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ARTICLE

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Continuous Preparation of Arylmagnesium Reagents in Flow with Inline IR Monitoring

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Supporting Information

ABSTRACT: A newly developed microscale ReactIR flow cell was used as a convenient and versatile inline analytical tool for Grignard formation in continuous flow chemical processing. The LiCl-mediated halogen/Mg exchange reaction was used for the preparation of functionalized arylmagnesium compounds from aryl iodides or bromides. Furthermore, inline IR monitoring was used for the analysis of conversion and possible byproduct formation, as well as a potential tool for elucidation of mechanistic details. The results described herein indicate that the continuous flow systems are effective for highly exothermic reactions such as the Grignard exchange reaction due to fast mixing and efficient heat transfer.

1. INTRODUCTION

The Grignard reaction[1] was discovered in 1900 and some 12 years later was deemed worthy of the Nobel Prize in chemistry. This reaction continues to be a key component of the synthesis chemist's armory owing to its ability to form carbon−carbon bonds in a wide variety of situations[2] and additionally to afford other useful functionality. This important transformation and the accompanying need for the preparation of the initial organomagnesium reagents, has resulted in innovations and improvements to the methodology[3] and in our understanding of the reaction processes.[4]

While many of these highly reactive Grignard reagents are now commercially available, the ingenuity of modern organic synthesis programs dictates the need for more functionalized and diverse systems. Indeed, many reliable and robust procedures for their batch-mode preparation are now available.[5] However, given that flow chemistry, reaction telescoping and continuous processing methods[6] are beginning to impact on the way we assemble molecules, it is therefore necessary to develop suitable protocols for the preparation and safe delivery of Grignard reagents under flow conditions.[7] In order to achieve this goal there are significant technical hurdles which must be overcome. First, the pumps and related hardware such as tubing, mixer chips and back-pressure regulators must accommodate potentially exothermic processes, provide a water and oxygen free environment and be capable of safe continuous production of material. Ideally, there needs to be a method for accurate inline reaction monitoring and control of the reaction[8] combined with the ability to progress the synthesized organomagnesium reagent in further chemical transformations.[9]

Here we report on the use of inline IR monitoring during the preparation of arylmagnesium reagents and their subsequent coupling with carbonyl compounds under continuous flow conditions.

2. RESULTS AND DISCUSSION

2.1. Inline FTIR Monitoring of Arylmagnesiumhalide Formation. Generally, only a few methods for preparation of Grignard reagents are in common use in organic synthesis. Explicitly, the Grignard reagents are mostly prepared by insertion of magnesium into a carbon/halide bond,[10] by a magnesium/halide exchange reaction,[11] via carbometalation,[12] hydrometalation,[13] or finally by selective deprotonation.[14] In the first two cases, it has been shown that the incorporation of LiCl as a promoter in the Grignard formation has a remarkable influence on the reaction outcome and on the reactivity of the resulting organometallic species.[15,16] Usually, the reactions proceed rapidly with characteristic exothermic behavior. The reaction control on scale can be very demanding. Considering the unique benefits of flow chemistry, these problems can be readily addressed. This is particularly noteworthy during the formation and use of Grignard reagents bearing sensitive functional groups, e.g., trifluoromethyl, chloro, or carbonyl derivatives where the stability of the species can play a significant role. Likewise, monitoring product quality during Grignard formation using titration or GC and/or NMR techniques can be somewhat convoluted. By contrast, the use of inline flow IR monitoring can permit real-time return of information.[17] While examples exist in the literature showing the use of IR probes as monitoring devices,[18] there is no general method for inline analysis in the preparation of Grignard species under continuous flow conditions.

In order to achieve this, the Grignard reagent formation was monitored by a new inline IR instrument, where we focused on the formation of *m*-methylphenylmagnesium chloride. This solution was initially prepared in batch by a typical insertion

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reaction process using *m*-iodotoluene and magnesium turnings in the presence of LiCl (Scheme 1).

The concentration of the reagent and the simultaneous conversion of substrate were verified by standard titration of the reaction mixture with I_2 and GC analysis of the protonated product (toluene). This experiment allowed us to compare data with the IR spectrum obtained from the same sample. We then examined the reagent using a newly developed Mettler Toledo ReactIR FD[19] equipped with a DiComp sensor[20] (Figure 1).

The measured IR spectra of THF and the 0.5 M *m*-methylphenylmagnesium chloride solution are displayed in Figure 2.

These IR spectra clearly show resonances at 1069 and 913 cm^{-1} for free THF solvent, while the shifted peaks at 1043 and 894 cm^{-1} indicate coordination of the THF with magnesium in the Grignard reagent (Scheme 2). The subtraction of the free THF spectrum from that of the Grignard reagent solution shows these peaks cleanly (Figure 2).

The IR peaks in the fingerprint region at 764 and 711 cm^{-1} confirm the presence of the aryl moiety in the reagent.

For a more detailed analysis of this reaction mixture we examined the influence of concentration of *m*-methylphenylmagnesium chloride solution on the intensity of peaks recorded in the IR spectrum. With this information we can then easily determine the concentration of other Grignard solutions. A similar calibration technique has been previously used by our group to determine inline concentrations of intermediates in real time, and then that information is used to accurately match the delivery of a third stream.[21] Several IR spectra with a range of THF solution concentrations of *m*-methylphenylmagnesium chloride were recorded to provide a suitable calibration curve. The previous 0.5 M THF solution of *m*-methylphenylmagnesium chloride was diluted with dry THF to generate those 0.4, 0.3, 0.2, and 0.1 M solutions. The IR spectra (Figure 3) were measured by directly injecting into the DiComp sensor of the ReactIR via a 5-mL syringe.

