

[a]The mixture of **1**, **2** (1 equiv with respect to **1**) and NH_4OAc (2 equiv with respect to **1**) was heated at 120 ºC (oil bath temp) under solvent free condition in the presence of the HBF_4-SiO_2 (2 mol%). [b]The amount of **1** used for the reaction. [c]Yield of **3** after purification (crystallisation, aq EtOH). [d]IR, NMR and APCI-MS.

Table 15. Catalyst recovery and reuse during the preparation of tetra substituted imidazole **5** via the 4-MCR of **1**, **2**, **4**, and NH_4OAc.[a]

Run	Scale[b] (mmol)	HBF_4-SiO_2 Used (g)	Recovered (g)	Recovery (%)	Yield (%)[c,d]
1st	50	1.0	0.9	90	95
2nd	40	0.50	0.48	96	95
3rd	30	0.25	0.21	84	89
4th	20	0.12	0.089	74	88
5th	10	0.05	0.042	84	85

[a]The mixture of **1**, **2** (1 equiv with respect to **1**), **4** (1 equiv with respect to **1**) and NH_4OAc (1 equiv with respect to **1**) was heated at 120 ºC (oil bath temp) under solvent free condition in the presence of the HBF_4-SiO_2 (2 mol%). [b]The amount of **1** used for the reaction. [c]Yield of **5** after purification (crystallisation, aq EtOH). [d]IR, NMR and APCI-MS.

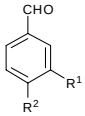
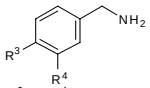
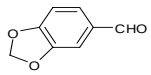
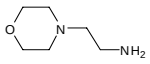
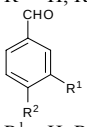
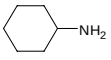
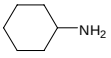
To assess the effect of various solvents used for the preparation of HBF_4–SiO_2 on its catalytic efficiency, aq HBF_4 was added to the slurry of SiO_2 (230-400 mesh) in various solvents (table 16). The resultant HBF_4–SiO_2 (experimental) was used as catalyst for the (i) 3-MCR to form **3** and (ii) the 4-MCR to form **5** (table 16). No significant variation of the catalytic activity was observed for HBF_4–SiO_2 prepared using Et_2O, DCE and EtOAc. Hence for further uses the catalyst was prepared using EtOAc as it is the preferred solvent based on the solvent selection guide of pharmaceutical industries.[40] However, protic polar solvents (H_2O and EtOH) appeared to be less effective for the purpose perhaps due to lack of removal of the trace amount of these solvents from the catalyst that would reduce its catalytic efficiency.

Table 16. Comparative catalytic behaviour of HBF_4-SiO_2 prepared using different organic solvent.

Entry	Solvent[a]	3-MCR to form **3**[b] Yield (%)[d,e]	4-MCR to form **5**[c] Yield (%)[d,e]
1	Et_2O	92	95
2	DCE	92	95
3	EtOAc	90	95
4	EtOH	85	88
5	H_2O	70	75

[a]The solvent used during the preparation of HBF_4-SiO_2 (experimental). [b]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv) and NH_4OAc (5 mmol, 2 equiv) was heated at 120 ºC (oil bath) in the presence of HBF_4-SiO_2 (2 mol %) under neat condition for 15 min. [c]The mixture of **1** (2.5 mmol), **2** (2.5 mmol, 1 equiv), **4** (2.5 mmol, 1 equiv) and) and NH_4OAc (2.5 mmol, 1 equiv) was heated at 120 ºC (oil bath) in the presence of HBF_4-SiO_2 (2 mol %) under neat condition for 10 min. [c]Yield after purification (crystallisation, aq EtOH). [e]IR, NMR and APCI-MS.

Table 13. Synthesis of 1,2,4,5-trisubstituted imidazoles via the 4-MCR of 1,2-diketone, aldehyde, amine, and NH_4OAc catalysed by HBF_4-SiO_2 and $Zn(BF_4)_2$.[a]

Entry	1,2-Diketone	Aldehyde	Amine	Method C		Method D	
				Time (min)	Yield (%)[b,c]	Time (min)	Yield(%)[b,c]
							
