Green Chemistry

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COMMUNICATION

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Although iron catalyzed cross-coupling reactions show extraordinary promise in reducing environmental impact of more toxic and scarce transition metals, one of the main challenges is the use of reprotoxic NMP (NMP = N-methylpyrrolidone) as the key ligand to iron in the most successful protocols in this reactivity platform. Herein, we report that non-toxic and sustainable N-butylpyrrolidone (NBP) serves as a highly effective substitute for NMP in iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of aryl chlorides with alkyl Grignard reagents. This challenging alkylation proceeds with organometallics bearing β-hydrogens with efficiency superseding or matching NMP with ample scope and broad functional group tolerance. Appealing applications are demonstrated in the cross-coupling in the presence of sensitive functional groups and the synthesis of several pharmaceutical intermediates, including dual NK1/serotonin inhibitor, fibrinolysis inhibitor and antifungal agent. Considering that the iron/NMP system has emerged as one of the most powerful iron cross-coupling technologies available in both academic and industrial research, we anticipate that this method will be of broad interest.

The development of sustainable protocols in metal-catalyzed cross-coupling is one of the key strategic priorities in modern organic synthesis.[1] In this context, homogenous iron catalysis has emerged as one of the most central avenues to address the challenge of toxicity of platinum group metals as well as to replace the scarce metal catalysts with more sustainable counterparts.[2,3] The natural abundance of iron as the 4th most common element in Earth's crust, its benign safety profile in presence in the living organisms as iron-dependent enzymes and the positive environmental profile rendered iron cross-coupling catalysis a highly attractive reactivity paradigm in organic synthesis.[4–7]

After the pioneering studies by Kochi,[8] the major breakthrough was achieved by Fürstner and co-workers, who demonstrated that homogenous iron/NMP system is highly effective for the historically challenging cross-coupling reactions of alkyl Grignard reagents with aryl chlorides.[9] The studies by the groups of Nakamura, Jacobi von Wangelin, Knochel, Garg, Bedford, Byers, Noël and others have provided much needed impetus to advance the efficiency of cross-coupling protocols using sustainable iron catalysis.[10,11] Out of several ligand systems developed, including phosphines, N-heterocyclic carbenes, β-diketiminates, diimines, salen-type ligands, bis-oxazolines, amines, heterocycles and amides, by far the most successful is the iron/NMP system developed by Fürstner.[9,10] The extraordinary practical utility of the iron/NMP cross-coupling system has been highlighted in numerous applications in both academic and industrial research, including the synthesis of APIs such as calcimimetic, antihypertensive, antidepressant, anti-inflammatory and antifibrinolytic agents, often proceeding on multikilogram scale.[3n] Despite the overwhelming success of the iron/NMP catalysis platform, the key challenge has been the reprotoxicity of NMP, which is currently classified as a "substance of very high concern" by the EChA and there are impending measures to restrict the use of NMP in Europe and in the US by EPA due to its detrimental toxicological properties.[12]

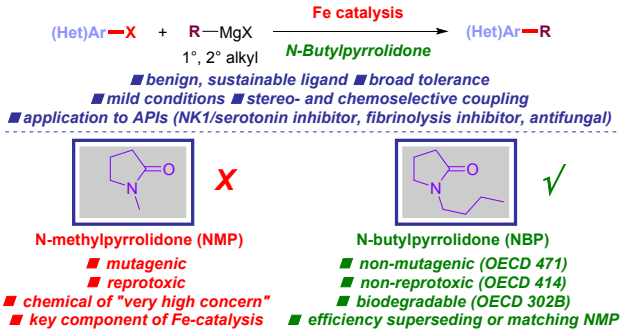

Fig. 1 Fe-catalyzed cross-coupling using N-butylpyrrolidone (NBP) (this study).