The recorded IR spectra are then correlated, by solvent spectra subtraction to show only the IR spectra of the Grignard reagent. Negative peaks at 1073 and 1058 cm^{-1} in figure 2 were caused by mathematical effects as a consequently similar wavelength of IR peaks of both coordinated and free THF. The calibration curve was then created from the intensities of the IR peaks at different concentrations. The height of the peaks at 1043 and 762 cm^{-1} was plotted against known concentrations and the calibration curve showed almost perfect linear correlation (Figure 4).[22]

Scheme 1. LiCl-assisted formation of arylmagnesium chloride

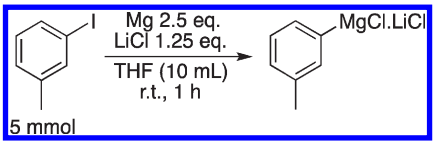

Figure 1. Mettler Toledo ReactIR FD.

Scheme 2. Aryl-Grignard−THF complex

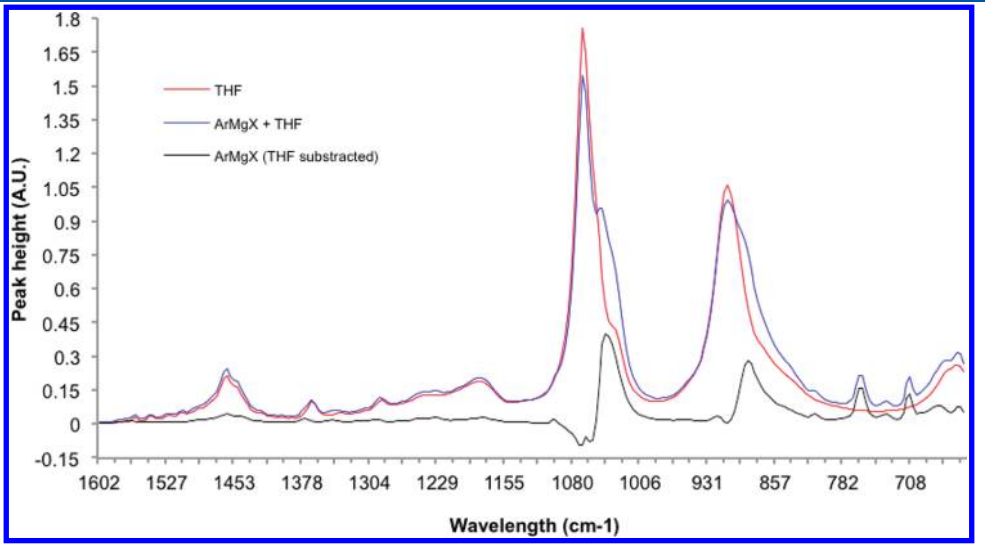

Figure 2. IR spectrum of THF and Grignard reagent.

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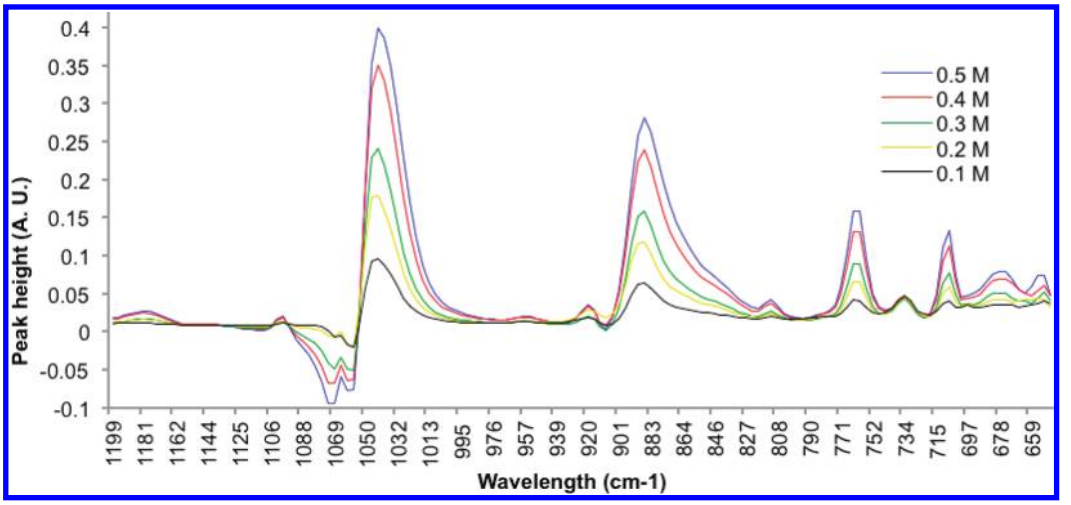


Figure 3. Intensity of IR peaks of Grignard reagent at different concentrations.