1	$R^1 = R^2 = Ph$	$R^1 = R^2 = H$	$R^3 = R^4 = H$	10	95	12	92
2	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = OMe$	$R^3 = R^4 = H$	15	93	15	90
3	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = Cl$	$R^3 = R^4 = H$	12	96	16	95
4	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = NO_2$	$R^3 = R^4 = H$	10	96	12	92
5	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = OH$	$R^3 = R^4 = H$	20	85	25	88
6	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = Cl$	$R^3 = Cl$; $R^4 = H$	20	90	20	85
7	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = NMe_2$	$R^3 = OMe$; $R^4 = OH$	35	82	40	80
8	$R^1 = R^2 = Ph$		$R^3 = R^4 = H$	18	94	20	92
9	$R^1 = R^2 = Ph$		$R^3 = R^4 = H$	25	93	25	90
10	$R^1 = R^2 = Ph$		$R^3 = R^4 = H$	15	96	18	95
11	$R^1 = R^2 = Me$	$R^1 = R^2 = H$	$R^3 = R^4 = H$	25	75	35	72
12	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = OMe$		30	88	25	85
13	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = Cl$	 R = H	18	94	15	90
14	$R^1 = R^2 = Ph$	$R^1 = R^2 = H$	R = Cl	20	95	20	92
15	$R^1 = R^2 = Ph$	$R^1 = R^2 = NMe_2$	R = OMe	28	90	25	88
16	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = H$		20	82	25	80
17	$R^1 = R^2 = Ph$	$R^1 = H$; $R^2 = Cl$		20	80	22	81

[a]**Method C:**The mixture of 1,2-diketone (2.5 mmol, 1 equiv), aldehyde (2.5 mmol, 1 equiv), amine (2.5 mmol, 1 equiv) and NH_4OAc (0.19 g, 2.5 mmol, 1 equiv) was heated at 120 °C in the presence of HBF_4-SiO_2 (2 mol%) under neat condition. **Method D:**The mixture of 1,2-diketone (2.5 mmol, 1 equiv), aldehyde (2.5 mmol, 1 equiv), amine (2.5 mmol, 1 equiv) and NH_4OAc (0.19 g, 2.5 mmol, 1 equiv) was heated at 120 °C in the presence of $ZnBF_4$ (10 mol%) under neat condition. [b]The yield of the corresponding 1,2,4,5-tetrasubstituted imidazoles obtained after purification (crystallization, aq EtOH). [c]All compounds were characterized by IR, NMR and MS (APCI).

Conclusions

Through this study we report conveninet syntheses of tri- and tetra-substituted imidazoles via 3-MCR and 4-MCR processes, respectively, catalysed by fluoroboic based catalyst systems. The catalyst systems HBF_4-SiO_2 (heterogenious) and $LiBF_4$ were found to be most effective for the preparation of 2,4,5-trisubstituted imidazoles during the 3-MCR of 1,2-diketone, aldehyde and NH_4OAc. Amongst the various ammonium salts used for the purpose as the nitrogen source best results were obtained with NH_4OAc and justified its universal use for such transformation. During the 4-MCR involving 1,2-diketone, aldehyde, amine, and NH_4OAc to form 1,2,4,5-tetrasubstituted imidazoles competitive formation of the 2,4,5-trisubstituted imidazole was found to be a potential problem and an issue not addressed/attended so far. Proper choice of the catalyst was the critical aspect in controlling the selectivity for which the catalyst (metal Lewis acid) derived from a weaker protic acid appeared to be a preferred choice. The relative catalytic efficiency of the Bronsted acid catalyst to offer selective formation of the tetra-substituted imidazole followed the order $HBF_4 > HClO_4 > TfOH$. In case of metal Lewis acids, the metal tetrafluoroborate proved to be the best suited catalyst for selective formation of the tetra substituted imidazole via the 4-MCR and the relative catalytic efficiency was in the order tetrafluoroborate> perchlorate> triflate. For various metal tetrafluoroborate the observed catalytic potential was: $Zn(BF_4)_2 > Co(BF_4)_2 > AgBF_4 \approx Fe(BF_4)_2 > NaBF_4 \approx LiBF_4 \approx Cu(BF_4)_2$. Immobilisation on solid support increased the catalytic efficiency which, however, is more significant/prominent for Bronsted acids (particularly inorganic protic acids) rather than the metal Lewis acids. The heterogenious catalyst system HBF_4–SiO_2 appeared to be the stand alone catalyst for the synthesis of tri- and tetra-substituted imidazoles via the 3-MCR and 4-MCR, respectively. Amongst the Lewis acids $LiBF_4$ is most effective for the 3-MCR and $Zn(BF_4)_2$ for the 4-MCR to form the tri- and tetra-substituted imidazoles

respectively. The heterogeneous catalyst HBF_4–SiO_2 can be recovered and reused for five consecutive times without any significant loss of its catalytic activity. The new catalytic procedures for the synthesis of tri- and tetra-substituted imidazoles fufill the tripple bottmline philosophy of green chemistry and are imoprtant addition to the tool box of medicinal chemists.

