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To be cited as: *ChemCatChem* 10.1002/cctc.201802032

Link to VoR: http://dx.doi.org/10.1002/cctc.201802032

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10.1002/cctc.201802032

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N-Methylcaprolactam as a Dipolar Aprotic Solvent for Iron-Catalyzed Cross-Coupling Reactions: Matching Efficiency with Safer Reaction Media

Elwira Bisz,*[a] Pamela Podchorodecka[a] and Michal Szostak*[a,b]

Abstract: *Although iron-catalysis provides a powerful alternative to the more conventional palladium and nickel in the cross-coupling arena, the major limitation is the necessity for carcinogenic N-methylpyrrolidone as a co-solvent in the vast majority of catalytic reactions. Herein, we introduce N-methylcaprolactam as an efficient, non-toxic and practical dipolar aprotic solvent for iron-catalyzed C(sp^2)–C(sp^3) alkylative cross-coupling of aryl chlorides and tosylates. The utility of this method is reflected by its wide substrate scope, high yields and capacity to cross-couple challenging alkyl organometallics prone to β-hydride elimination and homocoupling. Considering the broad utility of iron-catalyzed cross-coupling, we envision that N-methylcaprolactam will find wide application as a substitute for carcinogenic NMP.*

Iron-catalysis has emerged as the dominant direction in cross-coupling methods catalyzed by sustainable metals.[1–3] Following the early studies,[4] iron-catalysis has evolved to be among the most useful cross-coupling methods routinely applied in large-scale pharmaceutical manufacturing,[5] a feat that is still elusive for other base metals, including nickel.[6]

Despite tremendous progress in the field, iron-catalyzed cross-coupling reactions typically employ carcinogenic NMP (NMP = N-methylpyrrolidinone) as a co-solvent.[7,8] The use of N-methylpyrrolidinone is especially pervasive in iron-catalyzed C(sp^2)–C(sp^3) alkylative cross-coupling, which owing to mild conditions and broad functional group tolerance have proven indispensable in the preparation of complex architectures in the synthesis of bioactive molecules.[5,9–11] The toxicity of NMP has sparked the development of new alterative solvents for organic synthesis.[12,13] In the present context, the potential of N-methyl-caprolactam as a greener, non-toxic alternative solvent to NMP in organic synthesis is the focus of a recent patent by BASF.[14]

Stimulated by the growing potential of iron-catalyzed cross-coupling and serious toxicological concerns over NMP,[7,8] here, we report N-methyl-caprolactam as an efficient, non-toxic and practical substitute for NMP in iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of aryl chlorides and tosylates (Figure 1). In contrast to NMP, N-methylcaprolactam (N-Me-CPL) is not mutagenic or reprotoxic.[14] According to the ECHA (European Chemicals Agency), N-methylcaprolactam is classified at the same level of hazard category as ε-caprolactam, which is in sharp contrast to N-methylpyrrolidinone, which is a “substance of very high concern” and may “damage fertility or the unborn child.” [15]

As a product of N-alkylation of ε-caprolactam, one of the most popular precursors for the production of plastics and fibers via ring-opening polymerization, N-Me-CPL is cheap and available in large quantities.[16] Processes for the production of N-Me-CPL from ε-caprolactam on the industrial scale have been well-established, notably by cheap and sustainable alkylation with MeOH over acidic clay or alumina-based catalysts.[17]

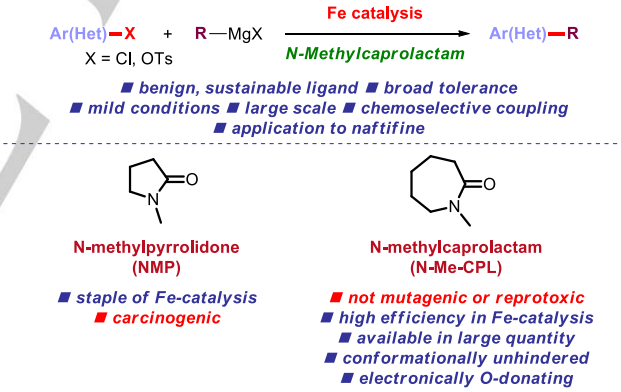

Figure 1. Fe-catalyzed cross-coupling using N-methylcaprolactam (this study).