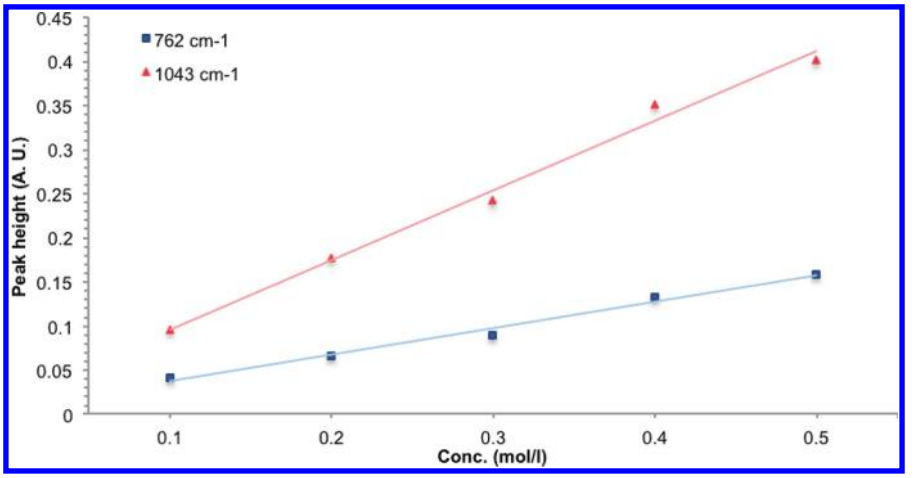
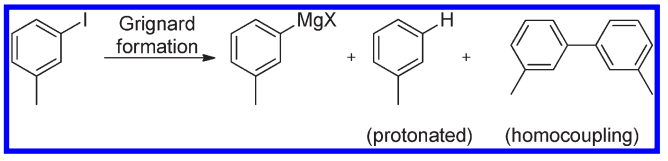


Figure 4. IR calibration chart of Grignard reagent.

Scheme 3. Possible products formed in Grignard formation reaction



Equipped with this chart one can easily analyze the concentration of the reactive Grignard reagent formed in the THF flow stream. In some cases the organomagnesium reagents can be accompanied by the formation of side products, we also used IR spectroscopy to characterize side products as either protonated or Wurtz coupled material (Scheme 3).

Thus, the complete IR spectra of all these components were recorded and their fingerprint region used to track changes in product makeup (Figure 5).

By magnification of the fingerprint region (Figure 6) the difference between the various products is instantly visible. In order to correctly assign these products in the reaction mixture, a combination of several fingerprint peaks can be used. In our particular case, protonated product: 734 and 697 cm^{-1}, substrate: 771 and 682 cm^{-1} and homocoupling product: 775 and 697 cm^{-1} allow us to rapidly analyze the reaction mixture in real time.

By completing a comprehensive IR study for the monitoring process of the formation of *m*-methylphenylmagnesium chloride, we could then focus on the Mg/halogen exchange reaction under appropriate flow conditions. We therefore devised a flow reactor arrangement to convert *m*-iodotoluene to the corresponding organomagnesium reagent with real-time in situ IR monitoring (Scheme 4).

Here 1-mL PTFE sample loops were used to introduce both aryl halide and a solution of *i*PrMgCl·LiCl. The two reagent streams were pumped[23] at a rate of 0.2 mL/min and united at a T-piece before entering a 10-mL reactor coil operating at rt. The DiComp sensor of the ReactIR FD was placed immediately after the coil to capture the structural information every 30 s. A final back-pressure regulator (75 psi) was placed at the end of the flow system to maintain constant pressure in the system. The output stream was directed to a flask filled with a saturated aqueous

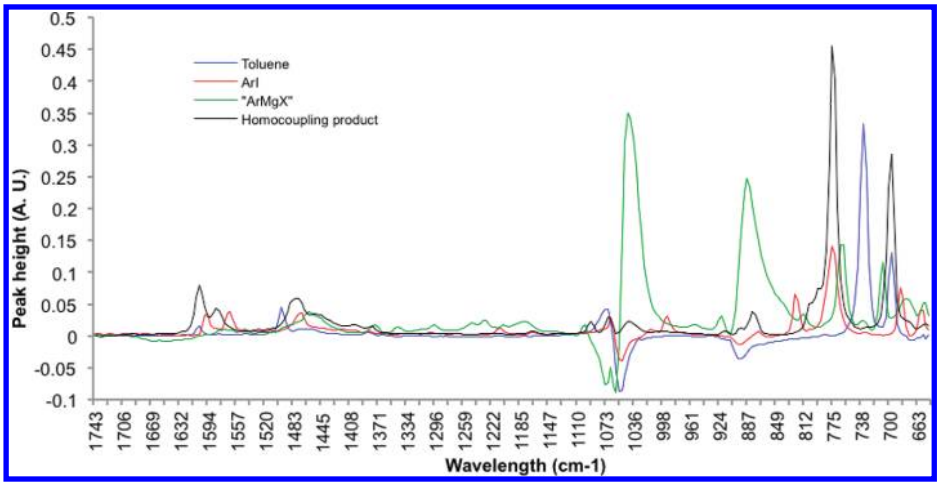


Figure 5. IR spectra of possible products in Grignard formation reaction.