Notes and references

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‡ **Experimental section:** The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Advance DPX 300 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. *J* values are given in Hz. The IR spectra were recorded either as KBr pellets (for solids) or neat (for liquids) on a Nicolet Impact 410 FTIR spectrometer. Mass spectra were recorded on a GCMS- QP 5000 (Shimadzu) [for EI], and Finnigan MAT-LCQ [for APCI] mass spectrometers. The reactions were monitored by TLC (Merck®, Silica gel 60 F_{254}). Evaporation of solvents was performed at reduced pressure, using a Bűchi rotary evaporator.

Preparation of fluoroboric acid adsorbed on silica-gel (HBF_4-SiO_2).
The HBF_4-SiO_2 was prepared following the procedure first time reported by its inventors.[37a] A magnetically stirred suspension of silica gel (26.7 g, 230-400 mesh) in EtOAc (75 mL) was treated with 40% aq HBF_4 (3.3 g; 8.25 mL, 15 mmol) for 3 h. The mixture was concentrated under rotary vacuum evaporation and the residue dried under vacuum (10 mm Hg) at 100°C for 72 h to afford HBF_4-SiO_2 (HBF_4: 0.5 mmol g^{-1}) as a free flowing powder.

Representative procedure for preparation of metal tetrafluoroborate immobilized on silica-gel.
Silica gel (1 g, 230–400 mesh) was added to the solution of $LiBF_4$ (0.1 g, 1.07 mmol) in EtOH (10 mL) and the mixture was stirred magneticall for 6 h at room temperature. The mixture was concentrated under rotary vacuum evaporation and the residue was dried under reduced pressure (10 mm Hg) at 100°C for 24 h to afford the SiO_2-supported metal tetrafluoroborate ($LiBF_4$: 10 % w/w or 0.97 mmol g^{-1}) as a free flowing powder.

Procedure for preparation of [NHC][BF_4] ionic liquid.[34]
Caprolactam 1.13 g (10 mmol) was added to 50% aq fluoroboric acid (1.26 mL, 10 mmol) and the resulrtant soklution was magnetically stiorred for 30 min at room temperature. The mixture was concentrated under rotary vacuum evaporation and resudue was dried under vacuum (5–10 mmHg) for 4 h at 90 °C to obtain a light yellow clear liquid.

General procedure for synthesis of 2,4,5 trisubstituted imidazoles. 2,4,5 Triphenyl imidazole 4 (Method A).
The mixture of **1** (0.52 g, 2.5 mmol, 1 equiv), **2** (0.25 mL, 2.5 mmol, 1 equiv) and NH_4OAc (0.39 g, 5 mmol, 2 equiv) was heated at 120 °C (bath temperature) in the presence of HBF_4-SiO_2 (0.04 g, contains 2 mol% of HBF_4) under neat condition. After the completion of the reaction (solid mass formation, 15 min), the reaction mixture was diluted with EtOH (10 mL) and passed through a plug of cotton to separate the catalyst. The cotton plug retaining the catalyst was washed with EtOH (2 × 2.5 mL). The combined filtrates were concentrated under rotary vacuum evaporation and the crude product recrystallized from aq EtOH to afford **3** (0.67 g, 92%) as white solid,[16a] m.p. 274 °C. IR (KBr) ν_{max} = 1216, 1638, 2470, 2993, 3434 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.91 (d, *J* = 9.5 Hz, 2 H, ArH), 7.59 (d, *J* = 8.5 Hz, 4 H, ArH), 7.29-7.48 (m, 9 H, ArH). MS (APCI) m/z: 297 (MH^+). The cotton plug retaining the catalyst was transferred to a rb flask (10 mL) and dried under rotary vacuum evaporation whereupon the catalyst came out of the cotton. The catalyst was activated under vacuum (10 mm Hg) at 80 ºC for 24 h and reused. The remaining reactions were performed following this general procedure and the physical data (mp, IR, NMR and MS) of all known compounds were identical with those reported in the literature.

