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Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Chlorobenzamides with Alkyl Grignard Reagents: Development of Catalyst System, Synthetic Scope, and Application

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Abstract. Direct preparation of alkylated amide-derivatives by cross-coupling chemistry using sustainable protocols is challenging due to sensitivity of the amide functional group to reaction conditions. Herein, we report the synthesis of alkyl-substituted amides by iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of Grignard reagents with aryl chlorides. The products of these reactions are broadly used in the synthesis of pharmaceuticals, agrochemicals and other biologically-active molecules. Furthermore, amides are used as versatile intermediates that can participate in the synthesis of valuable ketones and amines, providing access to motifs of broad synthetic interest. The reaction is characterized by its good substrate scope, tolerating a range of amide substitution, including sterically-bulky, sensitive and readily modifiable amides. The reaction is compatible with challenging organometallics possessing β-hydrogens, and proceeds under very mild, operationally-simple conditions. Optimization of the catalyst system demonstrated the beneficial effect of O-coordinating ligands on the cross-coupling. The reaction was found to be fully chemoselective for the mono-substitution at the less sterically-hindered position. Mechanistic studies establish the order of reactivity and provide insight into the role of amide to control mono-selectivity of the alkylation. The protocol provides the possibility for convenient access to alkyl-amide structural building blocks using sustainable cross-coupling conditions with high efficiency.

Keywords: iron catalysis; cross-coupling; amides; alkylation; sustainability; C(sp^2)–C(sp^3) Kumada coupling

Introduction

Aromatic amides are among the most important and prevalent building blocks in organic synthesis.[1–3] Alkyl-substituted amides and derivatives are extensively used in the synthesis of pharmaceuticals, agrochemicals and other biologically-active molecules.[4] Furthermore, amides are commonly used as versatile intermediates that can participate in the synthesis of valuable ketones and amines, providing access to motifs of broad synthetic interest.[3] As a consequence, new methods for the synthesis of functionalized amides and their analogues have a major impact on the development of many pharmaceuticals, bioactive products and fine chemicals.[4] The recent emergence of N–C amide cross-coupling methods, wherein the amide bond can be utilized as a synthetic acyl- or aryl equivalent, offers additional opportunities in the capacity of amides as versatile synthetic building blocks.[5]

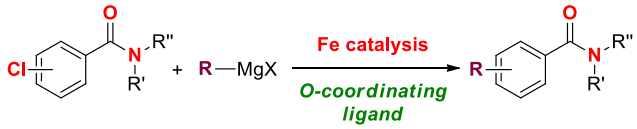
The recent remarkable advances in homogeneous iron-catalysis allow for mild, chemoselective access to a wide array of C–C bond forming processes that have found numerous applications in natural product synthesis, drug discovery and organic materials.[6–8] The increasing importance of sustainable methods in modern cross-coupling chemistry has in particular spurred the development of cost-effective protocols using earth-abundant, sustainable iron catalysis.[9] In this regard, cross-couplings using cheap and readily available Grignard reagents offer unique mechanistic opportunities to traditional protocols catalyzed by precious metals.[10–12] However, the use of amides in Kumada cross-cross coupling reactions is rare, most likely due to sensitivity of the amide functional group to reaction conditions.[13]

As part of our interest in iron catalysis and functionalization of amides by selective cross-coupling reactions,[14] herein, we report the synthesis of alkyl-substituted amides by iron-catalyzed C(sp^2)–C(sp^3) cross-coupling of Grignard reagents with aryl chlorides (Scheme 1).

The significance of the manuscript is as follows: (1) this full paper demonstrates and investigates the synthesis of alkylated benzamides. These derivatives are among the most important compounds in organic synthesis with applications ranging from pharmaceuticals to organic materials owing to the presence of the amide bond; (2) the manuscript, through product manipulations, shows the utility of the alkylated products to produce other important compounds that (i) are inaccessible from other

functional groups, including esters, (ii) thus far have been prepared by much longer, more costly and less sustainable synthetic routes. This clearly places the subject into the broader scientific context and demonstrates how the method can be productively utilized by scientists in other fields.

The reaction is characterized by its good substrate scope, tolerating a range of amide substitution, including sterically-bulky, sensitive and readily modifiable amides. The reaction proceeds under very mild, operationally-simple conditions and is compatible with challenging organometallics possessing β-hydrogens.[15] Through optimization, we demonstrate the beneficial effect of O-coordinating ligands on the cross-coupling. Intriguingly, we demonstrate that the reaction is fully chemoselective for the mono-substitution at the less sterically-hindered position. Through mechanistic studies, we establish the order of reactivity and provide insight into the key role of amide to control mono-selectivity of the alkylation. Finally, we demonstrate the potential of this amide alkylation method to provide direct access to functionalized amide, ketone and amine building blocks. This protocol provides convenient access to alkyl-amide structural building blocks using sustainable cross-coupling conditions with high efficiency.



[■ high value functionalized alkyl amides] [■ up to 97% yield]
[■ practical & mild conditions] [■ challenging alkyl nucleophiles]
[■ sustainable iron catalysis, broad scope] [■ high selectivity]

Scheme 1. Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Amides with Alkyl Grignard Reagents.