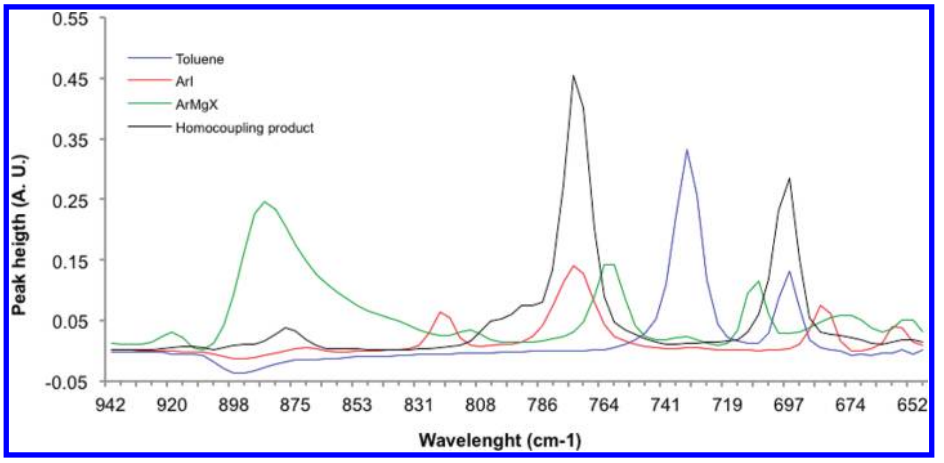
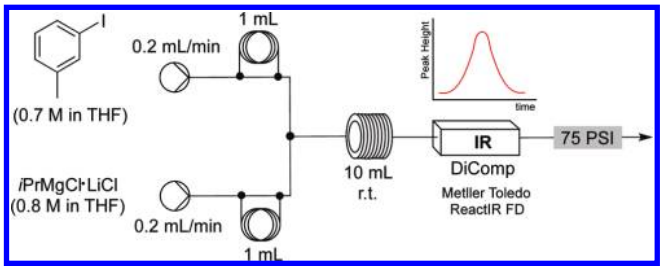


Figure 6. IR spectra of possible products in Grignard formation reaction.

Scheme 4. Schematic of flow setup for Mg/halogen exchange reaction



solution of NH_4Cl in order to safely quench the Grignard reagent for further analysis.

To determine the conversion and hence the concentration of the aryl Grignard reagent, the intensities of product IR peaks at 767 and 1043 cm^{-1} were monitored over a period of time (Figure 7).

This graph clearly shows that a level of diffusion occurs in the flow stream as is normal for small-scale flow experiments. The curve that is generated can then be used for the introduction of the third reactant. In principle, the amount of third reactant introduced can be adjusted on the basis of Grignard reagent concentration calculated from the IR calibration curve and the recorded peak height. Figure 8 shows the spectrum of 0.4 M ArMgCl prepared in batch and the IR spectrum of ArMgCl (at 45 min.) prepared using the flow setup shown above.

The IR spectrum (blue in figure 7) clearly shows the absence of starting material and expected formation of Grignard reagent but without detection of any side products at least to the sensitivity range[24] of the measurement of the IR experiment. In the case of the flow Mg/halogen exchange reaction, the concentration of reagent can only be calculated using the intensity of the peak at 767 cm^{-1} due to overlap of peaks at 1038 cm^{-1} which effect the intensity of the bands. Theoretically, the reaction would provide the aryl Grignard reagent as 0.35 M solution in THF at steady state. However, as we are operating under segmented flow conditions, the recorded intensity of the IR peak of product (767 cm^{-1}) at 45 min indicates a 0.33 M concentration.

Additionally, we have evaluated the use of IR spectroscopy to characterize the role of LiCl in THF. Accordingly, several IR experiments were performed. The first was a comparison of the IR spectra of *i*PrMgCl with *i*PrMgCl·LiCl reagent in THF. The IR spectra of these as 0.33 M solutions are shown in Figure 9.

As a result of LiCl incorporation one can notice shift and intensity changes in the spectra. For example there is a small shift

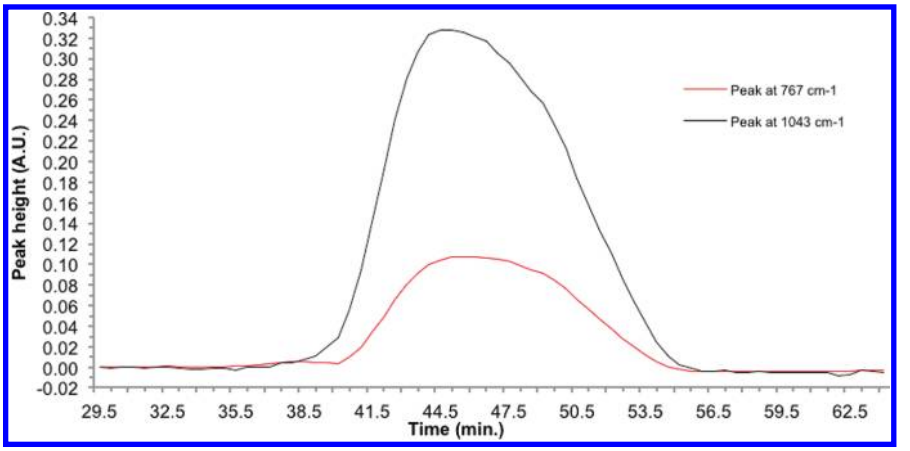


Figure 7. Real-time intensities of IR peaks of Grignard reagent.

