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Efficient use of a surfactant for copper-catalyzed coupling reaction of arylboronic acids with imidazoles in water

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ABSTRACT

Copper-catalyzed oxidative coupling of arylboronic acids with imidazoles in water was realized by using an amphiphilic surfactant. By choosing an appropriate surfactant, reactions of a variety of arylboronic acids proceeded smoothly under mild and base-free conditions, providing an efficient, practical, and greener method for the synthesis of *N*-arylimidazoles.

1. Introduction

The use of water as a solvent for organic synthesis has recently attracted considerable attention because it offers a range of advantages such as inexpensiveness, wide availability, non-toxicity, and nonflammability, thus providing highly economic and sustainable synthetic routes.[1] While its use is sometimes hampered by the insolubility of the polar organic molecules, the addition of an amphiphilic surfactant, forming micelles, has been known to have a positive effect for the reactions conducted in water, including transition-metal-catalyzed processes, resulting from hydrophobic and concentration effects in the microheterogeneous two-phase system.[2,3]

Arylamines are ubiquitous in biologically active molecules, ranging from natural products to medicinal agents. Among the methods to access such a motif, the copper-mediated or -catalyzed oxidative coupling of arylboronic acids with amines, so-called the Chan–Lam coupling, has certain advantages such as mild reaction conditions (e.g., room temperature, an ambient atmosphere), inexpensive copper-based catalyst systems, and wide availability of starting boronic acids.[4] Although considerable progress has been made in expanding the substrate scope of the process in the past decade,[5] the use of water as a reaction medium for this process has met with almost no success, presumably because arylboronic acids undergo side reactions such as oxidative phenol formation (Ar–B to Ar–OH) relatively easily in such an aqueous media.[6] Although there is only one example of the Chan–Lam coupling carried out in water, the yields are moderate to low and the substrate scope is relatively narrow.[7]

During the course of our research program aiming at an effective use of amphiphilic surfactants in organic synthesis,[8] we found that the Chan–Lam coupling can be successfully performed in water in the presence of a certain surfactant. Interestingly, a fluorous-type surfactant (F-PEG) has turned out to be efficient for some substrates, representing a rare example of using fluorous surfactants in organic synthesis.[9–11] In this paper, we describe the results of the studies in detail.

2. Results and discussion

To probe the viability of the anticipated Cu-catalyzed Chan–Lam coupling in water, we first carried out the reaction of 4-methoxyphenylboronic acid (**1a**) with imidazole (**2a**) in the presence of 10 mol % of $Cu(OAc)_2$/4,4′-dimethyl-2,2′-dipyridyl (**I**) catalyst system under an O_2 atmosphere (1 atm). However, the reaction provided the desired coupling product **3aa** only in 33% yield (entry 1). Thus, the effect of adding a surfactant (30 mol %) for the process was next evaluated (entries 2–9). As a result, it was found that a certain surfactant did enhance the process: Among the surfactants examined, Brij 30, Triton X-100, and fluorous-type F-PEG were superior to others for the reaction of **1a**, providing **3aa** in fairly good yields (entries 5, 6, and 9). Interestingly, the use of a ligand

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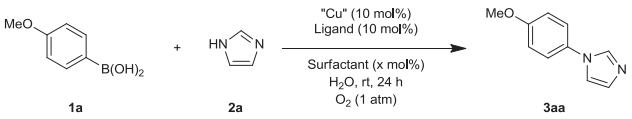
II,[12] possessing fluorous substituents, was crucial for better conversion when F-PEG was used (entry 9 vs entry 8). Intrigued by the reaction-improving effect of the surfactant, further examination of the reaction parameters was conducted using a combination of F-PEG and ligand **II**. Among a variety of the copper sources tested (entries 9–15), $Cu(OAc)_2$ turned out to be the best (entry 9). In addition, the optimal amount of a surfactant was found to be 50 mol % (entry 17 vs entries 9, 16, 18, and 19). Whereas the reaction performed under an air atmosphere gave **3aa** in yield similar to that from the reaction under an O_2 atmosphere (entry 20), essentially no product was obtained from the reaction under an Ar atmosphere (entry 21). At this juncture, it is worthy to note that F-PEG can be easily recovered after the coupling reaction and successfully reused for the same process[13] (Table 1).