Herein, we demonstrate that N-methyl-caprolactam is a new co-solvent for iron-catalyzed cross-coupling reactions that retains many characteristics of NMP. Specifically, (1) through examination of a series of challenging alkylation reactions using organometallics prone to β-hydride elimination,[18] we demonstrate that N-methyl-caprolactam results in comparable or higher yields than those obtained using reprotoxic N-methyl-pyrrolidone. (2) The method shows excellent functional group tolerance, including electrophilic functional groups that are incompatible with other Fe/ligand catalysts.[19] (3) The practical utility has been highlighted in the synthesis of naftifine, a best-selling antifungal drug. [20] Altogether, the study demonstrates N-Me-CPL as a highly effective green solvent alternative in iron-catalyzed cross-coupling reactions.

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Our study began by examining the reactivity of 1-chloro-4-(trifluoromethyl)benzene with tetradecyl magnesium chloride as our model system (Table 1). In this reaction, the 4-CF_3-containing substrate serves as an electronically-activated, non-coordinating arene. In the absence of co-solvent, the reaction is inefficient (entry 1), affording homocoupling, reduction and β-hydride elimination as the major products. We were pleased to find that under optimized conditions as little as 50 mol% of N-Me-CPL afforded a significant improvement in the cross-coupling (entries 2-4). There is a linear correlation between the quantity of N-Me-CPL used and the reaction efficiency (entries 2-7, Figure 2). Typically, 200 mol% of N-Me-CPL suffices to achieve close to quantitative conversions (entry 6). For comparison, the reaction using reprotoxic NMP (600 mol%) afforded the coupling product in 94% yield (entry 8). The efficiency of N-Me-CPL supersedes the reactivity of cyclic urea ligands[11a] despite much lower NIp to C=O donicity,[21] while the broad availability and low toxicity of caprolactam[14–17] afford the key practical advantages.

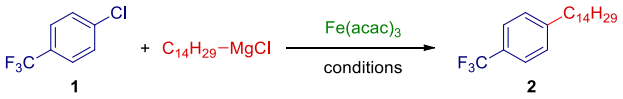
With the optimized conditions in hand, we next examined the scope and generality of this method (Table 2). We were pleased to find that N-methylcaprolactam serves as an effective ligand to iron in a series of challenging cross-couplings, including substrates bearing sensitive electrophilic functional groups, such as ester (entry 2), nitrile (entry 3), halide (entry 4), and sulfonamide (entry 5). Furthermore, various N-heterocycles, including simple (entry 6) and electronically-deactivated pyridine (entry 7) as well as quinoline (entry 8) afforded the coupling products in high yields. It is worthwhile to note that β-hydride elimination from the challenging organometallic[18] was not observed. Importantly, the efficiency of cross-coupling using N-methylcaprolactam was found to be higher or comparable than when using toxic N-methyl-pyrrolidone (entries 1-8, brackets).

Pleasingly, the reaction of a tosyl electrophile afforded the cross-coupling product with high C–O coupling selectivity (Scheme 1), demonstrating that after suitable O-activation phenols can be used as alternative electrophile sources to aryl chlorides in this cross-coupling.[1k]

A brief examination of alkyl Grignard nucleophiles was conducted (Scheme 2). Most importantly, challenging secondary Grignard reagents, such as cyclohexyl and isopropyl, are suitable nucleophiles for this coupling. Isomerization to the linear Grignard reagent was not observed, which is the major side reaction in Fe/NHC-catalysis.[19] Moreover, electronically-activated towards β-hydride elimination, phenethyl Grignard underwent smooth coupling, demonstrating another benefit of this mild cross-coupling using benign N-methylcaprolactam as a ligand.

The cross-coupling using N-methylcaprolactam could be readily performed on a gram scale to deliver the coupling product without modification of the reaction conditions (Scheme 3), attesting to the scalability of the method.

