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Iron/Tetramethylethylenediamine-Catalyzed Ambient-Temperature Coupling of Alkyl Grignard Reagents and Aryl Chlorides

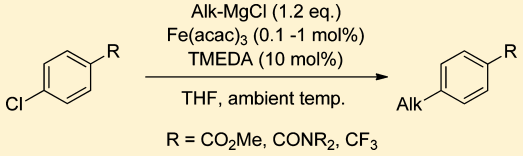
Philip J. Rushworth,[†] David G. Hulcoop,[‡] and David J. Fox*[,†]

[†]Department of Chemistry, University of Warwick, Coventry CV4 7AL, U.K.

[‡]Research and Development, GlaxoSmithKline, Gunnelswood Road, Stevenage SG1 2NY, U.K.

Supporting Information

ABSTRACT: Tetramethylethylenediamine (TMEDA) acts as cheap and readily removed ligand in the iron-catalyzed coupling of alkyl Grignard reagents and activated aryl chlorides. The use of TMEDA allows for low ligand and iron catalyst loading as well as an increased reaction concentration and an ambient reaction temperature on a mole scale.



More than 60% of carbon−carbon bond-forming reactions performed currently in medicinal chemistry are catalyzed by palladium species.[1] However, these reactions often require the addition of costly and structurally complex ligands, and the palladium species often present toxicity and price issues. Following the seminal publication by Kochi in 1971,[2] in which he described C−C bond formation between a vinyl halide and an alkyl Grignard reagent, the field of iron-catalyzed cross-coupling reactions has garnered considerable attention as an alternative to these palladium-catalyzed cross-coupling reactions, especially over the past decade.[3] As well as being considerably cheaper, less toxic, and more abundant than many transition metals, iron complexes are being increasingly used in a wide range of applications in catalysis, including drug and natural product syntheses.[3i,4] A number of catalyst and ligand systems have been reported for the coupling reaction between a carbon−halogen bond and a Grignard reagent. In 1998, Cahiez and co-workers demonstrated that by employing 1-methyl-2-pyrollidinone (NMP) as a cosolvent, the equivalents of the vinyl halide coupling partner could be dramatically reduced from those reported[4d] while maintaining high yields.[5] The discovery that the same cosolvent could be used to similarly improve the reactions of aryl chlorides and triflates with alkylmagnesium halides was subsequently published by Fürstner et al.[6] Interestingly, the coupling of chloroheterocycles does not always require NMP as a cosolvent.[6,7] These reaction conditions are tolerant of a variety of substrates with excellent selectivities and yields. However, NMP is a less-than-desirable reagent, because of the issues associated with both its removal from the products and its status as a possible reproductive toxin.[8] For the "reverse" reaction, i.e., that of an alkyl halide and an aryl Grignard reagent, the use of 1.2 equiv of tetramethylethylenediamine (TMEDA) gave good yields of the coupled product.[9] It has also been reported that substoichiometric quantities (10 mol %) of TMEDA can be used, either alone[10] or with hexamethylenetetraamine (HMTA),[11] while still giving excellent yields.[11] However, these conditions have not been applied to functionalized substrates or tested in the reaction of an aryl chloride and an alkyl Grignard reagent. More recently, the use of N-heterocyclic carbene (NHC)-type ligands has been reported for the cross-coupling of both aryl halides with aryl Grignard reagents[12] and phenol derivatives (aryl tosylates, sulfamates, or carbamates) with alkyl Grignard reagents.[13] These reactions require conditions more forcing than those previously described (long reaction times and high temperatures) and are again limited to relatively unfunctionalized substrates. Herein, we describe our initial results in the pursuit of a broad-spectrum catalyst/ligand system for carbon−carbon bond formation by cross-coupling of a carbon−halogen functionality with a Grignard reagent.

Initial investigations for the comparison of the variety of catalytic systems were based upon a model reaction. $Fe(acac)_3$ was selected as a cheap, readily available, and relatively nonhydroscopic source of iron. It has been proposed that Fe(III) salts are reduced to lower-oxidation state active catalysts by Grignard reagents.[2,6,11,14] Fürstner reports excellent yields from the reaction of methyl 4-chlorobenzoate **1** and alkyl Grignard reagents (>95%; ligand, 600 mol % NMP) using 5 mol % $Fe(acac)_3$.[6] With readily available starting materials, this was selected as our model substrate in the coupling reaction with ethylmagnesium chloride (Table 1).