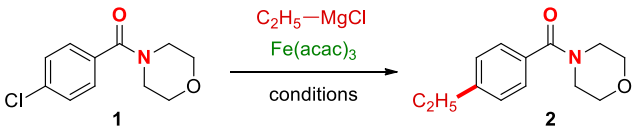
Results and Discussion

Optimization. Morpholinyl amide was selected as a substrate for optimization studies (Table 1). While it is well-established that amidic resonance in morpholinyl amides is in the range expected for planar amides ($PhCON(CH_2CH_2)_2O$, RE = 19.6 kcal/mol, RE = resonance energy),[16] these amides (1) are more sensitive to organometallic reagents due to chelate formation with the morpholinyl oxygen, and (2) are further useful in organic synthesis due to Weinreb amide-type reactivity.[17]

At the outset, control reactions were conducted to determine the effect of uncatalyzed background process (Table 1). As shown, alkylation at the C4 position was not observed in the absence of the iron catalyst under both rapid and slow addition protocols (entries 1-2) (*vide infra*). Under these conditions, 7-10% of the alkyl ketone product was formed, consistent with the high capacity of the morpholinyl amide to undergo nucleophilic acyl-type addition with Grignard reagents.[17] Furthermore, control reactions in the presence of iron under ligandless conditions delivered the cross-coupling product in a promising but unsatisfactory yield (entries 3-5).

Seminal studies by Fürstner and co-workers established the potential of iron-catalyzed aryl–alkyl C(sp^2)–C(sp^3) cross-coupling based on NMP (NMP = N-methyl-2-pyrrolidone).[6a,b,7,11a,b, 21e] At present, this catalytic system represents the catalyst of choice for the vast majority of iron-catalyzed cross-couplings in both academic and industrial settings.[18] Mechanistic studies showed that NMP forms O-coordinated catalytically active octahedral complexes of iron(II).[19,20] We were delighted to find that addition of NMP delivered the C4-alkylated product in excellent 92% yield (Table 2, entry 1). Importantly, under these conditions, the formation of ketone, dehalogenated and homocoupling products was not observed (<2%), consistent with the efficient stabilization of the active low-valent iron species by NMP. Further optimization revealed that temperature had a significant effect on the reaction (entry 2).

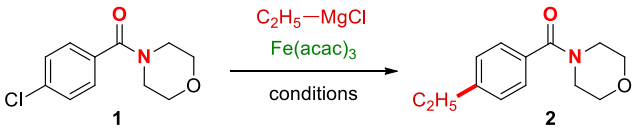
Table 1. Optimization of Fe-Catalyzed Cross-Coupling: Control Reactions.[a]



Entry	$Fe(acac)_3$ [mol%]	Ligand	*T* [°C]	Time [min]	Yield [%][b]
1	-	-	0	10	<2
2	-	-	23	3.5	<2
3	5	-	0	10	55
4	1	-	0	60	56
5	1	-	23	3.5	54

[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (1-5 mol%), THF (0.15 M), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), *T*, 3.5-60 min. Entries 1 and 3: RMgCl added dropwise over 1-2 s; Entries 2 and 4-5: RMgCl added 0.10 mmol/30 s. [b]Determined by ^1H NMR and/or GC-MS.

Table 2. Optimization of Fe-Catalyzed Cross-Coupling: Iron–NMP Catalytic System.[a]



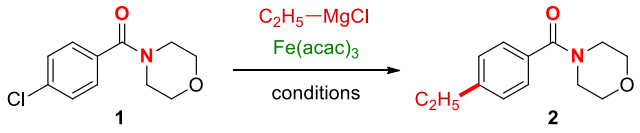
Entry	$Fe(acac)_3$ [mol%]	Ligand	*T* [°C]	Time [min]	Yield [%][b]
1	5	NMP	0	10	92
2	5	NMP	23	10	78
3	1	NMP	0	10	91
4	0.1	NMP	0	10	88
5[c]	1	NMP	0	10	84

[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (0.1-5 mol%), THF (0.15 M), NMP (600 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), *T*, 10 min. RMgCl added dropwise over 1-2 s. [b]Determined by ^1H NMR and/or GC-MS. [c]NMP (10 mol%).

Moreover, the catalyst loading could be decreased to 1.0% (entry 3) and even 0.1% (entry 4) with a minimal impact on the reaction efficiency. Finally, the reaction with low NMP loading (entry 5) afforded the desired product in high yield. Overall, these results demonstrate that iron-NMP catalyst is highly reactive for the coupling, and the by-products are not formed under these conditions.

Further optimization studies were conducted using bidentate TMEDA (TMEDA = N,N,N',N'-tetramethylethylenediamine) as a ligand to iron (Table 3). Fox and co-workers elegantly demonstrated that TMEDA serves as an efficient ligand in iron-catalysis;[21] however, these reactions are less convenient due to sequential addition protocol. Nevertheless, considering the importance of alkylated amide derivatives in organic synthesis, we were interested to fully examine the effect of the reaction conditions using iron-TMEDA catalysis.