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

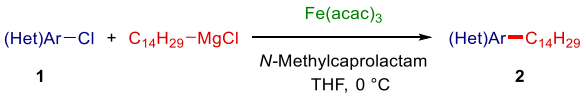


1 2

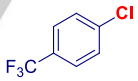
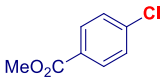
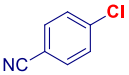
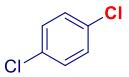
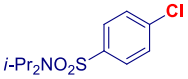
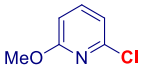
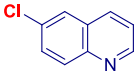
entry	$Fe(acac)_3$ (mol%)	ligand	mol%	time	yield (%)[b]
1	5	-	-	10 min	41
2	5	*N*-Methylcaprolactam	10	10 min	56
3	5	*N*-Methylcaprolactam	20	10 min	65
4	5	*N*-Methylcaprolactam	50	10 min	77
5	5	*N*-Methylcaprolactam	100	10 min	88
6	5	*N*-Methylcaprolactam	200	10 min	96
7	5	*N*-Methylcaprolactam	600	10 min	>98
8[c]	5	*N*-Methylpyrrolidone	600	10 min	94

[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.

Table 2. Scope of Fe-Catalyzed Cross-Coupling using N-Methylcaprolactam (N-Me-CPL) as Ligand[a]



1 2

entry	substrate	2	ligand (mol%)	yield (%)
1		**2a**	600	98 (94)
2		**2b**	200	96 (91)
3		**2c**	600	93 (91)
4[b]		**2d**	600	48 (58)
5		**2e**	200	98 (94)
6[c]		**2f**	600	89 (81)
7		**2g**	200	93 (95)
8		**2h**	200	95 (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 SI for details.

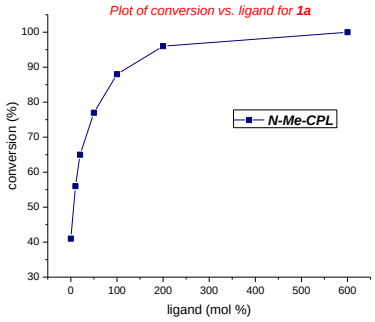


Figure 2. Plot of conversion vs. ligand for **1a** (4-CF_3-C_6H_4-Cl). Conditions: *n*-$C_{14}H_{29}$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand, THF, 0 °C.

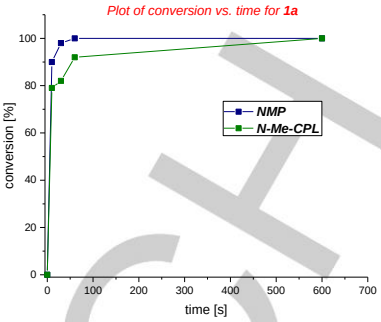
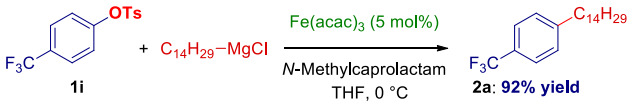
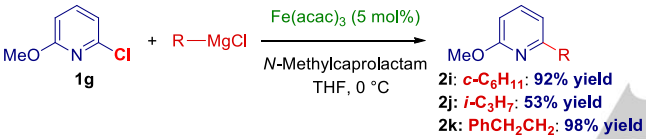


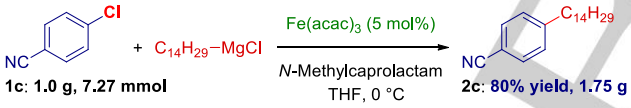
Figure 3. Kinetic profile of **1a** (4-CF_3-C_6H_4-Cl). Conditions: *n*-$C_{14}H_{29}$ (1.20 equiv), $Fe(acac)_3$ (5 mol%), ligand (200 mol%), THF (0.15 M), 0 °C.



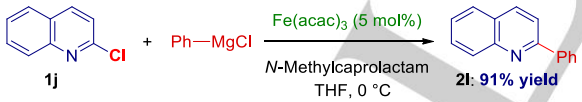
Scheme 1. Aryl tosylate $C(sp^2)$–$C(sp^3)$ cross-coupling.



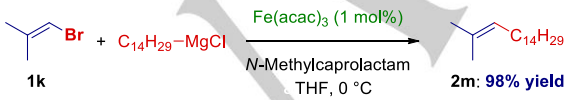
Scheme 2. Cross-coupling of Grignard reagents.



Scheme 3. Large scale cross-coupling.

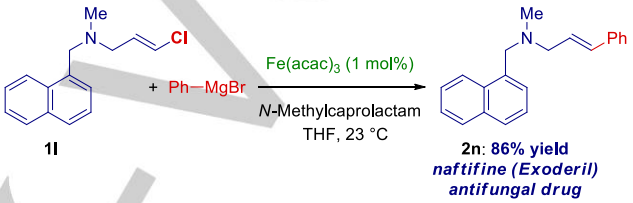


Scheme 4. Cross-coupling of aryl Grignard.