Substrate scope of the process was next investigated using the above-obtained optimal reaction conditions (conditions *A*: 10 mol % of ligand **I** and 50 mol % of Brij 30, conditions *B*: 10 mol % of ligand **I** and 50 mol % of Triton X-100, conditions *C*: 10 mol % of ligand **II** and 50 mol % of F-PEG). As shown in Table 2, several kinds of arylboronic acids **1a**–**h** have turned out suitable for the coupling and the corresponding *N*-arylimidazoles were obtained generally in good to high yields by choosing an appropriate surfactant (entries 1–8). Good functional group compatibility (e.g., alkoxycarbonyl and cyano groups, halogen atoms such as bromine and chlorine) was also observed in the process. On the other hand, the reactions of *meta*-aminophenylboronic acid **1i** only provided low yields (entry 9).

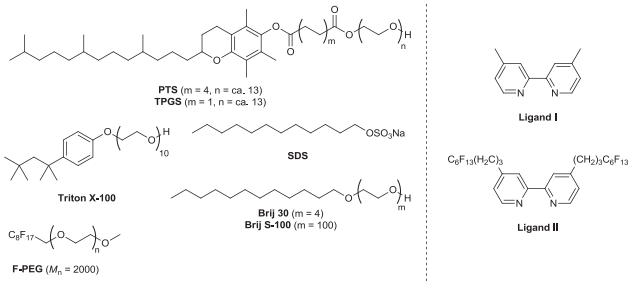
The efficiency of the catalytic system developed was further evaluated briefly by using several amines instead of imidazole (**2a**) as a nucleophile (Table 3). The reactions of benzimidazole (**2b**) and 2-phenylimidazole (**2c**) both afforded the desired coupling products in high yields especially when a fluorous-type surfactant was used (entries 1 and 2, conditions C). Use of 4-methylimidazole (**2d**) afforded the product as a mixture of regioisomers as in the case of the previous report (entry 3).[14] Unfortunately, only low to moderate yields were obtained from the reaction with pyrazole (**2e**) (entry 4).[15]

Table 1
Effect of reaction parameters[a]



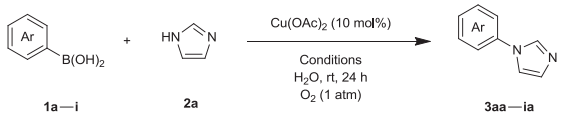
1a 2a 3aa

Entry	'Cu'	Ligand	Surfactant (*x* mol %)	Yield[b] (%)
1	$Cu(OAc)_2$	**I**	None	33
2	$Cu(OAc)_2$	**I**	SDS (30)	21
3	$Cu(OAc)_2$	**I**	TPGS (30)	53
4	$Cu(OAc)_2$	**I**	Brij S-100 (30)	53
5	$Cu(OAc)_2$	**I**	Brij 30 (30)	68
6	$Cu(OAc)_2$	**I**	Triton X-100 (30)	66
7	$Cu(OAc)_2$	**I**	PTS (30)	8
8	$Cu(OAc)_2$	**I**	F-PEG (30)	26
9	$Cu(OAc)_2$	**II**	F-PEG (30)	67
10	$Cu(OTf)_2$	**II**	F-PEG (30)	54
11	$CuBr_2$	**II**	F-PEG (30)	36
12	$CuCl_2$	**II**	F-PEG (30)	30
13	CuCl	**II**	F-PEG (30)	61
14	CuI	**II**	F-PEG (30)	62
15	Cu_2O	**II**	F-PEG (30)	46
16	$Cu(OAc)_2$	**II**	F-PEG (10)	64
17	$Cu(OAc)_2$	**II**	F-PEG (50)	*78*
18	$Cu(OAc)_2$	**II**	F-PEG (100)	70
19	$Cu(OAc)_2$	**II**	F-PEG (300)	67
20[c]	$Cu(OAc)_2$	**II**	F-PEG (50)	77
21[d]	$Cu(OAc)_2$	**II**	F-PEG (50)	Trace

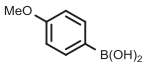
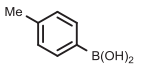
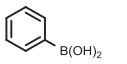
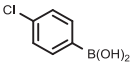
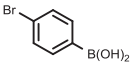
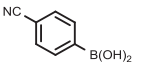
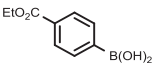
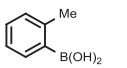
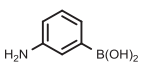


[a] Reaction conditions: **1a** (0.40 mmol), **2a** (0.20 mmol), 'Cu' (0.020 mmol), ligand (0.020 mmol), surfactant in H_2O (4–6 mL).
[b] Isolated yield.
[c] Carried out under air.
[d] Carried out under Ar.