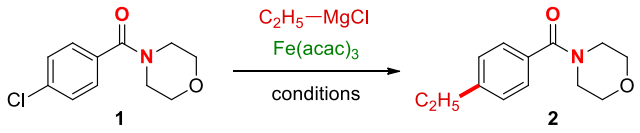
Table 3. Optimization of Fe-Catalyzed Cross-Coupling: Iron–TMEDA Catalytic System.[a]



Entry	$Fe(acac)_3$ [mol%]	Ligand	*T* [°C]	Time [min]	Yield [%][b]
1	1	TMEDA	23	3.5	90
2	1	TMEDA	0	3.5	89
3	1	TMEDA	-78	3.5	38
4[c]	1	TMEDA	23	1	73
5[d]	1	TMEDA	23	3.5	77
6[e]	1	TMEDA	23	3.5	81
7[f]	1	TMEDA	23	3.5	82
8[g]	1	TMEDA	23	3.5	80
9	5	TMEDA	23	3.5	60
10	0.1	TMEDA	23	3.5	85

[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (0.1-5 mol%), THF (0.15 M), TMEDA (10 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), *T*, 1-3.5 min. RMgCl added 0.10 mmol/30 s. [b]Determined by ^1H NMR and/or GC-MS. [c] RMgCl added dropwise over 1-2 s. [d]TMEDA (50 mol%). [e]TMEDA (20 mol%). [f]TMEDA (5 mol%). [g]TMEDA (1 mol%).

Table 4. Optimization of Fe-Catalyzed Cross-Coupling: Effect of Ligands.[a]

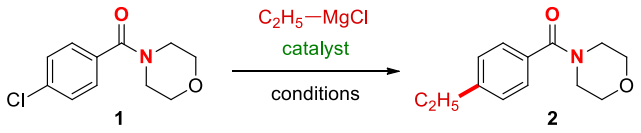


Entry	$Fe(acac)_3$ [mol%]	Ligand	*T* [°C]	Time [min]	Yield [%][b]
1	1	Et_3N	23	3.5	65
2	1	HMTA	23	3.5	67
3	1	DIPA	23	3.5	42
4	1	DABCO	23	3.5	84
5	1	isoquinoline	23	3.5	69
6	1	quinoline	23	3.5	84
7	1	styrene	23	3.5	51
8	1	SIPr	23	3.5	78
9	1	IMes	23	3.5	74
10	1	PPh_3	23	3.5	62

[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (1 mol%), THF (0.15 M), ligand (10 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), *T*, 3.5 min. RMgCl added 0.10 mmol/30 s. [b]Determined by ^1H NMR and/or GC-MS.

As shown in Table 3, the reaction conducted with TMEDA as a ligand (entry 1) generated the desired coupling product in excellent 90% yield with minor quantities of ketone and dehalogenation side-products. The temperature (entries 2-3) and the slow addition protocol (entry 4) had a major effect on the reaction efficiency. Furthermore, the reaction was found to be quite sensitive to the amount of TMEDA (entries 5-8) and iron (entry 9) used. Finally, the catalyst loading could be decreased to 0.1%, while maintaining high activity (entry 10). Collectively, the optimization studies with iron-TMEDA demonstrate that TMEDA can be used as a ligand in this cross-coupling; however, the protocol is less appealing due to the necessity for slow addition.

Table 5. Optimization of Fe-Catalyzed Cross-Coupling: Additional Optimization.[a]



Entry	Catalyst [mol%]	Ligand	*T* [°C]	Time [min]	Yield [%][b]
1[c]	1	TMEDA	23	3.5	92
2[c]	5	NMP	0	10	91
3[d]	5	DMPU	0	10	93
4[e]	5	DMI	0	10	92
5[f]	1	TMEDA	23	3.5	<2
6[f]	5	NMP	0	10	<2

[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (1-5 mol%), THF (0.15 M), ligand (10-600 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), *T*, 3.5-10 min. Entries 1 and 5: RMgCl added 0.10 mmol/30 s; Entries 2-4 and 6: RMgCl added dropwise over 1-2 s. TMEDA (10 mol%); NMP, DMPU, DMI (600 mol%). [b]Determined by ^1H NMR and/or GC-MS. [c]2-MeTHF instead of THF. [d]DMPU instead of NMP. [e]DMI instead of NMP. [f]$Co(acac)_3$ instead of $Fe(acac)_3$.

Subsequently, we evaluated the effect of different ligands on the cross-coupling (Table 4). Previous studies have demonstrated the viability of various N-, C- and P-based ligands in iron-catalyzed cross-coupling reactions.[6,7,11,12] In the event, in a screen of amine-based ligands we found that while Et_3N (entry 1), HMTA (HMTA = hexamethylenetetramine) (entry 2) and DIPA (DIPA = diisopropylamine) (entry 3) did not promote the desired coupling efficiently, DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane) was identified as a potentially suitable ligand (entry 4). This reactivity