Initially, five ligand combinations were screened at 0 °C, along with the reaction with no ligand, all with 5 mol % $Fe(acac)_3$ (Table 1, entries 1−8). As expected, Fürstner's conditions using NMP gave excellent results, with complete conversion of starting material to clean coupled product **2** with no impurities apart from NMP visible by ^{1}H NMR spectrometry (entries 2 and 3). The use of amine-based chelating ligands also gave good results (entries 4−7), with 50 mol % TMEDA giving the highest level of conversion. The NHC precursor ligand SIPr-HCl gave the lowest level of conversion of the reactions that included ligands (entry 8), but this value was still significantly higher than that of the reaction with no ligand (entry 1). In all of these reactions, the only

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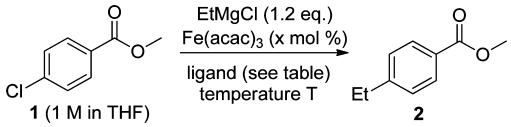
Table 1. Optimization of the Synthesis of Ester 2

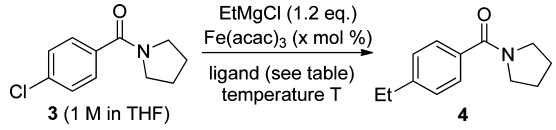


entry	$Fe(acac)_3$ (mol %)	ligand (mol %)	T (°C)	conversion (% by NMR)
1	5	none	0	55
2	5	NMP (600)	0	>99
3	5	NMP (300)	0	93
4	5	TMEDA (50)	0	76
5	5	TMEDA (10)	0	75
6	5	HMTA (5)	0	66
7	5	TMEDA (10)/ HMTA (5)	0	70
8	5	SIPr-HCl (15)	0	60
9	5	NMP (300)	20	88
10	5	TMEDA (10)	20	>99
11	5	TMEDA (10)/ HMTA (5)	20	93
12	2	TMEDA (10)	20	>99
13	1	TMEDA (10)	20	>99
14	0.1	TMEDA (10)	20	18

materials visible in the NMR spectra were the coupled product, residual starting material, and, in the case of Fürstner's conditions, residual NMP, with no discernible carbonyl addition products from the reaction of the Grignard reagent with the ester functionality. These results also demonstrate that the high levels of NMP loading used by Fürstner are necessary for complete conversion (entries 2 and 3). However, when the level of TMEDA was decreased from 50 to 10 mol %, there was no significant decrease in the level of conversion (entries 4 and 5). Many of the reported literature reactions are performed at low temperatures (≤0 °C). It would be preferable to perform these reactions at ambient temperature, especially if the reactions are to be performed on a larger scale. Pleasingly, the three best results from the initial screen gave comparable results when the reactions were performed at 20 °C, and in the cases of the amine-based ligands, the levels of conversion were significantly improved (entries 9−11) to the point where the use of TMEDA at 10 mol % gave complete conversion (>99%) with an 85% isolated yield (entry 10). While $Fe(acac)_3$ is not reported to be hygroscopic, it was noted that upon drying of the catalyst under vacuum, the level of conversion for this reaction (entry 10) increased from 95 to >99%. All of the subsequent reactions were therefore performed with vacuum-dried catalyst. The catalyst loadings typically used for these reactions are relatively high, especially when compared to the initial catalyst loadings of 0.06 mol % reported by Kochi et al.[2] Investigations into the loading of catalyst revealed that when using 10 mol % TMEDA, the loading of catalyst could be significantly reduced to 1 mol %, without any loss of conversion (entries 13 and 14). However, when the reaction was performed with 0.1 mol % $Fe(acac)_3$, the major product recovered (50%) was the tertiary alcohol from double addition at the carbonyl of the ester functionality (entry 14). By way of comparison with the aryl chloride starting material, the equivalent aryl bromide (methyl 4-bromobenzoate) and aryl triflate (methyl 4-trifluoromethylsulfonyloxybenzoate) (not shown) were reacted with EtMgCl using the conditions described for entry 10 [1 mol % $Fe(acac_3)$ and 10 mol % TMEDA at 20 °C]. In these reactions, the levels of conversion to 4-ethylbenzoate ester **2** were significantly lower than for the aryl chloride (99%), with values of 23% for the aryl bromide and 51% for the aryl triflate.

Despite a number of esters that are reported to undergo these coupling reactions, there are few examples in the literature of the application of this chemistry to *p*-chloroamides.[15] We subjected tertiary amide **3** to a similar range of catalyst−ligand combinations and conditions and were pleased to find not only that the reactions were successful but also that the TMEDA ligand gave results comparable to those of NMP for the synthesis of amide **4** (Table 2, entries 1−5).

Table 2. Optimization of the Synthesis of Amide 4



entry	$Fe(acac)_3$ (mol %)	ligand (mol %)	T (°C)	conversion (% by NMR)
1	5	none	0	50
2	5	NMP (600)	0	88
3	5	TMEDA (50)	0	94
4	5	TMEDA (10)	20	87
5	5	TMEDA (10)/ HMTA (5)	0	85
6	2	TMEDA (10)	20	94
7	1	TMEDA (10)	20	96
8	0.1	TMEDA (10)	20	97

The optimized conditions for ester **2** [1 mol % $Fe(acac)_3$ and 10 mol % TMEDA at 20 °C] gave good conversion (entry 4), with no side reactions observed. Because of the less reactive nature of amides toward Grignard reagents, the loading of the iron catalyst could be lowered from 5 to 0.1 mol % (entries 6−8), leading, surprisingly, to a slight increase in the overall level of conversion.