Table 2
Substrate scope of the process regarding arylboronic acids[a]

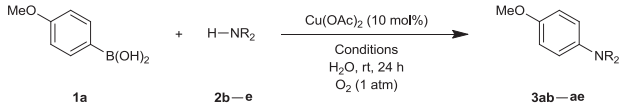


1a—i 2a 3aa—ia

Entry	Arylboronic acid	**1**	Conditions[c]	Yield[b] (%)
1		**1a**	A B C	68[d] 66[d] *78*
2		**1b**	A B C	58 — *72*
3		**1c**	A B C	<46[e] <44[e] *73*
4		**1d**	A B C	*74*[f] 24 49
5		**1e**	A B C	*74*[f] 61 26
6		**1f**	A B C	Trace *52*[g] 21
7		**1g**	A B C	22 *59* 21
8		**1h**	A B C	64 *80* 69
9		**1i**	A B C	17 *23* 9

[a] Reaction conditions: **1** (0.40 mmol), **2a** (0.20 mmol), $Cu(OAc)_2$ (0.020 mmol), ligand (0.020 mmol), surfactant in H_2O (6 mL).
[b] Isolated yield.
[c] Conditions *A*: 10 mol % of ligand **I** and 50 mol % of Brij 30, conditions *B*: 10 mol % of ligand **I** and 50 mol % of Triton X-100, and conditions *C*: 10 mol % of ligand **II** and 50 mol % of F-PEG.
[d] Surfactant of 30 mol % was used.
[e] Including impurities.
[f] Bipyridyl was used instead of ligand **I**.
[g] Pyridine of 5 equiv was added.

Table 3
Substrate scope of the process regarding amines[a]



Entry	H—NR_2	2	Conditions[c]	Yield[b] (%)
1		**2b**	A B C	23 51 *78*
2		**2c**	A B C	15 10 *68*
3		**2d**	A B C	38 (3:1)[d] 44 (2:1)[d] *48* (3:2)[d]
4		**2e**	A B C	44 *45* 24

[a] Reaction conditions: **1** (0.40 mmol), **2a** (0.20 mmol), $Cu(OAc)_2$ (0.020 mmol), ligand (0.020 mmol), surfactant in H_2O (6 mL).
[b] Isolated yield.
[c] Conditions *A*: 10 mol % of ligand **I** and 50 mol % of Brij 30, conditions *B*: 10 mol % of ligand **I** and 50 mol % of Triton X-100, conditions *C*: 10 mol % of ligand **II** and 50 mol % of F-PEG.
[d] Ratio of regioisomers.

3. Conclusions

We have described the copper-catalyzed coupling reaction of arylboronic acids with imidazoles in water containing an amphiphilic surfactant. By choosing an appropriate surfactant, the reactions of a variety of arylboronic acids proceed smoothly under mild, base-free conditions in aqueous media, providing a facile, efficient access to a biologically important *N*-arylimidazole nucleus. Further studies to broaden the substrate scope of the process as well as to improve the catalytic efficiency are vigorously underway in our laboratory.

4. Experimental section

4.1. General

Melting points were measured with a Yazawa micro melting point apparatus and uncorrected. IR spectra were recorded on a SHIMADZU IRAffinity. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 (400 MHz) or JNM-ECA600 (600 MHz) spectrometer. Chemical shifts (δ) are given from TMS (0 ppm) in $CDCl_3$ and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd,=double doublet, dt=double triplet, m=multiplet, and br s=broad singlet. ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 (100 MHz) or JNM-ECA600 (150 MHz) spectrometer. Chemical shifts (δ) are given from $^{13}CDCl_3$ (77.0 ppm). Mass spectra and high-resolution mass spectra were measured on a JEOL JMS-DX 303 and JMS-700/JMS-T 100 GC instruments, respectively. Elemental analyses were performed by Yanaco CHN CORDER MT-6. Boronic acids and other commercially available materials including copper salts and surfactants were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used as received. Fluorous-type surfactant 'F-PEG' was prepared using the method similar to the Mecozzi's synthesis.[9a,b] Fluorous-type ligand **II** was prepared according to the previously reported method.[12]