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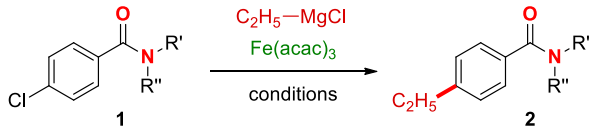
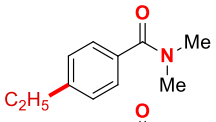
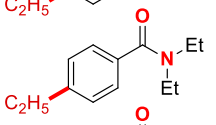
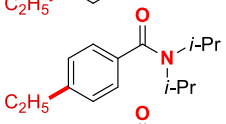
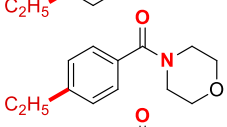
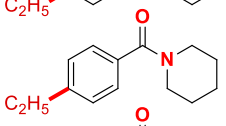
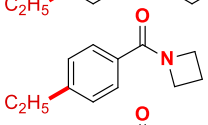
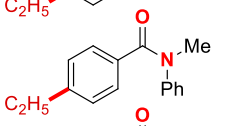
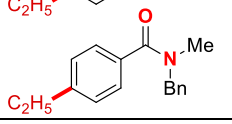
Table 6. Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Amides with Alkyl Grignard Reagents.[a]



1 2

Entry	Product	2	Ligand	Yield [%]
1		**2a**	NMP	91
2		**2a**	TMEDA	92
3		**2b**	NMP	93
4		**2b**	TMEDA	89
5		**2c**	NMP	86
6		**2c**	TMEDA	57
7		**2d**	NMP	89
8		**2d**	TMEDA	90
9		**2e**	NMP	90
10		**2e**	TMEDA	88
11		**2f**	NMP	71
12		**2f**	TMEDA	83
13		**2g**	NMP	94
14		**2g**	TMEDA	87
15		**2h**	NMP	96
16		**2h**	TMEDA	93

[a]Conditions: Iron–NMP: **1** (0.50 mmol), $Fe(acac)_3$ (5 mol%), THF (0.15 M), NMP (600 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), 0 °C, 10 min. RMgCl added dropwise over 1-2 s. Iron–TMEDA: **1** (0.50 mmol), $Fe(acac)_3$ (1 mol%), THF (0.15 M), TMEDA (10 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), 23 °C, 3.5 min. RMgCl added 0.10 mmol/30 s. See SI for details.

could be rationalized by steric interaction with the low-valent iron species. Moreover, comparison of isoquinoline (entry 5) and quinoline (entry 6) proved the latter to be more efficient. Electron-deficient ligand, styrene, (entry 7) had no effect on the coupling efficiency. Interestingly, strongly σ-donating NHC (NHC = N-heterocyclic carbene) ligands (entries 8-9) did not furnish the desired product in improved yields. Similarly, PPh_3 (entry 10) was found to have a negligible effect on the coupling. Overall, the studies with different ligands emphasize the high efficiency of NMP as the preferred ligand to iron in this coupling.

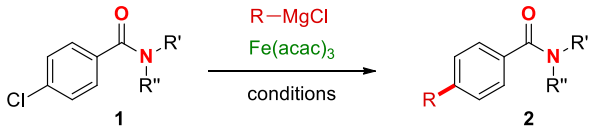
Additional optimization studies were conducted (Table 5). First, the coupling could be conducted in a sustainable solvent, 2-MeTHF, with no detectable decrease in the reaction efficiency (entries 1-2). This finding further establishes the potential of 2-MeTHF as a highly suitable, renewable solvent for iron-catalyzed cross-coupling reactions.[22] Next, we were pleased to find that urea ligands, DMPU and DMI (DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, DMI = 1,3-dimethyl-2-imidazolidinone), afforded the coupling product with efficiency comparable to NMP (entries 3-4). This reactivity further demonstrates the prospect of fine-tuning of benign O-coordinating ligands in iron-catalysis.[23] Finally, control reactions using Co instead of Fe (entries 5-6) demonstrate the essential catalytic role of iron.[24] In these cases, the Co catalyst did not promote any conversion to the desired product, and only dehalogenation was observed as a major side reaction.[25]

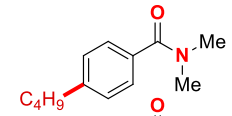
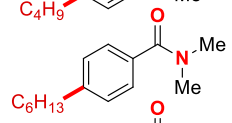
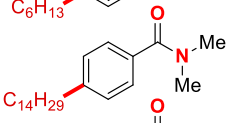
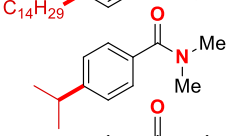
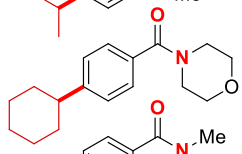
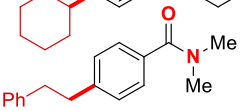
Scope Studies. With optimized conditions in hand, we next explored the scope of this iron-catalyzed alkylation (Table 6). In particular, we were interested to define the range of sterically- and electronically-differentiated amides that could participate in this cross-coupling protocol. These reactions were routinely conducted using both iron-NMP and iron-TMEDA reagent systems for comparison purposes. As shown in Table 6, the reaction tolerates a wide range of amides, including simple (entries 1-4) as well as extremely sterically-hindered amides (entry 5-6). The broad applicability is further demonstrated by coupling of cyclic amides, including the morpholinyl amide and common piperidinyl amide (entries 7-10) (*vide infra*). Furthermore, sensitive azetidinyl amide was found to be a good substrate for this coupling (entries 11-12) despite high ring strain and propensity for C-cleavage. Importantly, the high efficiency of the coupling in this case provides an alternative approach to ketone synthesis by stable tetrahedral intermediates of azetidinyl amides.[26] Moreover, we were pleased to find that activated amides, such as anilides, which are effective precursors for metal-catalyzed N–C cross-coupling[5] due to lower amidic resonance (PhCONMePh, RE = 13.5 kcal/mol),[27] coupled with high reaction selectivity (entries 13-14). Finally, cross-coupling of N-benzyl amide was well-tolerated under standard conditions (entries 15-16). These amides provide rapid access to secondary amides after N-Bn hydrogenolysis.[28] While both catalytic systems, namely iron-NMP and iron-TMEDA, performed efficiently with the exception of a sterically-hindered N,N-*i*-Pr_2 amide, the former system is vastly preferred due to operational simplicity of the coupling. Overall, the scope of the amide component in this coupling is broad and bodes well for an array of synthetic applications.