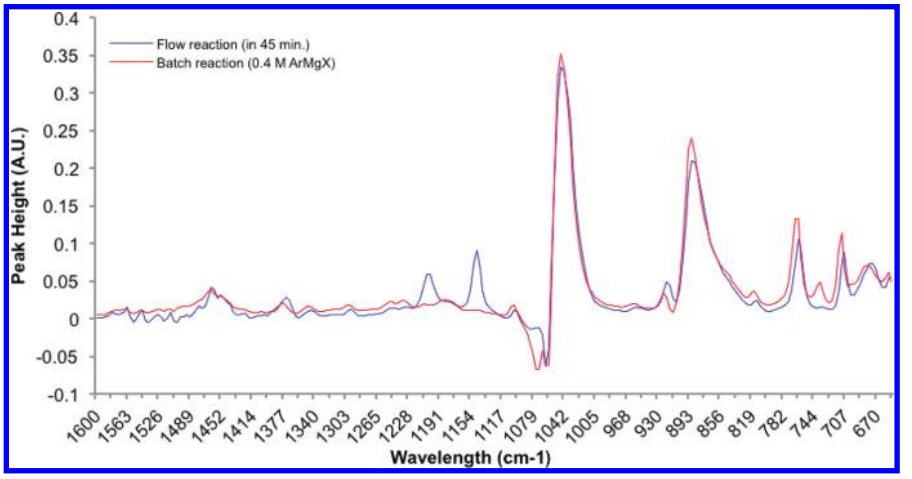


Figure 8. IR spectra of 0.4 M ArMgCl and ArMgCl prepared using flow setup.

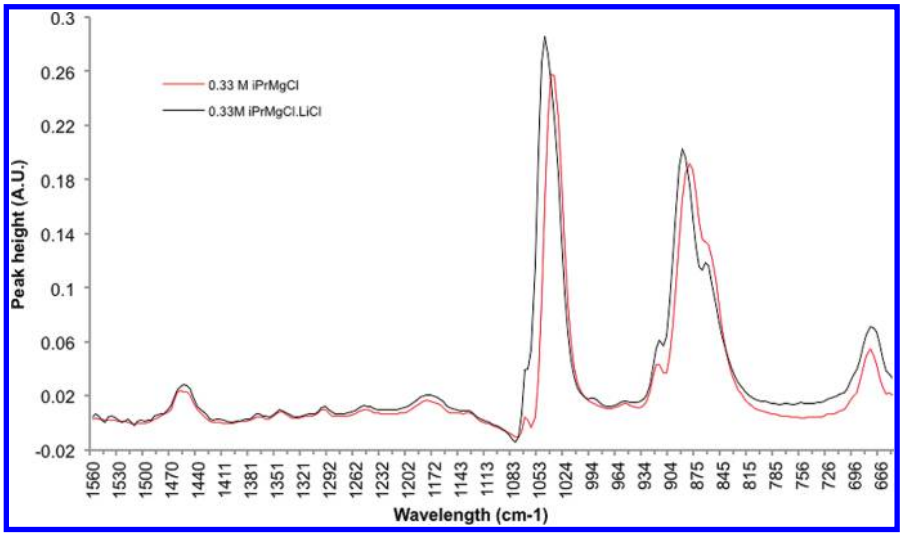


Figure 9. IR spectra of *i*PrMgCl and *i*PrMgCl·LiCl complex.

difference in the corresponding key bands (1035 vs 1045 cm^{-1}, 882 vs 890 cm^{-1}), while the intensities are quite similar. In the second experiment, the IR clearly indicates coordination of THF to the Mg atom of the Grignard species. Therefore, changing to toluene as solvent would help to define the role of THF (Scheme 5).[25]

To this Grignard solution in toluene was added dry THF, and the IR spectra of corresponding mixtures with 1, 2, 4, and 10 equiv of dry THF were measured (Figure 10).

The peaks at 871, 916, 1027, and 1072 cm^{-1} were compared in order to quantify the effect of THF coordination. The spectra demonstrate the coordination of THF (peaks at 871 and 1027 cm^{-1}) to ArMgCl and that further peaks at 916 and 1072 cm^{-1} (free THF) are observed when an excess of dry THF is added.

From these studies it is clear that inline IR spectroscopy is a very effective procedure to ensure the quality of prepared organomagnesium species in solution. Additionally, the information can be used to determine concentration of active reagents and/or the composition of more complex reaction streams to quickly optimize the reaction conditions.

2.2. LiCl-Mediated Halogen/Mg Exchange Reaction from Aryl iodides. The preparation of functionalized Grignard reagents via the LiCl-mediated halogen/magnesium exchange reaction is now recognized as an important advance in the area. Following on from the procedure reported by Krasovskiy et al., we selected *m*-iodotoluene as an initial starting material for our further optimization studies and subsequent reaction with carbonyl compounds. A new flow reactor arrangement was therefore developed using a combination of the Vapourtec R2+ together with an additional external Knauer K120 pump to deliver the carbonyl compound. As before, flow IR monitoring was used inline to determine the concentration of organomagnesium reagent. A 10-mL reaction coil was added to ensure complete coupling with the carbonyl species prior to quenching with aqueous NH_4Cl (Scheme 6).