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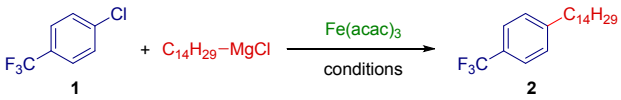
As part of our program on amide bonds,[13] we became interested in the use of O-coordinating ligands to iron as potential replacements to NMP in the iron/NMP catalysis platform.[14] The strong $n_N \rightarrow \pi^*_{C=O}$ conjugation renders amides versatile O-coordinating ligands in transition-metal-catalysis. Herein, we report that non-toxic and sustainable N-butylpyrrolidone (NBP) serves as a highly effective substitute for NMP in iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of aryl chlorides with alkyl Grignard reagents (Fig. 1). Considering that the iron/NMP system has emerged as one of the most powerful iron cross-coupling technologies available to date in both academic and industrial research,[9–11,2,3n] we anticipate that this method will be of broad interest.

The use of N-butylpyrrolidone as a benign solvent has been introduced by Hunt and co-workers in 2016.[15] There is an increasing demand to identify dipolar aprotic solvents that fulfill the criteria of nontoxic and sustainable solvent selection.[16] In this respect, N-butylpyrrolidone (NBP) is non-mutagenic (OECD 471), non-reprotoxic (OECD 414) and inherently biodegradable (OECD 302B), which compares very favorably with the conventional dipolar aprotic solvents, such as NMP, as well as other solvents that are less suitable for iron-catalyzed cross-coupling, including DMF, DMAc, DMSO or sulfolane.[17] In terms of sustainability, the synthesis of NBP from biomass feedstocks has been established. The environmental impact assessment of N-butylpyrrolidone has been made at IV_{TOTAL} of 1.69 \$ L^{-1} (IV_{TOTAL} = total impact value)[18] with favorable bulk price of 10.1 \$ kg^{-1}.[17]

Our study commenced with evaluation of NBP in the iron-catalyzed cross-coupling of 1-chloro-4-(trifluoromethyl) benzene with tetradecylmagnesium chloride at 0 °C (Table 1). This standard assay evaluates the cross-coupling of electronically-activated, non-coordinating electrophile with alkyl nucleophile containing β-hydrogens.[19] As shown, the reaction proceeds in modest 41% yield in the absence of ligand (entry 1). The use of NBP even at 10 mol% loading had a dramatic positive effect on the coupling resulting in 85% yield (entry 2). The evaluation of stoichiometry revealed that the use of 50-200 mol% of NBP gave the best results (entries 4-6). Most importantly, the comparison of NBP vs. NMP as a function of ligand loading revealed that NBP is the preferred ligand as the coupling is more efficient at lower loading (Figure 2). It is worthwhile to note that the standard loading of NMP in the literature is 600 mol%, while the efficient coupling with NMP ensues at 200 mol%.

Next, the substrate scope was evaluated using the iron/NBP catalyst system with a focus on challenging electrophiles that contain sensitive functional groups and are typically not tolerated by iron catalyst systems other than iron/NMP (Table 2).[3,10,11] The yields obtained using iron/NMP at 600 mol% NMP loading are shown in brackets. As such, the cross-coupling of electronically-activated CF_3-containing substrate (entry 1), ester-containing substrate (entry 2), nitrile-containing substrate (entry 3) as well as 1,4-dichlorobenzene (entry 4) proceeded in high yields that either supersede or match the iron/NMP system. It is noteworthy that Grignard addition to the electrophilic cyano and ester groups has not been observed. Moreover, dialkylation of 1,4-dichlorobenzene was not observed. Furthermore cross-coupling of sulfonamide-

Table 1. Optimization of Iron-Catalyzed Cross-Coupling[a]



1 2

entry	$Fe(acac)_3$ (mol%)	ligand	mol%	time	yield (%)[b]
1	5	-	-	10 min	41
2	5	NBP	10	10 min	85
3	5	NBP	20	10 min	93
4	5	NBP	50	10 min	96
5	5	NBP	100	10 min	98
6	5	NBP	200	10 min	98

[a]Conditions: ArCl (0.50 mmol), $Fe(acac)_3$ (5 mol%), THF (0.15 M), $C_{14}H_{29}MgCl$ (1.20 equiv, 1.0 M, THF), 0 °C, 10 min. RMgCl added dropwise over 1-2 s. [b]Determined by ^1H NMR and/or GC-MS. [c]See refs. 9a,b.