General procedure for synthesis of 2,4,5 trisubstituted imidazoles. 2,4,5 Triphenyl imidazole 4 (Method B)
The mixture of **1** (0.52 g, 2.5 mmol, 1 equiv), **2** (0.25 mL, 2.5 mmol, 1 equiv) and NH_4OAc (0.39 g, 5 mmol, 2 equiv) were heated at 120 °C (bath temperature) in the presence of $LiBF_4$ (10 mol%) under neat condition. After the completion of the reaction (solid mass formation, 20 min), the crude product recrystallized from aq EtOH to afford **3** (0.67 g, 92%) as white solid.[16a]

General procedure for synthesis of 1,2,4,5 tetrasubstituted imidazoles. 1-Benzyl-2,4,5-triphenyl imidazole 6 (Method C).
The mixture of **1** (0.52 g, 2.5 mmol, 1equiv), **2** (0.25 mL, 2.5 mmol, 1 equiv), NH_4OAc (0.19 g, 2.5 mmol, 1 equiv) and **4** (0.27 mL, 2.5 mmol, 1 equiv) were heated at 120 °C (bath temperature) in the presence of HBF_4-SiO_2 (0.04 g, contains 2 mol% of HBF_4) under neat condition. After the completion of the reaction (solid mass formation, 10 min), the reaction mixture was diluted with EtOH (10 mL) and passed through a plug of cotton to separate the catalyst. The cotton plug retaining the catalyst was washed with EtOH (2 × 2.5 mL). The combined filtrates were concentrated under rotary vacuum evaporation and the crude product recrystallized from aq EtOH to afford **5** (0.70 g, 95%) as white solid,[18a] m.p. 161 °C. IR (KBr): ν_{max} = 2985, 1600, 1580, 1500, 1480 cm^{-1}.^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, *J* = 4.7 Hz, 2 H, ArH), 7.57 (d, 2 H, *J* = 9.7 Hz, ArH), 6.80-7.39 (m, 16 H, ArH), 5.10 (s, 2 H, $PhCH_2$). MS (APCI) m/z: 373 (MH^+). The cotton plug retaining the catalyst was transferred to a rb flask (10 mL) and dried under rotary vacuum evaporation whereupon the catalyst came out of the cotton. The catalyst was activated under vacuum (10 mm Hg) at 100 ºC for 24 h and reused. The remaining reactions were performed following this general procedure and the physical data (mp, IR, NMR and MS) of all known compounds were identical with those reported in the literature.

General procedure for synthesis of 1,2,4,5 tetrasubstituted imidazoles. 1-Benzyl-2,4,5-triphenyl imidazole 6 (Method D).
The mixture of **1** (0.52 g, 2.5 mmol, 1equiv), **2** (0.25 mL, 2.5 mmol, 1 equiv), NH_4OAc (0.19 g, 2.5 mmol, 1 equiv) and **4** (0.27 mL, 2.5 mmol, 1 equiv) were heated at 120 °C (bath temperature) in the presence of $Zn(BF_4)_2$ (10 mol%) under neat condition. After the completion of the reaction (solid mass formation, 12 min), the reaction mixture was diluted with EtOH (10 mL) and passed through a plug of cotton to separate the catalyst. The cotton plug retaining the catalyst was washed with EtOH (2 × 2.5 mL). The combined filtrates were concentrated under rotary vacuum evaporation and the crude product recrystallized from aq EtOH to afford **5** (0.70 g, 95%) as white solid.[18a]

Experimental Procedure of Large Scale synthesis of trisubstituted Imidazole and Catalyst Reuse.
To a magnetically stirred mixture of **1** (10.4 g, 50 mmol, 1 equiv), **2** (5.0 mL, 50 mmol, 1 equiv) and NH_4OAc (7.8 g, 100 mmol, 2 equiv) was added HBF_4-SiO_2 (800 mg, 1 mmol, 2 mol%) and the reaction mixture was heated at 120 °C. After the completion of reaction (20 min, TLC), the reaction mixture was diluted with EtOH (50 mL), filtered through a plug of cotton (to separate the catalyst), and the cotton plug was washed with EtOH (2 × 20 mL). The combined filtrates were concentrated on a rotary evaporator to afford the crude product. The crude product was recrystallized from aq EtOH to afford **3** (13.5 g, 95%) as white solid.[16a] The cotton plug retaining the recovered catalyst was put in a rb flask (20 mL) and dried under rotary vacuum evaporation when the catalyst separated out from the cotton (720 mg, 90%). The catalyst was activated by heating under reduced pressure (10 mm Hg) at 80 °C for 24 h. The reaction was repeated at 40 mmol, 30 mmol, 20 mmol and 10 mmol scales the in presence of the recovered HBF_4-SiO_2 (0.5 g, 0.25 g, 0.12 g and 0.05 g, respectively) to afford 2,4,5 triphenyl imidazole **3** in 11.2 g (95 %), 8.0 g (90 %), 5.2 g (88 %), and 2.5 g (84 %), respectively, as white solid identical (spectral data) with an authentic sample.