Having defined a robust set of conditions that gave excellent results without the requirement for the use of NMP, we applied the same conditions to some of the other aryl chloride−Grignard reagent combinations (Figure 1). In most cases, levels of conversion were high (>90%) and gave clean products. Lower levels of conversion were seen with phenethyl side chains and the generally less reactive benzotrifluoride system (**12**−**15**). Interestingly, 2-chloropyridine and 4-chlorobenzonitrile (not shown) did not react using TMEDA as a ligand, unlike the case in which NMP is used when yields of up to 91% are reported.[17]

With a view to possible industrial applications of this chemistry, we were interested in the performance of this reaction on scale. We were able to perform the reaction on a much larger scale, successfully coupling 1 mol (210 g) of *N*-(4-chlorobenzoyl)pyrrolidine **3** with ethylmagnesium chloride and 0.1 mol % $Fe(acac)_3$ at 20−30 °C. This was done at a total aryl halide concentration of 0.625 M, a concentration significantly higher than those previously reported. This reaction gave a crude yield of 99% (200.5 g), with ^{1}H NMR spectrometry showing 98% conversion to product **4**.

In conclusion, we have developed a clean, effective ambient-temperature protocol for the coupling of a number of activated aryl chlorides with alkyl Grignard reagents using TMEDA as the ligand and loadings of iron catalyst lower than those

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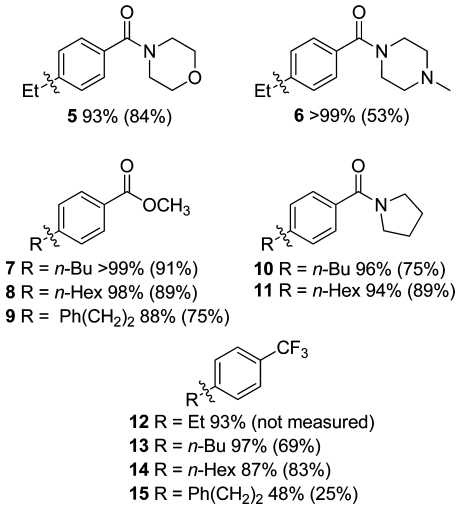

Figure 1. Conversions by ^{1}H NMR (and isolated yields) for the coupling of aryl chlorides with Grignard reagents. Reaction conditions: ArCl (1 mmol), RMgCl in THF (1.2 mmol), TMEDA (0.1 mmol), THF (1 mL), and dried $Fe(acac)_3$ (0.001 mmol for amides and $ArCF_3$ and 0.01 mmol for esters) at 20 °C under N_2.

previously reported. We have also demonstrated that these types of reactions are amenable to scale, increasing the likelihood that this chemistry could be adopted as an alternative to precious metal catalysis in an industrial setting.

EXPERIMENTAL SECTION

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, in $CDCl_3$, and shifts are given relative to Me_4Si. Coupling constants (J) are rounded to the nearest 0.5 Hz. ^{1}H and ^{13}C assignments were based on ^{1}H−^{1}H COSY, HSQC, and HMBC two-dimensional NMR spectra. HRMS measurements were performed on an ion trap spectrometer. All starting materials are commercially available and were used without any further purification. Grignard reagents were titrated before being used versus menthol in THF using 1,10-phenanthroline as an indicator. pH 2 buffer is an aqueous solution (0.25 M H_2SO_4 and 0.75 M Na_2SO_4).

Synthesis of Aryl Chlorides. *Methyl 4-Chlorobenzoate* ***1***. Acetyl chloride (17.77 mL, 0.25 mol) was added to MeOH (100 mL) dropwise at 0 °C. To the resultant solution was added a suspension of 4-chlorobenzoic acid (15.65 g, 0.1 mol) in MeOH (100 mL) dropwise at 0 °C. The reaction mixture was stirred at 65 °C for 16 h. The crude reaction mixture was concentrated *in vacuo* to give the product (15.12 g, 88%) as a white solid: mp 43−44 °C; δ_H (400 MHz, $CDCl_3$) 7.97 [2H, d, J 8.5, 2 × (CO)CC*H*], 7.41 (2H, d, J 8.5, 2 × ClCC*H*), 3.92 (3H, s, CO_2CH_3); δ_C (100 MHz, $CDCl_3$) 166.3 (CO), 139.4 (ClC), 131.0 [(CO)C*C*H], 128.7 (Cl*C*CH), 128.6 [(CO)*C*], 52.3 (CO_2CH_3); IR (ATR) 1718 (CO_2Me), 760 (C−Cl) cm^{-1}; LRMS (GC−MS) m/z calcd for $C_8H_7ClO_2$ 170.0, found 170.0. These data are consistent with those previously reported.[16]