4.2. Synthesis of fluorous surfactant (F-PEG)

Under an Ar atmosphere, Et_3N (10.5 mL, 75.0 mmol) was added to a mixture of [poly(ethylene glycol)methyl ether (M_n=2000)] (9.9 g, 5.0 mmol) and *p*-toluenesulfonyl chloride (4.8 g, 25.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the reaction mixture was stirred for 3 h at the same temperature, and then stirred at room temperature overnight. The solvent was evaporated and the residue was reprecipitated in Et_2O/^{i}PrOH (4:1). The resulting precipitates were filtrated and washed with Et_2O to give the tosylated product (11.4 g, >99%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.45 (s, 3H), 3.38 (s, 3H), 3.53–3.81 (m, PEG–H), 7.34 (d, 2H, *J*=8.1 Hz), 7.79 (d, 2H, *J*=8.1 Hz); IR (neat): 2863, 2855, 2365, 2163, 1471, 1343, 1112, 1060, 841, 699 cm^{-1}.

NaH (0.53 g, 13.0 mmol, 60% dispersion in oil) was added to a solution of $C_8F_{17}CH_2OH$ (2.7 g, 6.4 mmol) in THF (100 mL) and stirred at room temperature for 1 h. The above tosylated product (2.3 g, 2.0 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated and the residue was diluted with H_2O, and then extracted with $CHCl_3$ (30 mL×3). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was reprecipitated in Et_2O and the resulting precipitates were filtrated and dissolved in CH_2Cl_2, and then reprecipitated in hexane. The resulting precipitates were filtrated and washed with hexane to give F-PEG (2.3 g, 81%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.38 (s, 3H), 3.45–3.83 (m, PEG-H), 4.04 (t, 2H, *J*=14.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 59.0, 70.46, 70.51, 70.6, 70.7, 71.9, 72.3; IR (neat): 3800, 3674, 3587, 3438, 2194, 2157, 1962, 1651, 1107, 843 cm^{-1}.

4.3. Synthesis of fluorous-type ligand (II)

Under an Ar atmosphere, BuLi (7.3 mL, 19.0 mmol, 2.6 M in hexanes) was added to a THF solution (50 mL) of ^{i}Pr$_2$NH (0.81 mL, 11.3 mmol) at −78 °C and stirred for 20 min at the same temperature. The reaction mixture was stirred for 30 min at 0 °C and then cooled to −78 °C. A THF solution (30 mL) of 4,4′-dimethyl-2,2′-bipyridine (0.92 g, 5.0 mmol) was added and stirred for 3 h at the same temperature, and then 3-(perfluorohexyl)ethyl iodide (4.8 g, 10.2 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h and stirred at room temperature overnight. The mixture was diluted with brine and extracted with Et_2O (30 mL×3). The organic layer was dried over Na_2SO_4 and the solvent was removed under the reduced pressure. The residue was purified by recrystallization from MeOH to give ligand **II** (0.53 g, 12%) as brown scales. Mp 112–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.02–2.19 (m, 8H), 2.82 (t, 4H, *J*=7.8 Hz), 7.17 (dd, 2H, *J*=5.3, 1.7 Hz), 8.28 (s, 2H), 8.61 (d, 2H, *J*=5.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 21.0, 30.4 (t, *J*=22.2 Hz), 34.6, 121.1, 123.8, 149.3, 150.6, 156.3; LRMS (EI) *m*/*z*: 876 (M^+); HRMS: calcd for $C_{28}H_{18}F_{26}N_2$: 876.1055, found: 876.1044; IR (neat): 3800, 3674, 3587, 3438, 2194, 2157, 1962, 1651, 1107, 843 cm^{-1}.