Representative Experimental Procedure of Large Scale synthesis of Tetrasubstituted Imidazole and Catalyst Reuse.
To a magnetically stirred mixture of **1** (10.4 g, 50 mmol, 1 equiv), **2** (5.0 mL, 50 mmol, 1 equiv), NH_4OAc (3.9 g, 50 mmol, 1 equiv) and **4** (5.3 g, 50 mmol, 1 equiv) was added HBF_4-SiO_2 (800 mg, 1mmol, 2 mol %) and the reaction mixture was heated at 120 °C. After the completion of reaction (20 min, TLC), the reaction mixture was diluted with EtOH (50 mL), filtered through a plug of cotton (to separate the catalyst), and the cotton plug was washed with EtOH (2 × 20 mL). The combined filtrates

were concentrated on a rotary evaporator to afford the crude product. The crude product was recrystallized from aq EtOH to afford **5** (18.3 g, 95%) white solid.[18a] The cotton plug retaining the recovered catalyst was put in a rb flask (20 mL) and dried under rotary vacuum evaporation when the catalyst separated out from the cotton (720 mg, 90%). The catalyst was activated by heating under reduced pressure (10 mm Hg) at 80 °C for 24 h. The reaction was repeated at 40 mmol, 30 mmol, 20 mmol and 10 mmol scales the in presence of the recovered HBF_4-SiO_2 (0.5 g, 0.25 g, 0.12 g and 0.05 g, respectively) to afford **5** in 14.6 g (95 %), 10.3 g (89 %), 6.8 g (88 %), and 3.2 g (85 %), respectively as white solid identical (spectral data) with an authentic sample.

The physical data (IR, NMR and MS) of new compounds are provided below.

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (Table 11, Entry 6) White Solid (1.0 g, 95 %), m.p. 177-178 °C. IR (KBr) ν_{max} = 3420, 3006, 1606, 1483, 1275, 1092, 832, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.58 (m, 4 H ArH), 7.31-7.40 (m, 5 H, ArH), 7.12-7.24 (m, 7 H, ArH), 6.7 (d, J = 8.4 Hz, 2 H, ArH), 5.04 (s, 3 H, $PhCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 138.4, 135.7, 134.1, 133.4, 130.9, 130.6, 130.2, 130.2, 130.1, 129.2, 129.0, 128.9, 128.5, 128.9, 128.2, 127.3, 126.8, 126.6, 47.7. HRMS (ESI) m/z calcd for $C_{28}H_{20}Cl_2N_2Na^+$ [M + Na^+], 477.0896; Found 477.0894.

1-(4-Methoxy-2-hydroxybenzyl)-2-(4-dimethylaminophenyl)-4,5-diphenyl-1*H*-imidazole (Table 11, Entry 7) White Solid (0.97 g, 82 %), m.p. 271-272 °C. IR (KBr) ν_{max} = 3430, 2994, 1610, 1396, 1280, 834, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2 H ArH), 7.45(d, J = 8.8 Hz, 2 H, ArH), 7.24 (m, 1 H, ArH), 7.08-7.18 (m, 5 H, ArH), 6.65 (d, J = 7.2 Hz, 2 H, ArH), 6.60 (t, J = 6.3 Hz, 2 H, ArH), 6.54 (d, J = 8.8 Hz, 2 H, ArH), 6.12-6.15 (m, 1 H, ArH), 6.12 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 2.88 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 148.2, 146.4, 146.2, 131.1, 129.9, 129.5, 128.5, 128.3, 128.0, 126.8, 117.0, 116.2, 115.2, 112.5, 112.0, 110.9, 56.0, 47.8, 40.2. HRMS (ESI) m/z calcd for $C_{31}H_{29}N_3O_2Na^+$ [M + Na^+], 498.2152; Found 498.2164.