N-(4-Chlorobenzoyl)pyrrolidine ***3***. To a solution of pyrrolidine (159 mL, 1.91 mol) in CH_2Cl_2 (600 mL) was added 4-chlorobenzoyl chloride (122 mL, 0.95 mol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction mixture was diluted with pH 2 buffer (600 mL). The organic layer was collected, washed with Na_2CO_3, dried (Na_2SO_4), and concentrated *in vacuo* to afford the product as a colorless oil that crystallized on standing to give white needles (192 g, 96%): mp 73−74 °C; δ_H (400 MHz, $CDCl_3$) 7.47 [d, 2H, J 8.5, 2 × (CO)CC*H*], 7.37 (2H, d, J 8.5, 2 × ClCC*H*), 3.62 (2H, t, J 7.0, NCH_2), 3.40 (2H, t, J 6.5, NCH_2), 1.94 (2H, sext, J 7.0, NCH$_2$CH_2), 1.88 (2H, sext, J 6.5, NCH$_2$CH_2); δ_C (100 MHz, $CDCl_3$) 168.3 (CO), 135.5 (quat.), 135.4 (quat.), 128.5 [(CO)C*C*H], 128.3 (Cl*C*CH), 49.4 (NCH_2), 46.1 (NCH_2), 26.2 (NCH$_2$CH_2), 24.2 (NCH$_2$CH_2); IR (ATR) 1623 (CONR$_2$), 758 (C−Cl) cm^{-1}; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{11}H_{13}ClNO$ 210.0680, found 210.0676. These data are consistent with those previously reported.[17]

N-(4-Chlorobenzoyl)morpholine. To a solution of morpholine (0.87 mL, 10 mmol) in CH_2Cl_2 (10 mL) was added 4-chlorobenzoyl chloride (0.64 mL, 5 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction mixture was diluted with pH 2 buffer (20 mL). The organic layer was collected, washed with Na_2CO_3, dried (Na_2SO_4), and concentrated *in vacuo* to afford the product as a colorless oil that crystallized on standing to give a white solid (1.05 g, 93%): mp 75−76 °C; δ_H (400 MHz, $CDCl_3$) 7.42−7.33 (4H, m, 4 × Ar*H*), 4.02−3.25 (8H, m, 4 × CH_2); δ_C (100 MHz, $CDCl_3$) 169.2 (CO), 135.9 (quat.), 133.5 (quat.), 128.7 (ArCH), 128.6 (ArCH), 66.7 (NCH_2), 48.1 (OCH_2), 42.7 (OCH_2); IR (ATR) 1620 (CONR$_2$), 1111 (C−O), 754 (C−Cl) cm^{-1}; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{11}H_{13}ClNO_2$ 226.0629, found 226.0632. These data are consistent with those previously reported.[17]

1-(4-Chlorobenzoyl)-4-methylpiperazine. To a solution of *N*-methylpiperazine (2.22 mL, 20 mmol) in CH_2Cl_2 (20 mL) was added 4-chlorobenzoyl chloride (1.28 mL, 10 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and partitioned between pH 2 buffer (20 mL) and EtOAc (20 mL). The aqueous layer was collected, basified (Na_2CO_3), and extracted with EtOAc. The organic layers were combined, washed with a saturated aqueous Na_2CO_3 solution, dried (Na_2SO_4), and concentrated *in vacuo* to afford the product as a yellow oil that crystallized on standing to give a light yellow solid (2.124 g, 89%): mp 68−69 °C; δ_H (400 MHz, $CDCl_3$) 7.39 (2H, d, J 8.5, 2 × ClCC*H*), 7.35 [2H, d, J 8.5, 2 × (CO)CC*H*], 4.00−3.15 [4H, m, (CO)NCH_2], 2.55−2.18 (4H, m, MeNCH_2), 2.32 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.1 (CO), 135.7 (quat.), 134.1 (quat.), 128.7 (ArCH), 128.5 (ArCH), 55.0 [(CO)NCH_2], 54.7 [(CO)NCH_2], 47.6 (MeNCH_2), 46.0 (CH_3), 42.1 (MeNCH_2); IR (ATR) 2798 (NCH_2), 1615 (CONR$_2$), 752 (C−Cl) cm^{-1}; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{12}H_{16}ClN_2O$ 239.0946, found 239.0943. This compound is known but has previously been reported without spectroscopic data.[18]

Coupling Reactions. *General Procedure A.* To a solution of methyl 4-chlorobenzoate **1** (0.170 g, 1 mmol), $Fe(acac)_3$ (3.5 mg, 0.01 mmol), and TMEDA (14.9 μL, 0.1 mmol) in dry THF (1 mL) in an oven-dried flask under an inert atmosphere at room temperature was added the alkyl Grignard reagent (1.2 mmol, solution in THF) in 0.1 mmol portions every 30 s. Upon completion of the addition, the reaction mixture was stirred for an additional 1 min before the reaction was quenched with a pH 2 buffer solution (2.5 mL). The reaction mixture was diluted with EtOAc (2.5 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product.

General Procedure B. To a solution of *N*-(4-chlorobenzoyl)-pyrrolidine **3** (0.210 g, 1 mmol), $Fe(acac)_3$ (0.35 mg, 0.1 mol %), and TMEDA (14.9 μL, 0.1 mmol) in dry THF (1 mL) in an oven-dried flask under an inert atmosphere at room temperature was added the alkyl Grignard reagent (1.2 mmol, solution in THF) in 0.1 mmol portions every 30 s. Upon completion of the addition, the reaction mixture was stirred for a further 1 min before the reaction was quenched with a pH 2 buffer solution (2.5 mL). The reaction mixture was diluted with EtOAc (2.5 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product.