Scheme 5. Cross-coupling of alkenyl halide.

Importantly, this benign cross-coupling method is not limited to $C(sp^2)$–$C(sp^3)$ disconnection as demonstrated in the $C(sp^2)$–$C(sp^2)$ biaryl coupling to afford 2-phenylquinoline with high reaction efficiency (Scheme 4).



Scheme 6. Synthesis of naftifine (Exoderil).

The practical utility was further highlighted in the alkenyl–alkyl cross-coupling of a model alkenyl bromide selected for comparison with the Fe/NMP-catalyzed cross-coupling (Scheme 5). 1,1-Disubstitued olefins are particularly challenging substrates for iron-catalyzed alkenylation of Grignard nucleophiles,[22] which demonstrates a significant potential of N-methylcaprolactam for organic synthesis.

Finally, to highlight the practical value of this method, we have demonstrated a short synthesis of naftifine, a best-selling antifungal drug (Scheme 6).[20] The use of a benign ligand N-methylcaprolactam presents a key advantage from the environmental and operational standpoints.[23]

To gain insight into the efficiency of N-Me-CPL, preliminary kinetic studies were conducted (Figure 3). Pleasingly, these investigations revealed similar kinetics to Fe-NMP, attesting to the high reactivity of the iron/N-Me-CPL catalyst system.

In summary, we have reported N-methylcaprolactam as an efficient, non-toxic and practical substitute for N-methyl-pyrrolidone in iron-catalyzed cross-coupling reactions of aryl chlorides and tosylates. N-methyl-caprolactam is available in large commercial quantities, is not mutagenic or reprotoxic, and has been shown to promote iron-catalyzed cross-couplings in yields higher or comparable to NMP. The practical value has been demonstrated in the cross-coupling of a broad range of electrophiles bearing sensitive functional groups using challenging alkyl organometallics prone to β-hydride elimination. Furthermore, this benign method has been showcased in the synthesis of a pharmaceutical agent. Considering the broad utility of iron-

catalyzed cross-coupling, notably, in pharmaceutical and natural product research, this study offers a new option to synthesize biologically-active compounds in a green manner, matching or superseding the previous-state-of-art method using co-solvent with unfavourable toxicological and environmental profile. Further studies on the development of green ligands for iron-catalyzed cross-couplings and reaction conditions for coupling of additional classes of substrates are ongoing in our laboratory and these results will be reported in due course. Given the broad utility of iron-catalyzed cross-couplings in modern organic synthesis, structural modifications of O-coordinating ligands offer new vistas to improve the efficiency and safety profile of this important catalysis manifold.

Acknowledgements

We gratefully acknowledge Narodowe Centrum Nauki (grant no. 2014/15/D/ST5/02731, E.B., M.S.), Rutgers University (M.S.) and the NSF (CAREER CHE-1650766, M.S.) for generous financial support.

Keywords: iron catalysis • cross-coupling • sustainability • green solvents • catalysis

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10.1002/cctc.201802032

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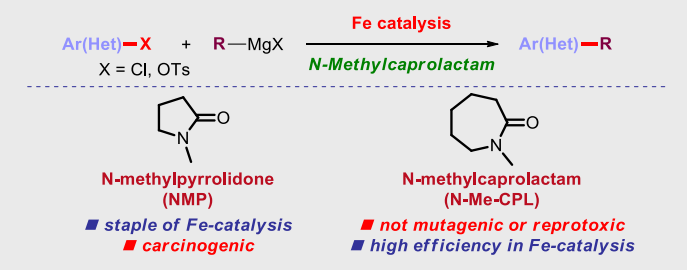

N-Methylcaprolactam as a Dipolar Aprotic Solvent for Iron-Catalyzed Cross-Coupling Reactions: Matching Efficiency with Safer Reaction Media

Elwira Bisz, Pamela Podchorodecka, Michal Szostak**

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Herein, we introduce N-methyl-caprolactam as an efficient, non-toxic and practical dipolar aprotic solvent for iron-catalyzed C(sp^2)–C(sp^3) alkylative cross-coupling. The utility of this method is reflected by its wide substrate scope, high yields and capacity to cross-couple challenging alkyl organometallics.

Keywords: iron catalysis, cross-coupling, sustainability, green solvents, catalysis