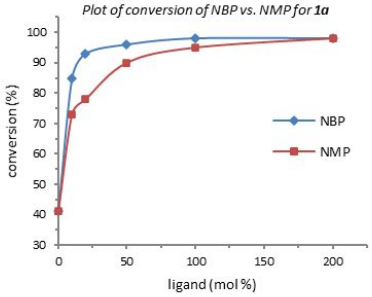


Fig. 2 Plot of conversion NBP vs. NMP for 1a (4-CF_3-C_6H_4-Cl). Conditions: $C_{14}H_{29}MgCl$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand (0-200 mol%), THF, 0 °C, 10 min.

containing arenes is feasible without scission of the sulfonamide bond (entry 5). Finally, heterocycles, such as pyridines (entries 6-7) and quinolines (entry 8) are well-tolerated giving access to valuable alkylated heteroaromatics.

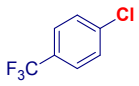
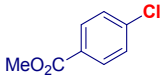
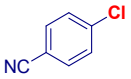
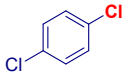
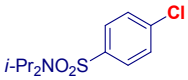
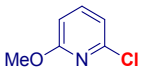
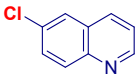
The use of other alkyl Grignard reagents was briefly investigated (Scheme 1). As such, challenging 2° Grignard reagents that are prone to β-hydride elimination, such as cyclohexyl and isopropyl are well-tolerated using the iron/NBP system as is the use of phenethyl Grignard reagents that are poised to elimination to give styrenes.

We were pleased that the protocol could be extended to aryl Grignard reagents, such as the synthesis of 2-arylquinolines (Scheme 2), which are important components of OLEDs.[20]

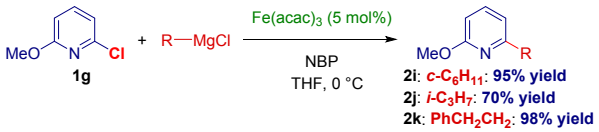
The functional group tolerance of the present system was further tested using aryl chlorides bearing activated amide, sulfonamide and ester as electrophiles (Scheme 3). Anilides, such as **1i** and phenolic esters such as **1k** feature decreased resonance around the C(O)–X bond (isomerization barrier, C–O/C–N, 12-13 kcal/mol) and have recently emerged as acyl C–N and C–O electrophiles in cross-coupling.[21] On the other hand, desulfamoylative coupling by C–S scission is well-known.[22] We were pleased to find the excellent compatibility of the present iron coupling protocol with the sensitive C–N/C–O/C–S functional

groups, which shows complementary nature of the iron catalysis platform to the more common Pd- and Ni-catalyzed strategies in organic synthesis.

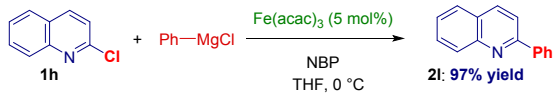
Table 2. Scope of Fe-Catalyzed Cross-Coupling using N-Butylpyrrolidone (NBP) as Ligand[a]

entry	substrate	2	ligand (mol%)	yield (%)
1		**2a**	200	98 (94)
2		**2b**	200	98 (91)
3		**2c**	600	84 (91)
4[b]		**2d**	300	64 (58)
5		**2e**	200	98 (94)
6[c]		**2f**	600	87 (81)
7		**2g**	200	98 (95)
8		**2h**	200	98 (92)

[a]Conditions: ArCl (0.50 mmol), Fe(acac)$_3$ (5 mol%), THF (0.15 M), $C_{14}H_{29}MgCl$ (1.20 equiv, 1.0 M, THF), 0 °C, 10 min. Yield in brackets corresponds to the yield reported using NMP (600 mol%). See, refs. 9a,b. [b]60 min. [c]$C_{14}H_{29}MgCl$ (2.0 equiv), 60 min. See ESI for details.