4-(2-(2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)morpholine (Table 7, Entry 12) White Solid (0.9 g, 88 %), IR (KBr) ν_{max} = 3420, 2896, 1625, 1385, 1280, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62-7.66 (m, 2 H, ArH), 7.51-7.53 (m, 2 H, ArH), 7.41-7.48 (m, 5 H, ArH), 7.17-7.21 (m, 2 H, ArH), 7.10 (m, 1 H, ArH), 6.98-7.02 (m, 2 H, ArH), 4.00 (t, J = 7.32 Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.48 (t, J = 4.60 Hz, 4 H, CH_2), 2.23 (t, J = 7.16 Hz, 2 H, CH_2), 2.04 (t, J = 4.52 Hz, 4 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 147.8, 137.5, 134.5, 131.5, 131.0, 130.6, 129.2, 129.1, 128.7, 128.4, 126.8, 126.2, 123.7, 114.0, 66.7, 58.2, 55.4, 53.4, 41.8. HRMS (ESI) m/z calcd for $C_{28}H_{29}N_3O_2Na^+$ [M + Na^+], 462.2152; Found 462.2164.

1-(4-Methoxyphenyl)-2-(4-dimethylaminophenyl)-4,5-diphenyl-1*H*-imidazole (Table 11, Entry 15) white solid (1.0 g, 90 %), IR (KBr) ν max = 3425, 2982, 1625, 1390, 1282, 847, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.62 (m, 2 H, ArH), 7.33-7.35 (m, 2 H, ArH), 7.12-7.27 (m, 8 H, ArH), 6.97-7.70 (m, 2 H, ArH), 6.76-6.80 (m, 2 H, ArH), 6.57-6.60 (m, 2 H, ArH), 3.79 (s, 3 H, OCH_3), 2.94 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 150.0, 147.7, 137.6, 134.8, 131.2, 131.1, 130.4, 130.3, 129.8, 129.7, 128.2, 128.0, 127.6, 127.4, 126.3, 118.4, 114.1, 111.5, 55.3, 40.2. HRMS (ESI) m/z calcd for $C_{30}H_{27}N_3ONa^+$ [M + Na^+], 468.2046; Found 468.2046.

2-(4-Chlorophenyl)-1-cyclohexyl-4,5-diphenyl-1H-imidazole (Table 11, Entry 17) White solid (1.0 g, 80 %), IR (KBr) ν_{max} = 3746, 3449, 2925, 1747, 1447, 1366, 1275, 1216, 1091, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.58 (m, 2 H, ArH), 7.39-7.48 (m, 9 H, ArH), 7.06-7.16 (m, 3 H, ArH), 3.88-3.95 (m, 1H, cyCH), 1.62-1.85 (m, 4 H, $cyCH_2$), 1.42-1.58 (m, 3 H, $cyCH_2$), 0.99-1.10 (m, 2 H, $cyCH_2$), 0.79 (m, 1 H, $cyCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 138.0, 135.0, 134.4, 132.3, 132.1, 131.3, 130.9, 129.4, 128.9, 128.7, 128.6, 127.9, 126.6, 126.1, 58.4, 33.6, 26.2, 25.0. HRMS (ESI) m/z calcd for $C_{27}H_{25}ClN_2H^+$ [M + H^+], 413.1779; Found 413.1790.

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Catalytic procedures for multicomponent synthesis of imidazoles: selectivity control during the competitive formation of tri- and tetra-substituted imidazoles

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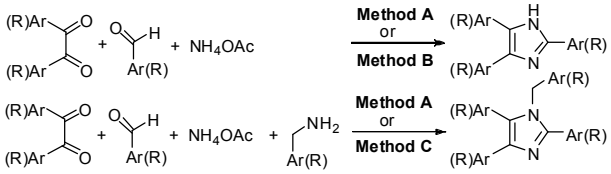

Method A: HBF_4-SiO_2 (2 mol%), neat, 120 °C, 10 - 35 min
Method B: $LiBF_4$ (10 mol%), neat, 120 °C, 12 - 40 min
Method C: $Zn(BF_4)_2$ (10 mol%), neat, 120 °C, 12 - 35 min

Fluoroboric acid derived catalyst systems for selectivity control in the multicomponent reactions for synthesis of tri- and tetra-substituted imidazoles.