General Procedure C. To a solution of 4-chlorobenzotrifluoride (0.133 mL, 1 mmol), $Fe(acac)_3$ (0.35 mg, 0.1 mol %), and TMEDA (14.9 μL, 0.1 mmol) in dry THF (1 mL) in an oven-dried flask under an inert atmosphere at room temperature was added the alkyl Grignard reagent (1.3 mmol, solution in THF) in 0.1 mmol portions every 60 s. Upon completion of the addition, the reaction mixture was stirred for a further 5 min before the reaction was quenched with a pH 2 buffer solution (2.5 mL). The reaction mixture was diluted with EtOAc (2.5 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product.

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Methyl 4-Ethylbenzoate **2**. Prepared according to General Procedure A using EtMgCl: conversion 95% (by HPLC), >99% (by NMR); isolated yield 0.140 g, 85%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.96 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.27 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.91 (3H, s, OCH_3), 2.71 (2H, q, *J* 7.5, CH_2CH_3), 1.26 [3H, t, *J* 7.5, CH_2CH_3]; δ_C (100 MHz, $CDCl_3$) 167.2 (*C*O), 149.7 (CH_2C), 129.7 [(CO)*C*CH], 127.9 (CH_2CCH), 127.6 [(CO)*C*], 51.9 (OCH_3), 28.9 (CH_2CH_3), 15.2 (CH_2CH_3); IR (ATR) 1719 (CO_2Me) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{10}H_{13}O_2$ 165.0910, found 165.0912. These data are consistent with those previously reported.[19]

Methyl 4-Butylbenzoate **7**. Prepared according to General Procedure A using *n*-BuMgCl: conversion 93% (by HPLC), >99% (by NMR); isolated yield 0.174 g, 91%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.0, 2 × COC*CH*), 7.22 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.88 (3H, s, OCH_3), 2.64 (2H, t, *J* 7.5, CCH_2), 1.60 (2H, quint., *J* 7.5, CCH_2CH_2), 1.34 (2H, sext., *J* 7.0, CH_3CH_2), 0.92 (3H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 167.0 (*C*O), 148.3 (CH_2C), 129.5 [(CO)*C*CH], 128.3 (CH_2CCH), 127.5 [(CO)*C*], 51.8 (OCH_3), 35.6 (CCH_2), 33.1 (CCH_2CH_2), 22.2 (CH_2CH_3), 13.8 (CH_2CH_3); IR (ATR) 1720 (CO_2Me) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{12}H_{17}O_2$ 193.1223, found 193.1226. These data are consistent with those previously reported.[20]

Methyl 4-Hexylbenzoate **8**. Prepared according to General Procedure A using *n*-hexylMgCl: conversion 95% (by HPLC), 98% (by NMR); isolated yield 0.196 g, 89%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.94 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.23 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.89 (3H, s, OCH_3), 2.65 (2H, t, *J* 7.5, CCH_2), 1.62 (2H, quint., *J* 7.5, CCH_2CH_2), 1.37−1.24 (6H, m, 3 × alkyl CH_2), 0.88 (3H, t, *J* 6.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.2 (*C*O), 148.5 (CH_2C), 129.6 [(CO)*C*CH], 128.4 (CH_2CCH), 127.6 [(CO)*C*], 51.9 (OCH_3), 36.0 (CCH_2), 31.6 (alkyl CH_2), 31.0 (CCH_2CH_2), 28.9 (alkyl CH_2), 22.5 (alkyl CH_2), 14.0 (CH_2CH_3); IR (ATR) 1720 (CO_2Me) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{14}H_{21}O_2$ 221.1536, found 221.1538. These data are consistent with those previously reported.[21]

Methyl 4-Phenethylbenzoate **9**. Prepared according to General Procedure A using $PhCH_2CH_2MgCl$: conversion 88% (by NMR); isolated yield 0.180 g, 75%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.94 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.30−7.14 (5H, m, 5 × Ar*H*), 7.14 (2H, d, *J* 7.0, 2 × *o*-Ph), 3.90 (3H, s, OCH_3), 3.01−2.91 (m, 4H, CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 167.1 (*C*O), 147.2 [(CO)-CCHCHC], 141.1 (*i*-Ph), 129.7 [(CO)CCH], 128.5 [(CO)CCHCH], 128.4 (Ph), 128.4 (Ph), 128.0 [(CO)*C*], 126.1 (*p*-Ph), 52.0 (CH_3), 37.9 ($PhCH_2CH_2$), 37.4 ($PhCH_2$); IR (ATR) 1717 (CO_2Me) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{16}H_{17}O_2$ 241.1223, found 241.1224. These data are consistent with those previously reported.[22]