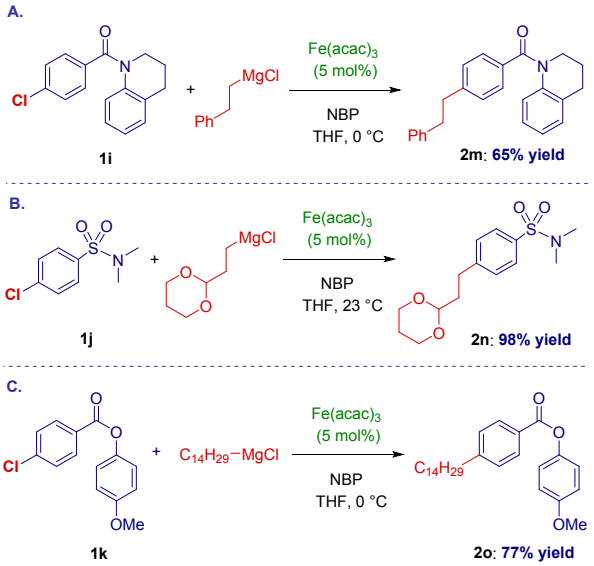


Scheme 1. Cross-coupling of Grignard reagents.

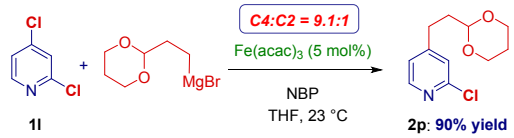


Scheme 2. Cross-coupling of aryl Grignard reagent.

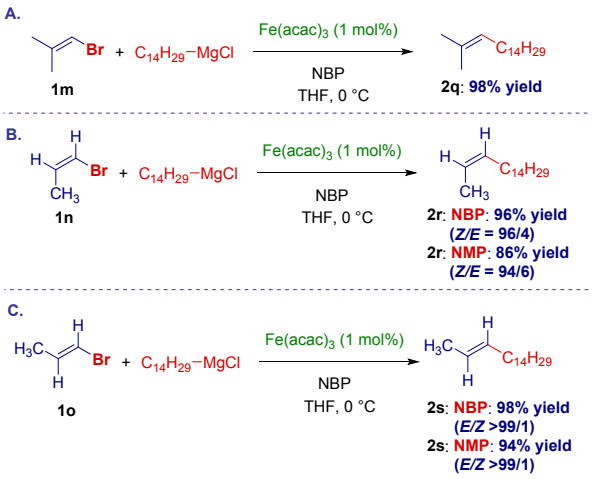
Site-specific coupling using functionalized Grignard reagent is also feasible (Scheme 4). This reaction differentiates between C2 and C4 positions of the pyridine ring presumably on the basis of steric hindrance at C2. Interestingly, the regioselectivity using iron/NBP (C4:C2 = 9.1:1) supersedes this observed using the iron/NMP system (C4:C2 = 4.8:1).[23]



Scheme 3. Cross-coupling of in the presence of (A) activated amide; (B) sulfonamide; (C) activated ester.



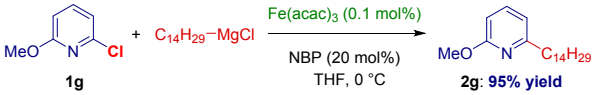
Scheme 4. Site-specific cross-coupling.



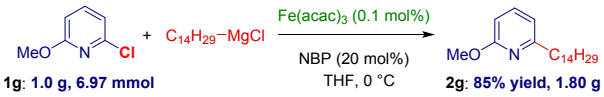
Scheme 5. Stereospecific cross-coupling.