Next, we sought to define the scope of the alkyl coupling partner. Mechanistically, the cross-coupling with alkyl Grignard reagents is challenging due to slow transmetalation as well as competing β-hydride elimination and dimerization processes.[11,15] We were pleased to find that the coupling was compatible with various 1° and 2° alkyl Grignard reagents (Table 7), including long-chain 1° Grignard reagents (entries 2-

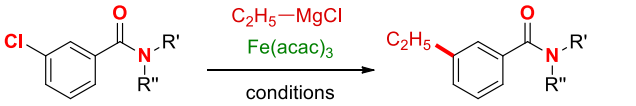
10.1002/adsc.201800849

Table 7. Iron-Catalyzed $C(sp^2)$–$C(sp^3)$ Cross-Coupling of Amides with Alkyl Grignard Reagents.[a]

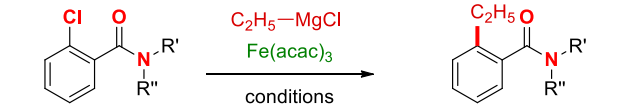


Entry	Product	2	Ligand	Yield [%]
1		**2i**	NMP	94
2		**2j**	NMP	93 (93)[b]
3		**2k**	NMP	94
4		**2l**	NMP	53
5		**2m**	NMP	93
6		**2n**	NMP	62

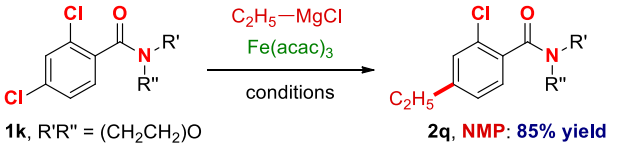
[a]Conditions: **1** (0.50 mmol), $Fe(acac)_3$ (5 mol%), THF (0.15 M), NMP (600 mol%), C_2H_5MgCl (1.20 equiv, 2.0 M, THF), 0 °C, 10 min. RMgCl added dropwise over 1-2 s. [b] Yield using *n*-Hex-MgBr. See SI for details.



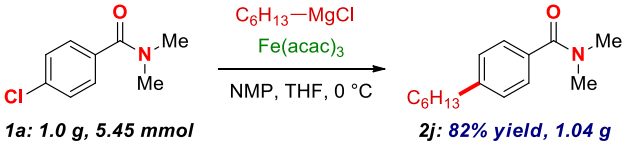
Scheme 2. Cross-Coupling of meta-Substituted Amides.



Scheme 3. Cross-Coupling of ortho-Substituted Amides.



Scheme 4. Chemoselective Mono-Cross-Coupling.



Scheme 5. Large Scale Cross-Coupling.

3), more-sterically congested 2° alkyl Grignard reagents (entries 4-5), and activated Grignard reagents prone to β-hydride elimination (entry 6). Of note, isomerization of *i*-Pr to *n*-Pr was not observed under the reaction conditions (entry 4), attesting to the mild nature of this catalytic system (cf. iron-NHC). Moreover, both alkyl-magnesium chlorides and alkyl-magnesium bromides could be utilized with similar high levels of efficiency (entry 3), which is in contrast to several other iron-catalyzed cross-coupling protocols.[6f]

Furthermore, we were delighted to find that cross-coupling at the meta-position is also feasible (Scheme 2). This reactivity pattern delivers valuable meta-alkyl-substituted amide derivatives and is not reliant on the conjugation with the amide carbonyl. As expected, the reaction underscores the high efficiency of NMP as a ligand to iron (cf. TMEDA). Intriguingly, full substrate recovery of the ortho-substituted amide was observed under the developed reaction conditions (Scheme 3). This is likely due to rigidity of the six substituents comprising the amide bond due to resonance,[1,16] which prevents oxidative addition at the sterically-hindered position. Accordingly, we hypothesized that selective mono-alkylation at the less sterically-hindered position could be achieved using this mild protocol. In the event, excellent selectivity was observed in the coupling of the 2,4-disubstituted precursor (Scheme 4).[29] The product 4-alkyl-2-chloro-benzamides are common intermediates in the synthesis of pharmaceuticals (*vide infra*).