N-(4-Ethylbenzoyl)pyrrolidine **4**. Prepared according to General Procedure B using EtMgCl: conversion 97% (by NMR); isolated yield 0.183 g, 92%, off-white solid; mp 85−86 °C; δ_H (400 MHz, $CDCl_3$) 7.45 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.21 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.64 (2H, t, *J* 7.0. NCH_2), 3.45 (2H, t, *J* 6.5, NCH_2), 2.67 (2H, q, *J* 7.5, CCH_2), 1.95 (2H, quint., *J* 6.5, NCH_2CH_2), 1.86 (2H, quint., *J* 6.5, NCH_2CH_2), 1.24 (3H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 169.8 (*C*O), 146.1 (CH_2CCH), 134.5 [(CO)*C*], 127.6 (CH_2CCH), 127.2 [(CO)*C*CH], 49.6 (NCH_2), 46.1 (NCH_2), 28.7 (CH_2CH_3), 26.4 (NCH_2CH_2), 24.4 (NCH_2CH_2), 15.3 (CH_2CH_3); IR (ATR) 1605 ($CONR_2$) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{13}H_{18}NO$ 204.1383, found 204.1383. These data are consistent with those previously reported.[23]

N-(4-Butylbenzoyl)pyrrolidine **10**. Prepared according to General Procedure B using *n*-BuMgCl: conversion 95% (by HPLC), 96% (by NMR); isolated yield 0.172 g, 75%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.44 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.19 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.64 (2H, t, *J* 7.0, NCH_2), 3.44 (2H, t, *J* 6.5, NCH_2), 2.62 (2H, t, *J* 7.5, CCH_2), 1.94 (2H, quint., *J* 7.0, NCH_2CH_2), 1.85 (2H, quint., *J* 6.5, NCH_2CH_2), 1.60 (2H, quint., *J* 7.5, CCH_2CH_2), 1.35 (2H, sext., *J* 7.5, CH_3CH_2), 0.92 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 169.7 (*C*O), 144.7 (CH_2CCH), 134.4 [(CO)*C*], 128.0 (CH_2CCH), 127.0 [(CO)*C*CH], 49.5 (NCH_2), 46.0 (NCH_2), 35.3 (CCH_2), 33.3 (CCH_2CH_2), 26.3 (NCH_2CH_2), 24.3 (NCH_2CH_2), 22.1 (CH_2CH_3), 13.8 (CH_3); IR (ATR) 1620 ($CONR_2$) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{15}H_{22}NO$ 232.1696, found 232.1693. This compound has not previously been reported.

N-(4-Hexylbenzoyl)pyrrolidine **11**. Prepared according to General Procedure B using *n*-hexylMgCl: conversion 94% (by HPLC), 94% (by NMR); isolated yield 0.230 g, 89%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.44 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.19 (2H, d, *J* 8.0, 2 × CH_2CCH), 3.64 (2H, t, *J* 7.0, NCH_2), 3.45 (2H, t, *J* 6.5, NCH_2), 2.62 (2H, t, *J* 7.5, CCH_2), 1.95 (2H, quint., *J* 6.5, NCH_2CH_2), 1.86 (2H, quint., *J* 6.5, NCH_2CH_2), 1.60 (2H, quint., *J* 7.5, CCH_2CH_2), 1.38−1.24 (6H, m, 3 × alkyl CH_2), 0.88 (3H, t, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 169.8 (*C*O), 144.8 (CH_2CCH), 134.5 [(CO)*C*], 128.1 (CH_2CCH), 127.1 [(CO)*C*CH], 49.6 (NCH_2), 46.1 (NCH_2), 35.8 (CCH_2), 31.6 (alkyl CH_2), 31.2 (CCH_2CH_2), 28.9 (alkyl CH_2), 26.4 (NCH_2CH_2), 24.4 (NCH_2CH_2), 22.5 (CH_2CH_3), 14.0 (CH_3); IR (ATR) 1621 (CO_2Me) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{17}H_{26}NO$ 260.2009, found 260.2008. This compound has not previously been reported.

N-(4-Ethylbenzoyl)morpholine **5**. Prepared according to General Procedure B using EtMgCl: conversion 93% (by NMR); isolated yield 0.185 g, 84%, colorless oil; δ_H (400 MHz, $CDCl_3$) 7.33 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.23 (2H, d, *J* 8.0, 2 × CH_2CCH), 4.00−3.35 [m, 8H, $N(CH_2CH_2)O$], 2.67 (2H, q, *J* 7.5, CH_2CH_3), 1.24 (2H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 170.6 (*C*O), 146.3 (CH_2CCH), 132.6 [(CO)*C*], 128.0 (CH_2CCH), 127.3 [(CO)*C*CH], 66.9 (NCH_2CH_2O), 28.7 (CH_2CH_3), 15.4 (CH_3); IR (ATR) 1628 ($CONR_2$) 1111 (C−O) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1330. This compound is known but has previously been reported without characterization data.