We were further interested to test the cross-coupling of vinyl halides (Scheme 5). In a representative example to cross-couple a challenging 1,1-disubstituted alkenyl bromide, the iron/NBP system afforded the product in quantitative yield (Scheme 5A). Furthermore, the potential for olefin isomerization was investigated using Z- and E-alkenyl bromide (Scheme 5B-C). The reactions proceeded with retention of the olefin geometry, consistent with stereospecific coupling.[24]

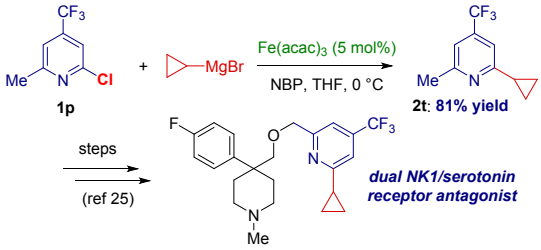
Having demonstrated the high efficiency of the iron/NBP system, we were delighted to find that the cross-coupling at the low catalyst loading (0.1 mol%) is also feasible (Scheme 6).[14g] As expected, the reactions using iron/amide systems are easily scalable and this is possible even at low catalyst loading (Scheme 7).



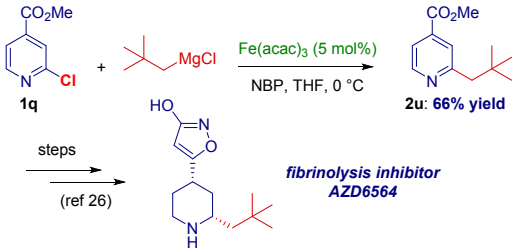
Scheme 6. Cross-coupling at low catalyst loading.



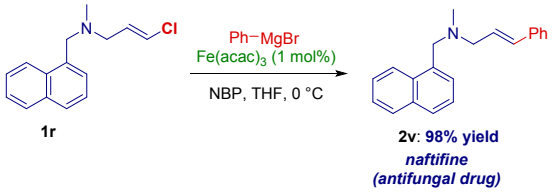
Scheme 7. Gram scale cross-coupling at low catalyst loading.



Scheme 8. Key cross-coupling in the synthesis of a dual NK1/ serotonin receptor antagonist.



Scheme 9. Key cross-coupling in the synthesis of a fibrinolysis inhibitor, AZD6564.



Scheme 10. Key cross-coupling in the synthesis of naftifine.

Several additional points should be noted: (1) aryl triflates and aryl tosylates are suitable coupling partners under the reaction conditions (4-CF_3-C_6H_4-OTf: 85% yield; 4-CF_3-C_6H_4-OTs: 90% yield); (2) we have obtained x-ray structure of one the cross-coupling products confirming the linear connectivity of alkylated arenes (CCDC 2101109, **2e**, Chart 1); (3) the conditions using NBP as the solvent in the absence of THF result in lower yield; (4) vinyl Grignard reagents are not compatible with the reaction conditions; (5) in general low catalyst loading can be used with activated heterocyclic substrates, while we recommend that for less activated substrates standard loading is used.[14g] Mechanistically, previous studies have shown that *O*-coordinating ligands form catalytically active octahedral complexes of iron(II).[11h,i] We hypothesize that NBP could form similar complexes of iron. Future work will be focused on expansion of the reaction scope and exploring the variation of N-pyrrolidine ligands. These studies will be reported in due course.

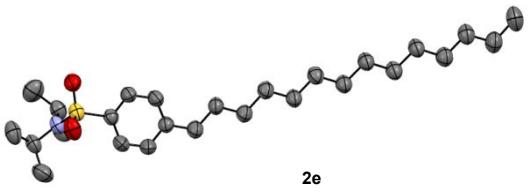
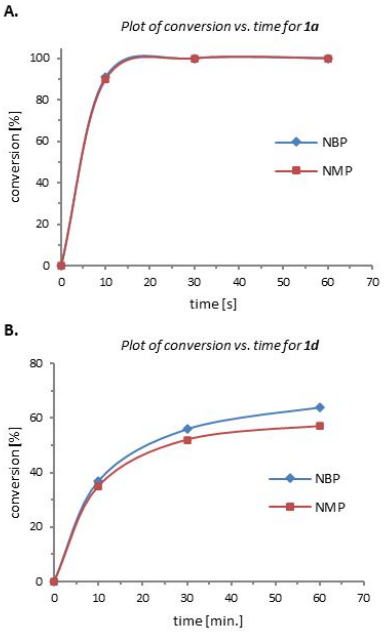


Chart 1 X-ray structure of **2e**. 50% ellipsoids. Hydrogen atoms are omitted for clarify. CCDC 2101109.