In this configuration, a solution containing *i*PrMgCl·LiCl in THF was introduced at 0.2 mL/min to join at the T-piece with a second stream (flow rate 0.2 mL/min) containing *m*-iodotoluene in THF. The combined mixture was then delivered to the first 10-mL tubular coil reactor (PTFE, 1 mm i.d.) operating at room temperature. A second T-piece was used to combine a third stream containing the carbonyl compound in THF at a flow rate of 0.4 mL/min which then passes at room temperature to the final reactor coil. The timing of the third stream addition was adjusted on the basis of the IR readout.[26] Using the previous established IR calibration curves, we observed full conversion of starting material after 45-min processing time.

Following a screen of reaction parameters, we examined the scope of the process under the optimized reaction conditions with different aryl iodides and carbonyl compounds. The *i*PrMgCl·LiCl reagent was obtained from commercial sources. We then examined the metal exchange process of a range of aryl

Scheme 5. Formation of Grignard reagent in toluene using 1 equiv of THF

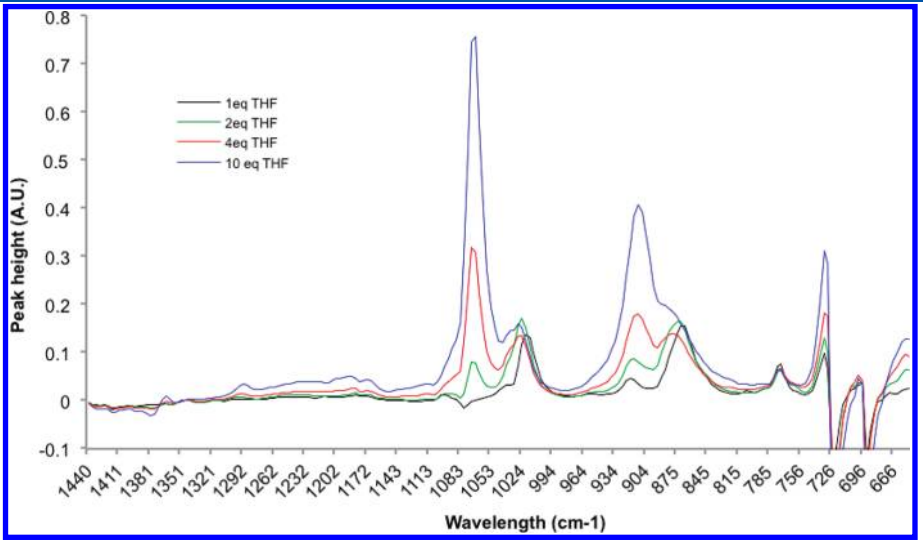


Figure 10. IR spectrum of Grignard reagent solution in toluene with added THF.

Scheme 6. Schematic of flow setup for the LiCl-mediated I/Mg exchange reaction

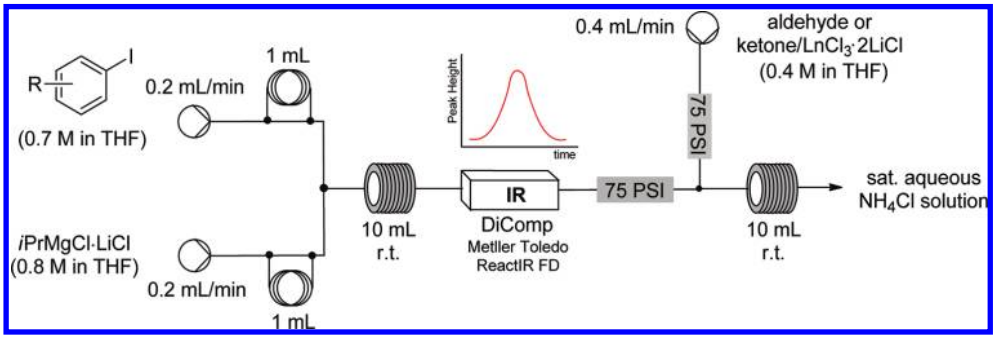


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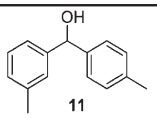
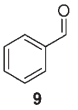
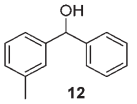
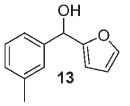
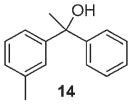
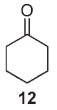
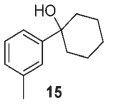
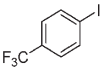
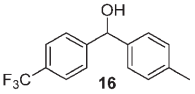
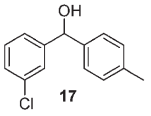
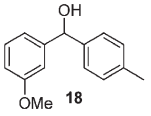
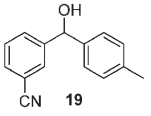
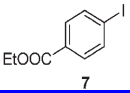
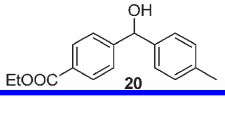
Table 1. Preparation and following reactions of functionalised Grignard reagents[c]

Entry	Aryl iodide	Electrophile	Product	Yield[a] [%]	Time [h]
1	 1	 8	 11	95	0.75
2	 1	 9	 12	88	0.75
3	 2	 10	 13	89	0.75
4[b]	 1	 11	 14	82	0.75
5[b]	 1	 12	 15	85	0.75
6	 3	 8	 16	95	0.75
7	 4	 8	 17	90	0.75
8	 5	 8	 18	89	0.75
9	 6	 8	 19	88	0.75
10	 7	 8	 20	65	0.75

[a] Isolated yield after purification by flash chromatography on silica gel. [b] Stoichiometric $LnCl_3 \cdot 2LiCl$ was premixed with the ketone and then transferred to the reaction via a third pump. [c] Reaction conditions: 1 equiv of aryl iodide **1**−**7** and 1.1 equiv *i*PrMgCl·LiCl were dissolved each in 1 mL of THF, flow solvent THF 0.2 or 0.1 mL/min, reaction time 0.75 h. See Experimental Details.

iodides (**1**−**7**) to afford the corresponding Grignard reagents and quench these inline with carbonyl components to give final coupled products (Table 1).