4.4. Representative procedure for N-arylation of imidazoles

4.4.1. Coupling reaction using Brij 30 as a surfactant (Table 2, entry 1, conditions A). Under an O_2 atmosphere, a mixture of 4-methoxyphenylboroic acid (**1a**, 60.8 mg, 0.40 mmol), imidazole (**2a**, 13.6 mg, 0.20 mmol), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol), ligand **I** (3.7 mg, 0.020 mmol), and Brij 30 (21.8 mg, 0.060 mmol) in H_2O (4 mL) was stirred at room temperature for 24 h. The mixture was diluted with brine and extracted with AcOEt (30 mL×3). The

organic layer was washed with H_2O (10 mL×3) and dried over $MgSO_4$. The solvent was removed under the reduced pressure and the residue was purified by SiO_2 column chromatography using AcOEt to give *N*-(4-methoxyphenyl)imidazole (**3aa**) (23.7 mg, 68%).

4.4.2. Coupling reaction using Triton X-100 as a surfactant (Table 2, entry 1, conditions B). Under an O_2 atmosphere, a mixture of 4-methoxyphenylboroic acid (**1a**, 60.8 mg, 0.40 mmol), imidazole (**2a**, 13.6 mg, 0.20 mmol), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol), ligand **I** (3.7 mg, 0.020 mmol), and Triton X-100 (38.8 mg, 0.060 mmol) in H_2O (4 mL) was stirred at room temperature for 24 h. The mixture was diluted with brine and extracted with AcOEt (30 mL×3). The organic layer was washed with H_2O (10 mL×3) and dried over $MgSO_4$. The solvent was removed under the reduced pressure and the residue was purified by SiO_2 column chromatography using AcOEt to give *N*-(4-methoxyphenyl)imidazole (**3aa**) (23.0 mg, 66%).

4.4.3. Coupling reaction using F-PEG as a surfactant (Table 2, entry 1, conditions C). A mixture of $Cu(OAc)_2$ (3.6 mg, 0.020 mmol), ligand **II** (21.6 mg, 0.020 mmol), and F-PEG (0.25 g, 0.10 mmol) in MeOH (1 mL) was heated to dissolve all the reagents added completely and MeOH was removed under the reduced pressure. H_2O (6 mL) was added to the residue and then 4-methoxyphenylboroic acid (**1a**, 60.8 mg, 0.40 mmol) and imidazole (**2a**, 13.6 mg, 0.20 mmol) were added. The whole reaction mixture was stirred under an O_2 atmosphere at room temperature for 24 h. The mixture was diluted with brine and extracted with AcOEt (30 mL×3). The organic layer was washed with H_2O (10 mL×3) and dried over $MgSO_4$. The solvent was removed under the reduced pressure and the residue was purified by SiO_2 column chromatography using AcOEt to give *N*-(4-methoxyphenyl)imidazole (**3aa**) (26.4 mg, 78%).

*4.4.4. N-(4-Methoxyphenyl)imidazole (**3aa**)* .[16] Obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.85 (s, 3H), 6.98 (d, 2H, *J*=8.8 Hz), 7.18–7.26 (m, 2H), 7.30 (d, 2H, *J*=8.8 Hz), 7.78 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 55.4, 114.7, 118.5, 123.0, 129.9, 130.5, 135.6, 158.4; LRMS (EI) *m*/*z*: 174 (M^+); HRMS: calcd for $C_{10}H_{10}N_2O$: 174.0793, found: 174.0770; IR (neat): 3113, 2836, 1609, 1590, 1515, 1465, 1242, 1055, 828, 730 cm^{-1}.

*4.4.5. N-(4-Methylphenyl)imidazole (**3ba**).*[16] Obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.41 (s, 3H), 7.20 (br s, 1H), 7.25–7.28 (m, 5H), 7.83 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 20.9, 118.3, 121.4, 130.2, 130.3, 135.0, 135.6, 137.4; LRMS (EI) *m*/*z*: 158 (M^+); HRMS: calcd for $C_{10}H_{10}N_2$: 158.0844, found: 158.0827; IR (neat): 3113, 2861, 1520, 1487, 1303, 1112, 1056, 963, 810, 730 cm^{-1}.