Cross-coupling of other halide precursors was evaluated using our model morpholinyl amide (not shown). We found that the 4-bromo analogue gave low yield of the desired product (TMEDA: 36% yield; NMP: 13% yield), while the 4-fluoro analogue gave little to no conversion (TMEDA: 13%; NMP: <2%). Thus, the use of cheap and readily available aryl chlorides is another advantage of this protocol.

The scalability of this sustainable iron-catalyzed cross-coupling method was evaluated. The alkylation of a model N,N-Me_2 amide could be conveniently carried out on a gram scale and afforded the desired product in 82% isolated yield (Scheme 5), attesting to the synthetic utility of the method.

Limitations of the current cross-coupling method are presented in Figure 1. We note that the method does not work with alkyl-Grignard reagents that cannot promote the formation of low-valent iron species, including MeMgBr. Furthermore, the method is chemoselective for benzamide substrates in that aliphatic amides are recovered unchanged from the cross-coupling conditions. In general, we focused on benzamide substrates because these substrates are not

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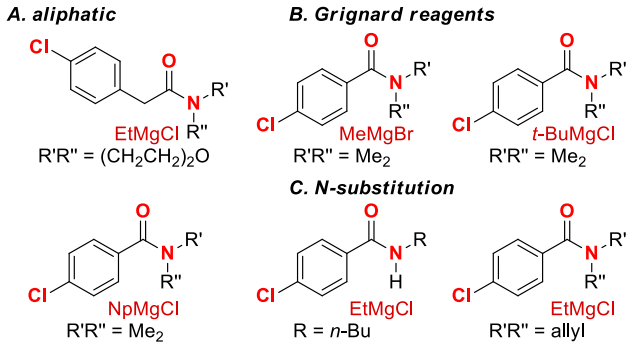
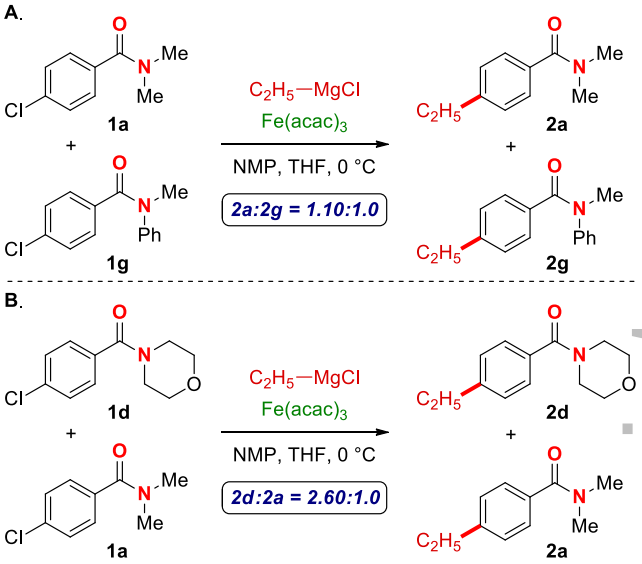


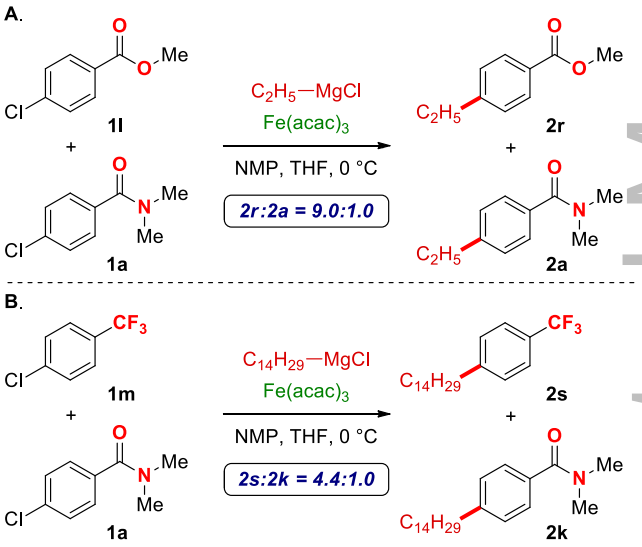
Figure 1. Limitations of the Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling of Amides with Alkyl Grignard Reagents. Note that the reactants are shown below the structures of starting materials. Np = neopentyl.

activated and therefore best suited for examination of the reaction scope and limitations. Heteroaromatic and polyaromatic substrates are well-known to be activated in iron-catalyzed cross-couplings. Studies to address the cross-coupling of heteroaromatic and polyaromatic substrates as well as conjugated amides are currently ongoing. Likewise, future studies will address the use of functionalized Grignard reagents in this and related iron-catalyzed cross-couplings. Studies to address the current limitations of iron-catalysis in cross-coupling of substrates containing polar functional groups are currently underway in our laboratories.