1-(4-Ethylbenzoyl)-4-methylpiperazine **6**. Prepared according to General Procedure B using EtMgCl: conversion >99% (by NMR); isolated yield 0.123 g, 53%, colorless oil; δ_H (400 MHz, $CDCl_3$) 7.33 [2H, d, *J* 8.0, 2 × (CO)CC*H*], 7.22 (2H, d, *J* 8.0, 2 × CH_2CCH), 4.05−3.25 [4H, m, (CO)NCH_2], 2.67 (2H, q, *J* 7.5, CH_2CH_3), 2.57−2.22 (m, 4H, CH_2NCH_3), 2.32 (3H, s, NCH_3), 1.24 (3H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 170.5 (*C*O), 146.1 (CH_2CCH), 133.1 [(CO)*C*], 127.9 (CH_2CCH), 127.2 [(CO)*C*CH], 46.0 (NCH_3), 28.7 (CH_2CH_3), 15.4 (CH_2CH_3); IR (ATR) 2792 (NCH_2), 1628 ($CONR_2$) cm^{-1}; HRMS (ESI) *m*/*z* [M + H^+] calcd for $C_{14}H_{21}N_2O$ 233.1648, found 233.1650. This compound is known but has previously been reported without characterization data.

4-Ethylbenzotrifluoride **12**. Prepared according to General Procedure C using EtMgCl: conversion 93% (by NMR), 97% (by HPLC); compound not isolated; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.0, 2 × F_3CCCH), 7.30 (2H, d, *J* 8.0, 2 × CH_2CCH), 2.71 (2H, q, *J* 7.5, CH_2), 1.26 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 148.3 (CH_2CCH), 128.2 (CH_2CCH), 128.0 (q, F_3CCCH, J_{CF} 32.2), 125.2 (q, F_3CCCH, J_{CF} 3.7), 124.2 (q, F_3C, J_{CF} 271.7), 28.8 (CH_2), 15.3 (CH_3); δ_F (376 MHz, $CDCl_3$) −62.3; IR (ATR) 1323 (C-F) cm^{-1}; LRMS (GC−MS) *m*/*z* [M] calcd for $C_9H_9F_3$ 174.1, found 174.0. These data are consistent with those previously reported.[24]

4-Butylbenzotrifluoride **13**. Prepared according to General Procedure C using *n*-BuMgCl: conversion 97% (by NMR), 96% (by HPLC); isolated yield 140 mg, 69%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* 8.0, 2 × F_3CCCH), 7.27 (2H, d, *J* 8.0, 2 × CH_2CCH), 2.66 (2H, t, *J* 8.0, CCH_2), 1.66−1.55, (2H, m, CCH_2CH_2), 1.35 (2H, sext., *J* 7.5, CH_2CH_3), 0.93 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 147.0 (CH_2CCH), 128.7 (CH_2CCH), 128.0 (q, F_3CC, J_{CF} 32.2), 125.1 (q, F_3CCCH, J_{CF} 3.8), 124.4 (q, F_3C, J_{CF} 271.6), 35.5 (CCH_2), 33.3 (CCH_2CH_2), 22.3 (CH_2CH_3), 13.9 (CH_3); δ_F (376 MHz, $CDCl_3$) −62.3; IR (ATR) 1323 (C-F) cm^{-1}; LRMS (GC−MS) *m*/*z* [M] calcd for $C_{11}H_{13}F_3$ 202.1, found 201.9. These data are consistent with those previously reported.[25]

4-Hexylbenzotrifluoride **14**. Prepared according to General Procedure C using *n*-hexylMgCl: conversion 87% (by NMR), 93% (by HPLC); isolated yield 192 mg, 83%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.51 (2H, d, *J* 8.0, 2 × F_3CCCH), 7.26 (2H, d, *J* 8.0, 2 × CH_2CCH), 2.65 (2H, t, *J* 7.5, CCH_2), 1.61 (2H, quint., *J* 7.5, CCH_2CH_2), 1.37−1.24 (6H, m, 3 × alkyl CH_2), 0.88 (3H, t, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 147.0 (CH_2C), 128.7 (CH_2CCH), 128.0

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(q, F_3CC, J_{CF} 32.2), 125.1 (q, F_3CCCH, J_{CF} 3.8), 124.4 (q, F_3C, J_{CF} 271.5), 35.8 (CCH_2), 31.7 (alkyl CH_2), 31.2 (CCH_2CH_2), 28.9 (alkyl CH_2), 22.6 (alkyl CH_2), 14.0 (CH_3); δ_F (376 MHz, $CDCl_3$) −62.3; IR (ATR) 1323 (C-F) cm^{-1}; LRMS (GC−MS) m/z [M] calcd for $C_{13}H_{17}F_3$ 230.1, found 230.0. These data are consistent with those previously reported.[26]

4-Phenethylbenzotrifluoride ***15***. Prepared according to General Procedure C using $PhCH_2CH_2MgCl$: conversion 48% (by NMR), 56% (by HPLC); isolated yield 62 mg, 25%, yellow oil; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, J 8.0, F_3CCCH), 7.31−7.24 (m, 4H, ArH), 7.20 (1H, t, J 7.5, p-PhH), 7.15 (2H, d, J 7.5, 2 × o-PhH), 3.02−2.89 (m, 4H, CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 145.8 (i-Ar), 141.0 (i-Ar), 128.8, 128.4, 126.1, 125.2 (q, F_3CCCH, J_{CF} 3.8), 37.6 (CH_2), 37.5 (CH_2); δ_F (376 MHz, $CDCl_3$) −62.3; IR (ATR) 1322 (C-F) cm^{-1}; LRMS (GC−MS) m/z [M] calcd for $C_{15}H_{13}F_3$ 250.1, found 249.3. These data are consistent with those previously reported.[27]