*4.4.6. N-Phenylimidazole (**3ca**).*[16] Obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.22 (br s, 1H), 7.30 (br s, 1H), 7.35–7.41 (m, 3H), 7.46–7.51 (m, 2H), 7.87 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 118.2, 121.4, 127.4, 129.8, 130.4, 135.6, 137.3; LRMS (EI) *m*/*z*: 144 (M^+); HRMS: calcd for $C_9H_8N_2$: 144.0687, found: 144.0677; IR (neat): 3407, 3116, 1718, 1600, 1507, 1303, 1056, 963, 757, 685 cm^{-1}.

*4.4.7. N-(4-Chlorophenyl)imidazole (**3da**).*[17] Obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.23 (br s, 1H), 7.26 (br s, 1H), 7.34 (d, 2H, *J*=8.8 Hz), 7.46 (d, 2H, *J*=8.8 Hz), 7.83 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 118.2, 122.7, 130.1, 130.8, 133.2, 135.6, 135.9; LRMS (EI) *m*/*z*: 178 (M^+); HRMS: calcd for $C_9H_7^{35}ClN_2$: 178.0298, found: 178.0292; IR (neat): 3407, 3116, 1718, 1600, 1507, 1303, 1056, 963, 757, 685 cm^{-1}.

*4.4.8. N-(4-Bromophenyl)imidazole (**3ea**).*[18] Recrystallized from AcOEt/hexane, colorless needles, mp 120–122 °C (lit.[18] mp 120–122 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.23 (br s, 1H), 7.26 (br s, 1H), 7.28 (dt, 2H, *J*=9.3, 2.5 Hz), 7.61 (dt, 2H, *J*=9.3, 2.5 Hz), 7.84 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$/TMS) δ (ppm): 118.2, 121.0, 123.0, 130.8, 133.0, 135.5, 136.4; LRMS (EI) *m*/*z*: 222 (M^+); HRMS: calcd for $C_9H_7BrN_2$: 221.9793, found: 221.9774; IR (neat): 3853, 3753, 3587, 3503, 1696, 1653, 1559, 1507, 748, 658 cm^{-1}.

*4.4.9. N-(4-Cyanophenyl)imidazole (**3fa**).*[19] Recrystallized from Et_2O/hexane, yellow prisms, mp 143–145 °C (lit.[19] mp 152–154 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.28 (br s, 1H), 7.35 (br s, 1H), 7.54 (d, 2H, *J*=8.8 Hz), 7.81 (d, 2H, *J*=8.8 Hz), 7.96 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$/TMS) δ (ppm): 111.2, 117.7, 117.8, 121.4, 131.5, 134.2, 135.3, 140.5; LRMS (EI) *m*/*z*: 169 (M^+); HRMS: calcd for $C_{10}H_7N_3$: 169.0640, found: 169.0647; IR (neat): 3903, 3753, 2960, 2854, 2372, 2359, 1733, 1559, 1271, 831 cm^{-1}.

*4.4.10. N-(4-Ethoxycarbonylphenyl)imidazole (**3ga**).*[18] Recrystallized from Et_2O, colorless needles, mp 103–104 °C (lit.[18] mp 101–103 °C); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.42 (t, 3H, *J*=7.1 Hz), 4.42 (q, 2H, *J*=7.1 Hz), 7.25 (br s, 1H), 7.36 (br s, 1H), 7.47 (d, 2H, *J*=8.3 Hz), 7.95 (br s, 1H), 8.17 (d, 2H, *J*=8.3 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$/TMS) δ (ppm): 14.4, 61.4, 117.9, 120.7, 129.5, 131.2, 131.6, 135.5, 140.7, 165.6; LRMS (EI) *m*/*z*: 216 (M^+); HRMS: calcd for $C_{12}H_{12}N_2O_2$: 216.0899, found: 216.0900; IR (neat): 3852, 3674, 2926, 2853, 2374, 1733, 1652, 1508, 1369, 1122 cm^{-1}.

*4.4.11. N-(2-Methylphenyl)imidazole (**3ha**).*[20] Obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.19 (s, 3H), 7.06 (s, 1H), 7.21–7.36 (m, 5H), 7.59 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$/TMS) δ (ppm): 17.5, 120.5, 126.5, 126.8, 128.7, 129.3, 131.2, 133.8, 136.6, 137.4; LRMS (EI) *m*/*z*: 158 (M^+); HRMS: calcd for $C_{10}H_{10}N_2$: 158.0844, found: 158.0827; IR (neat): 3110, 2861, 1502, 1309, 1240, 1057, 963, 817, 761, 662 cm^{-1}.