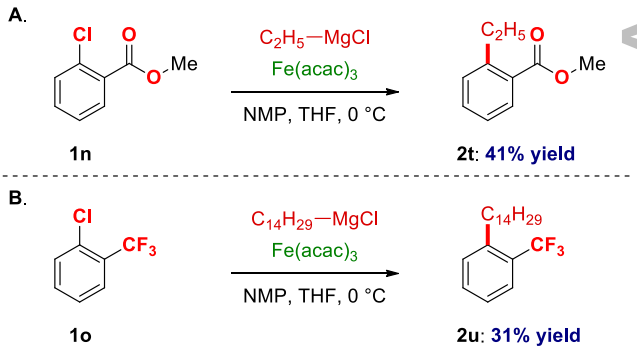
Mechanistic Studies. Considering the unique features of this iron-catalyzed alkylation method, several studies were performed to gain insight into the reaction mechanism. The well-established kinetic analysis by intermolecular competition experiments was used to determine relative reactivity rates.[30] First, intermolecular competition studies established that the electronic nature of the amide bond does not affect the reactivity (N,N-Me_2:N,N-Ph/Me = 1.10:1.00, Scheme 6A), despite a significant difference in resonance stabilization of the amide bond. Second, morpholinyl amides were found to be inherently more reactive (N,N-morpholine:N,N-Me_2 = 2.60:1.00, Scheme 6B). Collectively, this suggests coordination to the amide bond during the reaction by a σ-coordination of the oxygen (cf. π-coordination of the amide bond). Based on relative energetics of the amide bond (RE = 19.6 kcal/mol vs. RE = 13.5 kcal/mol), as measured by resonance energies, morpholinyl amides should not be more reactive than anilides. Moreover, intermolecular competition studies determine that esters (CO_2Me:N,N-Me_2 = 9:1) and trifluoromethyl arenes (CF_3:N,N-Me_2 = 4.4:1) couple preferentially to amides (Scheme 7). This establishes the following order of reactivity of aryl electrophiles in the iron-catalyzed cross-coupling: ester > CF_3 > amide, and is broadly consistent with electronic stabilization of the aromatic ring.[31] Finally, control experiments with ortho-substituted ester and trifluoromethyl electrophiles demonstrate that these substrates undergo cross-coupling under the developed reaction conditions (Scheme 8), indicating a key role of amide bond conformation to control to alkylation mono-selectivity. Overall, the mechanistic studies emphasize the role of chelation and amide rigidity in this iron-catalyzed alkylation of amides. Further studies on the mechanism are ongoing.



Scheme 6. Intermolecular Competition Experiments: Amides.

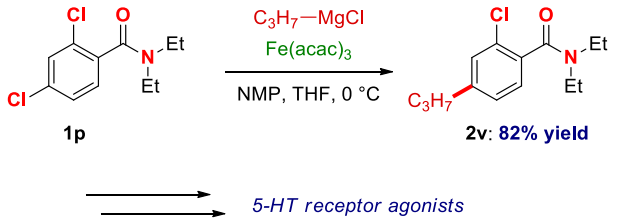


Scheme 7. Intermolecular Competition Experiments: Esters and Trifluoromethyl Arenes.

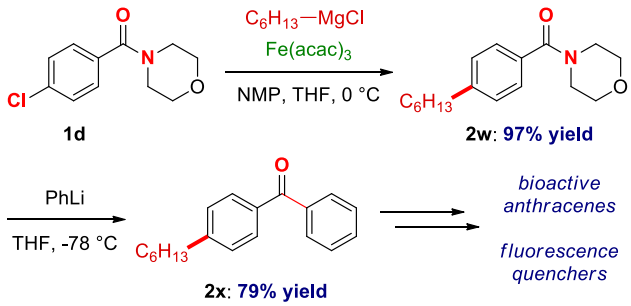


Scheme 8. Cross-Coupling of ortho-Substituted Esters and Trifluoromethyl Arenes.

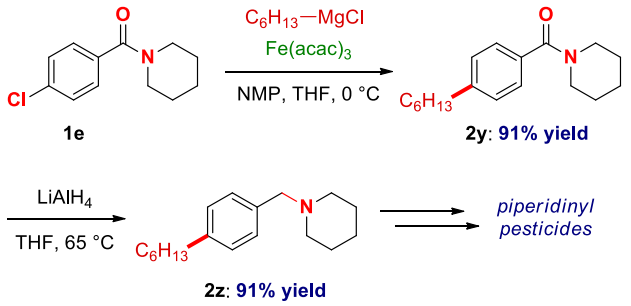
Application. As noted in the introduction, the alkylated amide products obtained in this process are valuable intermediates extensively used in the synthesis of pharmaceuticals, agrochemicals and functional materials. To demonstrate the versatility of the amide products, we conducted a series of transformations (Schemes 9-11).



Scheme 9. Synthesis of 5-HT Receptor Agonists.



Scheme 10. Synthesis of Functionalized Ketones via Iron-Catalyzed Cross-Coupling/Weinreb-Amide-Type Addition.



Scheme 11. Synthesis of Functionalized Amines via Iron-Catalyzed Cross-Coupling/Reduction.