All products **11**−**20** were isolated in good to excellent yields. Seemingly, the reactions of the Grignard reagents with carbonyl compounds under the continuous flow conditions were superior in most cases when compared to batch reactions. The additional formation of up to 20% of the ketone byproduct via Oppenhauer oxidation can be observed when the reactions are conducted in batch mode at room temperature. For this reason batch reactions are best conducted at −10 °C. In some of our flow experiments for the addition of Grignards to ketones (**14** and **15**, entries 4 and 5, Table 1), the use of a Lewis acid ($LnCl_3 \cdot 2$ LiCl) avoided byproduct formation through aldol reactions.[27] The presence of electron-withdrawing or -donating groups was tolerated as in 4-iodobenzotrifluoride, 3-chloroiodobenzene, and 3-iodoaniline as substrates (entries 6, 7, and 8, Table 1). In all these cases the corresponding Grignard reagent was formed within 45 min and reacted to give the alcohols (**16**−**18**) after coupling with tolyl aldehyde **8**. We have also examined the formation of a Grignard

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Scheme 7. Schematic of flow setup for the LiCl-mediated Br/Mg-exchange reaction

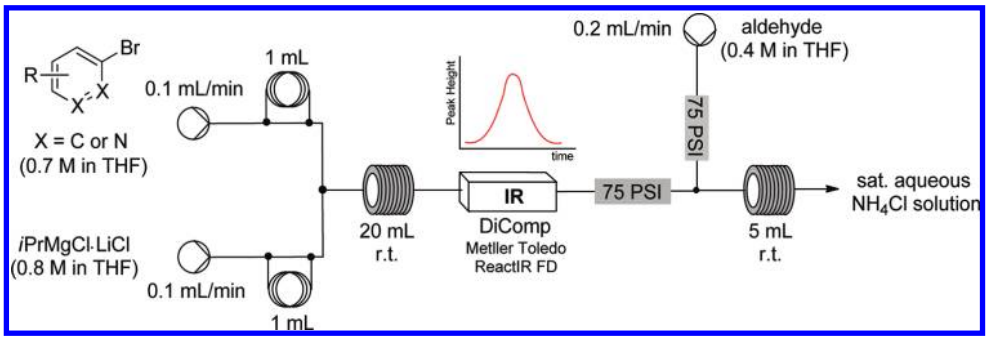
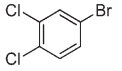
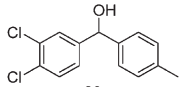
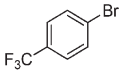
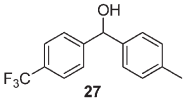
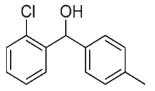
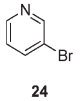
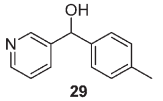
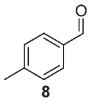
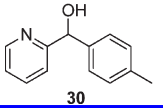


Table 2. Preparation and the following reactions of functionalised Grignard reagents[b]

Entry	Aryl halide	Electrophile	Product	Yield[a] [%]	Time [h]
1	 21	 8	 26	88	0.75
2	 22	 8	 27	79	2.2
3	 23	 8	 28	80	2.2
4	 24	 8	 29	81	2.2
5	 25	 8	 30	72	2.2

[a] Isolated yield after purification by flash chromatography on silica gel. [b] Reaction conditions: 1 equiv of aryl bromide **20**−**25** and 1.1 equiv *i*PrMgCl·LiCl were each dissolved in 1 mL THF, flow solvent THF 0.1 mL/min, reaction time 2.2 h. See Experimental Details.

reagent containing nitrile or ester functionalities. With a nitrile group present, the reaction proceeds well (entry 9, Table 1). Although for aryliodides containing an ethylester group we obtained only moderate yields (62% yield, entry 10, Table 1) due to side reactions. In order to examine the scalability of the Grignard formation in continuous flow process, we have prepared alcohol **11** on a 100 mmol scale. The larger volumes of *i*PrMgCl·LiCl that are involved required pumping of the starting materials directly through the pump heads of the Vapourtec R2/4+ flow unit. Here 19.6 g of compound **11** was obtained over 9.5 h processing time without any visible precipitation caused by hydrolysis reaction. The yield of the pure isolated product (93% yield) matched closely the yield of the small-scale reaction.

2.3. LiCl-Mediated Halogen/Mg Exchange Reaction Using Aryl bromides. Aryl bromides are known to be less reactive in the exchange reaction and often require higher reaction temperatures, which are not compatible with the presence of sensitive functional groups.[28] While optimizing the Grignard formation an increase in homocoupling product at higher temperatures was observed, in particular when starting from electron-rich aromatic bromides. We therefore focused our attention on activated aryl bromides (**1**−**3**), which required shorter processing time (2 h). The flow apparatus was constructed similarly to the previous arrangement (Scheme 7).