It is worthwhile to point out that low price of the ligand and scalability of the iron/NMP system are among the key advantages of this system over other iron-catalyzed cross-coupling protocols, which has enabled broad industrial applications.[3n]

To further highlight the potential practical applications of the iron/NBP system we applied this protocol to the synthesis of APIs. As shown, we were able to effect this alkyl C(sp^2)–C(sp^3) cross-coupling in the synthesis of a key intermediate of NK1/serotonin receptor agonist using cyclopropyl magnesium bromide (Scheme 8),[25] fibrinolysis inhibitor using sterically-hindered neopentyl magnesium chloride (Scheme 9),[26] and arylmagnesium bromide in the synthesis of naftifine, an antifungal agent (Scheme 10).[27] These successful processes demonstrate attractive applications of iron-catalyzed cross-coupling in medicinal chemistry that might be difficult to effect using other methods.



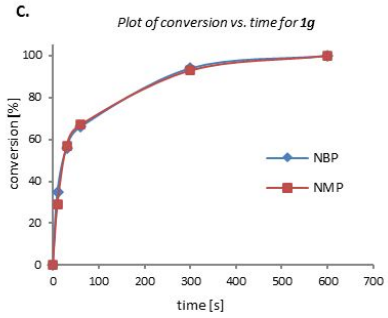


Fig. 3 Kinetic profiles. (A) **1a** (1-chloro-4-(trifluoromethyl)benzene). Conditions: *n*-$C_{14}H_{29}$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand (200 mol%), THF (0.15 M), 0 °C. (B) **1d** (1,4-dichlorobenzene). Conditions: *n*-$C_{14}H_{29}$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand (300 mol%), THF (0.15 M), 0 °C. (C) **1g** (2-chloro-6-methoxypyridine). Conditions: *n*-$C_{14}H_{29}$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand (200 mol%), THF (0.15 M), 0 °C.

Finally, kinetic studies were conducted to gain preliminary insight into the relative reaction rates using iron/NBP vs. iron/NMP systems (Fig. 3). For this study, we selected electronically-differentiated electrophiles, including 1-chloro-4-(trifluoromethyl) benzene, 1,4-dichlorobenzene and 2-chloro-6-methoxypyridine. As shown, the use of NBP matches (Fig. 3A and 3C) or supersedes (Fig. 3B) the reactivity rates using NMP in this catalytic system.

In summary, the iron/NMP system represents the most successful iron catalyst cross-coupling platform developed to date, which has been strategically employed in a plethora of cross-coupling processes in both academic and industrial projects. In contrast to benign and sustainable iron, the main limitation of this system is the use of reprotoxic NMP, which is already subject to regulatory guidelines. In this communication, we have discovered that non-toxic and sustainable N-butylpyrrolidone (NBP) serves as a highly effective substitute for NMP in iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling of aryl chlorides with alkyl Grignard reagents. Crucially, the catalytic system shows broad functional group tolerance, efficiency and selectivity that supersedes or matches the classical iron/NMP system. The system is readily available for reactions using sensitive functional groups that are beyond other Fe-catalyzed systems for cross-coupling. Other noteworthy features include ease of scale-up and applications in the synthesis of APIs. We believe that iron/NBP should be routinely utilized as a substitute for iron/NMP in cross-coupling protocols. Further studies on the mechanism and applications of iron-catalyzed cross-coupling are ongoing in our laboratory and will be reported in due course.

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