First, the selective mono-alkylation provides direct access to chloro-containing alkyl-amide building blocks that have been broadly utilized in the pharmaceutical industry. For example, iron-catalyzed *n*-propylation affords the corresponding N,N-diethylamide derivative, which has been employed as an intermediate in the synthesis of 5-HT receptor agonists (Scheme 9).[32] The traditional route involves the Pd-catalyzed Stille coupling of the more expensive 4-Br-derivative, clearly establishing advantage of the iron-catalyzed method. Second, the facility of cross-coupling of morpholinyl amides in the current protocol offers a unique access to alkyl-aryl ketones by exploiting the Weinreb amide-type reactivity of the alkylated products. For example, iron-catalyzed cross-coupling of *n*-hexyl group followed by phenyllithium addition affords a functionalized diaryl ketone that has been used as an intermediate in the synthesis of biologically-active anthracene derivatives (Scheme 10).[33] Moreover, similar hydrophobic ketones are broadly used as fluorescence quenchers.[34] Finally, iron-catalyzed alkylation/reduction of a piperidinyl amide furnishes benzyl piperidines, which are used as pesticides and drug pharmacophores (Scheme 11).[35] Overall, the presented reactions highlight the potential of this amide alkylation method to provide direct access to functionalized molecules of broad synthetic interest.

Conclusions

In summary, we have reported the synthesis of alkyl-substituted amides by iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling of Grignard reagents with aryl chlorides. The reaction occurs in high yield, under very mild, operationally-simple conditions, and provides valuable alkyl-amide products, which have useful applications in the synthesis of pharmaceuticals, agrochemicals and functional materials. This sustainable, iron-catalyzed alkylation method is characterized by a broad scope, tolerating a wide range of amides, including sterically-bulky, sensitive and readily modifiable amides. The reaction is compatible with challenging organometallics possessing β-hydrogens. We have further demonstrated the advantage of using O-coordinating ligands in iron-catalyzed cross-coupling, which allows for the rapid addition of Grignard reagents during the process. The reaction was successfully applied to the synthesis of functionalized amide, ketone and amine building blocks, illustrating broad applicability of this approach. Mechanistic and control experiments outlined the reactivity trends in iron-catalyzed cross-coupling and clearly indicated the key importance of the amide bond to control chemoselectivity of the substitution at the less sterically-hindered position. The subtle effect of the morpholinyl amide uncovered in this study provides further evidence for chelation as an effective method in iron-catalyzed cross-coupling. This mild protocol is practical, sustainable and cost-effective. Given the importance of functionalized amides in organic synthesis, we anticipate that this process will find wide application. Further work to expand the scope to other substrates and base metal catalysts are ongoing and these studies will be reported in due course.

Experimental Section

General Information. General methods have been published.[23]

Materials. Iron(III) acetylacetonate (CAS: 14024-18-1) was purchased from Sigma-Aldrich (cat. no. F300, 97%) and used as received. Cobalt(III) acetylacetonate (CAS: 21679-46-9) was purchased from Sigma-Aldrich (cat. no.

494534, 99.99%). All Grignard reagents were purchased from Sigma-Aldrich and titrated prior to use.[36]

Note regarding the rate of addition and definition of "dropwise addition." It is well-established that the rate of addition of the Grignard reagent may be critical to the outcome of iron-catalyzed cross-couplings. For the purpose of developing methods that are highly operationally-convenient, we prefer the rapid addition protocol using NMP as a ligand. In this protocol, the Grignard reagent is added rapidly in one-shot to the reaction mixture. We also recognize that in some cases "slow addition protocol" may be preferred. In the case of TMEDA as a ligand, the Grignard reagent is added at a rate of 0.10 mmol every 30 s. In some protocols, the use of slow-addition syringe pump protocol is preferred. We recommend that screening of the rate of addition of the Grignard reagent is included during the optimization of iron-catalyzed cross-coupling reactions to expedite reaction development.

General Procedure for Iron-Catalyzed Cross-Coupling using NMP as a Ligand. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, typically, 0.50 mmol, 1.0 equiv) and $Fe(acac)_3$ (typically, 5 mol%), placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under vacuum. THF (0.15 M) and ligand were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of Grignard reagent (typically, 1.2 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for the indicated time at 0 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 *N*, 1.0 mL) and Et_2O (1 x 30 mL), the organic layer was extracted with HCl (1.0 *N*, 2 x 10 mL), dried and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure for Iron-Catalyzed $C(sp^2)$–$C(sp^3)$ Cross-Coupling. 1.0 g Scale. An oven-dried, two-necked flask (250 mL) equipped with a stir bar was charged with 4-chloro-*N*,*N*-dimethylbenzamide (1.00 g, 5.45 mmol, 1.0 equiv) and $Fe(acac)_3$ (96.2 mg, 0.27 mmol, 5 mol%). THF (0.35 M) and ligand (600 mol%) were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of *n*-$C_6H_{13}MgCl$ (2.0 M in THF, 3.27 mL, 1.20 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for 10 min at 0 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 *N*, 3 mL) and Et_2O (1 x 100 mL), the organic layer was extracted with HCl (1.0 *N*, 2 x 10 mL), dried and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product; 82% (1.04 g).

Acknowledgements

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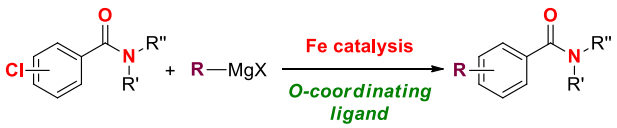

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