N-(4-Ethylbenzoyl)pyrrolidine ***4***. To a solution of *N*-(4-chlorobenzoyl)pyrrolidine (209.7 g, 1.00 mol), $Fe(acac)_3$ (0.353g, 1 mmol), and TMEDA (15.0 mL, 0.1 mol) in dry THF (800 mL) was added EtMgCl (600 mL, 2 M solution in THF, 1.2 mol) *via cannula* at a rate that kept the internal temperature of the reaction mixture below 30 °C (roughly 1 h). Immediately following the completion of the addition, the reaction mixture was added *via cannula* to a pH 2 buffer solution (1.6 L) (over 45 min) and stirred at room temperature for 16 h. The organics were collected. The aqueous was extracted with EtOAc, and organics were combined, washed with a saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as a yellow solid (200.5 g, 99%). The purity (by NMR) was >98%. A sample was recrystallized for characterization: mp 85−86 °C. Characterization data are consistent with those listed above.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H, ^{13}C, and ^{19}F NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: d.j.fox@warwick.ac.uk.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451−3479.

(2) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487−1489.

(3) (a) Wolfgang, F. *Synlett* **2001**, 1901−1904. (b) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, *2004*, 2081−2091. (c) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624−629. (d) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654−1658. (e) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844−9845. (f) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108−1117. (g) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317−3321. (h) Plietker, B. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2008. (i) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500−1511. (j) Bolm, C. *Nat. Chem.* **2009**, *1*, 420. (k) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674−10676. (l) Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900−11903.

(4) (a) Kim, M. J.; Lee, J.; Kang, S. Y.; Lee, S.-H.; Son, E.-J.; Jung, M. E.; Lee, S. H.; Song, K.-S.; Lee, M.; Han, H.-K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3420−3425. (b) Nicolaou, K. C.; Sun, Y.-P.; Korman, H.; Sarlah, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5875−5878. (c) Liang, Y.; Jiang, X.; Yu, Z.-X. *Chem. Commun.* **2011**, *47*, 6659−6661. (d) Barbier, J.; Wegner, J.; Benson, S.; Gentzsch, J.; Pietschmann, T.; Kirschning, A. *Chem.—Eur. J.* **2012**, *18*, 9083−9090. (e) Risatti, C.; Natalie, K. J.; Shi, Z.; Conlon, D. A. *Org. Process Res. Dev.* **2013**, *17*, 257−264.

(5) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199−1205.

(6) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863.

(7) (a) Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett.* **2012**, *14*, 4818−4821. (b) Malhotra, S.; Seng, P. S.; Koenig, S. G.; Deese, A. J.; Ford, K. A. *Org. Lett.* **2013**, *15*, 3698−3701.

(8) (a) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133−137. (b) Reisch, M. *Chem. Eng. News* **2008**, *86*, 32.

(9) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687.

(10) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161−4163.

(11) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364−4366.

(12) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949−11963.

(13) (a) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796−3799. (b) Agrawal, T.; Cook, S. P. *Org. Lett.* **2013**, *15*, 96−99.

(14) (a) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. *Chem. Commun.* **2006**, 1398−1400. (b) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078−6079. (c) Kleimark, J.; Hedström, A.; Larsson, P.-F.; Johansson, C.; Norrby, P.-O. *ChemCatChem* **2009**, *1*, 152−161. (d) Hedström, A.; Bollmann, U.; Bravidor, J.; Norrby, P.-O. *Chem.—Eur. J.* **2011**, *17*, 11991−11993.

(15) The coupling of an amide-containing aryl iodide utilizing an iron catalyst has been reported, but with the use of a magnesium-derived copper reagent rather than a Grignard reagent. See: Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654−1657.

(16) Ushijima, S.; Moriyama, K.; Togo, H. *Tetrahedron* **2012**, *68*, 4701−4709.

(17) Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575−2577.

(18) Kalyanasundaram, M.; Mathew, N.; Paily, K. P.; Prabakaran, G. *Acta Trop.* **2009**, *111*, 168−171.

(19) Rahaim, R. J.; Maleczka, R. E. *Org. Lett.* **2011**, *13*, 584−587.

(20) Das, A.; Chaudhuri, R.; Liu, R.-S. *Chem. Commun.* **2009**, 4046−4048.

(21) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609−612.

(22) Belger, C.; Plietker, B. *Chem. Commun.* **2012**, *48*, 5419−5421.

(23) Holland, H. L.; Morris, T. A.; Nava, P. J.; Zabic, M. *Tetrahedron* **1999**, *55*, 7441−7460.

(24) Chun, Y. S.; Shin, J. Y.; Song, C. E.; Lee, S.-g. *Chem. Commun.* **2008**, 942−944.

(25) Cahiez, G.; Gager, O.; Buendia, J.; Patinote, C. *Chem.—Eur. J.* **2012**, *18*, 5860−5863.

(26) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005−3008.

(27) Molander, G. A.; Yun, C.-S. *Tetrahedron* **2002**, *58*, 1465−1470.