*4.4.12. N-(3-Aminophenyl)imidazole (**3ia**).*[18] Obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.87 (br s, 2H), 6.64–6.68 (m, 2H), 6.75–6.77 (m, 1H), 7.18–7.25 (m, 3H), 7.83 (br s, 1H); LRMS (EI) *m*/*z*: 159 (M^+); HRMS: calcd for $C_9H_9N_3$: 159.0796, found: 159.0784; IR (neat): 3419, 3327, 3207, 1607, 1588, 1507, 1236 cm^{-1}.

*4.4.13. N-(4-Methoxyphenyl)benzimidazole (**3ab**).*[19] Obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.89 (s, 3H), 7.07 (d, 2H, *J*=8.8 Hz), 7.29–7.35 (m, 2H), 7.41(d, 2H, *J*=8.8 Hz), 7.44–7.47 (m, 1H), 7.86–7.88 (m, 1H), 8.05 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 55.6, 110.3, 115.1, 120.5, 122.5, 123.5, 125.7, 129.1, 134.2, 142.5, 143.8, 159.3; LRMS (EI) *m*/*z*: 224 (M^+); HRMS: calcd for $C_{14}H_{12}N_2O$: 224.0950, found: 224.0964.

*4.4.14. N-(4-Methoxyphenyl)-2-phenylimidazole (**3ac**).* Obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.82 (s, 3H), 6.90(d, 2H, *J*=8.8 Hz), 7.10 (s, 1H), 7.13 (d, 2H, *J*=8.8 Hz), 7.22–7.26 (m, 4H), 7.39–7.42 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 55.4, 114.5, 123.1, 127.0, 128.1, 128.05, 128.08, 128.7, 130.3, 131.5, 146.7, 159.2; LRMS (EI) *m*/*z*: 250 (M^+); HRMS: calcd for $C_{16}H_{14}N_2O$: 250.1106, found: 250.1102.

*4.4.15. N-(4-Methoxyphenyl)-4-methylimidazole (**3ad-1**).*[14] *and N-(4-methoxyphenyl)-5-methylimidazole (**3ad-2**)* Obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.13 (s, 1.2H), 2.29 (s, 1.8H), 3.84 (s, 1.8H), 3.86 (s, 1.2H), 6.88 (s, 0.4H), 6.92 (s, 0.6H), 6.97 (d, 1.2H *J*=9.0 Hz), 6.99 (d, 0.8H, *J*=9.2 Hz), 7.20 (d, 0.8H,

J=9.2 Hz), 7.27 (d, 1.2H, J=9.0 Hz), 7.52 (s, 0.4H), 7.65 (d, J=1.4 Hz, 0.6H); LRMS (EI) m/z: 188 (M^+).

*4.4.16. N-(4-Methoxyphenyl)pyrazole (**3ae**).*[19] Obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.84 (s, 3H), 6.43 (t, 1H, J=1.9 Hz), 6.97 (d, 2H, J=9.0 Hz), 7.59 (d, 2H, J=9.0 Hz), 7.69 (d, 1H, J=1.9 Hz), 7.82 (d, 1H, J=1.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/TMS) δ (ppm): 55.5, 107.1, 114.5, 120.9, 126.8, 134.0, 140.6, 158.2; LRMS (EI) m/z: 174 (M^+); HRMS: calcd for $C_{10}H_{10}N_2O$: 174.0793, found: 174.0809.

4.4.17. Recovery and reuse of F-PEG. According to the procedure in Section 4.4.3, the reaction of **1a** with **2a** in the presence of F-PEG was carried out. After the reaction was complete, Et_2O (5 mL) was added to the reaction mixture and the organic layer was washed with H_2O (5 mL×5). The combined aqueous layer was evaporated to remove H_2O and the residue was purified by short path SiO_2 column chromatography using $CHCl_3$ to give F-PEG (96% recovery). The recovered F-PEG was subjected to the same coupling, which resulted in the successful formation of the coupling product **3aa** in 78% yield.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.042.

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