Using aryl bromides as starting materials the three flow stream system again utilises a combination of the Vapourtec R2+ and an external Knauer K120 pump. However, a modified 20-mL tubular coil (PTFE, wm mi.d.) was used to accommodate the slower Mg/bromide exchange reactions. Typically, the solution containing *i*PrMgCl·LiCl in THF was introduced at 0.1 mL/min to mix with the second stream (flow rate 0.1 mL/min) containing aryl bromides **21**−**25** in THF. A further T-piece was used to combine the organomagnesium reagent with a third aldehyde stream. Similar to earlier reactions, IR monitoring was used to

coordinate the addition of the third stream (flow rate: 0.2 mL/min) followed by a further 5-mL reaction coil (PTFE, 1/16" o.d.) held at room temperature. Finally, the output from this coil was directed into a saturated aqueous ammonium chloride solution. The results from these experiments using aryl bromides and *p*-tolualdehyde are shown in Table 2.

The initial exchange reaction of 3,4-dichlorobromobenzene **21** (entry 1, Table 2) and 2-chlorobromobenzene **23** (entry 3, Table 2) are very efficient and comparable with aryl iodides. The procedure can be readily adapted for bromopyridines as starting materials that led to alcohols **29** and **30** (entries 4 and 5, Table 2) in high yields.

3. CONCLUSIONS

This new flow chemical approach leading to the formation of Grignard reagents which are not commercially available should find numerous applications in organic synthesis programmes.

Additionally, the newly developed microscale ReactIR flow cell from Mettler-Toledo proved to be a convenient and versatile inline analytical tool for analysis during Grignard formation.

4. EXPERIMENTAL DETAILS

4.1. General Remarks. *NMR spectra:* recorded on a Bruker DPX-400 spectrometer. Corresponding solvent signal served as an internal standard: for ^{1}H NMR spectra in $CDCl_3$—the singlet of $CHCl_3$ at δ 7.26 (ppm), for ^{13}C NMR spectra in $CDCl_3$—the triplet at δ 77.16 ppm. Values of the coupling constant, *J*, are given in hertz (Hz).

High-resolution mass spectra (HRMS): recorded with a Waters Micromass LCT Premier spectrometer or an ABI/MDS Sciex Q-STAR Pulsar. Unless otherwise stated, the mass reported corresponds to the most abundant isotopes (e.g., ^{35}Cl).

Infrared Spectra. Conventional infrared spectra were recorded neat on Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories.

Tetrahydrofuran (THF). THF was dried by distillation from sodium wire using Ph_3CH as an indicator. Commercially available reagents were used as supplied. The reagent *i*PrMgCl·LiCl was supplied from Sigma-Aldrich (CAS: 807329-97-1).

Flash column chromatography: was carried out either manually [Merck 9385 Silica gel-Breckland 60 (0.040−0.063 mm)] or on a Biotage SP4 chromatography apparatus using Snap cartridges

GC Analysis and Iodometric Titration. For reactions in batch, the completion of the halogen/magnesium exchange was checked by GC analysis using tetradecane as internal standard. The yield of the magnesium reagent was determined by iodometric titration.

Flow reactions: were performed using a combination of Vapourtec R2/R4+ and Knauer 100 pumps, equipped with PTFE tubing (diameter 1 mm, reactor volume 10 mL). The mixing of the solution was achieved through a standard T-piece. The system was initially dried by flowing dry THF for 12 h at a flow rate of 0.1 mL/min. Additionally, we ensured constant reaction conditions by flowing dry THF for 2 h at a flow rate of 0.1 mL/min before injection of the reaction solutions. The injection ports were flushed with 5 mL of dry THF before filling the PEEK loops with the starting materials.

The FT-IR device used in this work is a ReactIR FD fitted with a room temperature deuterated triglycine sulfate (DTGS) detector. The ReactIR instrument was directly connected to a newly developed, microscale flow cell. The flow cell comprises an integrated 9 bounce attenuated total reflectance (ATR) gold sealed diamond sensor (referred to as DiComp) that allows in situ, real-time monitoring of a continuous flow stream. The full infrared spectral region is available with this micro flow cell (650−1950 cm^{-1} and 2250−4000 cm^{-1}) excluding the diamond "blind spot" which only allows very weak absorbance in this region. The IR flow cell has a removable head, allowing for easy cleaning, and an internal volume of 50 μL. It can be heated up to 120 °C using an external controller, and it can be operated at up to 7 bar pressure. OmniFit connections (1/4-28-UNF) enable the IR flow cell to be easily incorporated into any continuous flow chemical processing setup.

An integrated resistive thermal device (RTD) temperature sensor is also built into the cell in order to track its temperature, paying deference to the fact that the IR spectroscopy is temperature dependent. While the flow stream is running through the cell, scans are taken at predefined intervals. The system is controlled, and the raw data are collected and analyzed by the iC IR reaction analysis software (version 4.2).

The IR spectra of Grignard solutions prepared in batch were measured using a PTFE tubing connected to a syringe adapter, and the solutions were injected directly to the probe from a 5-mL syringe. The probe was dried by flushing with 15 mL of dry THF before each IR experiment.

4.2. Inline FT-IR Monitoring of ArMgX Formation. *Preparation of 0.5 M THF Solution of m-Methylphenylmagnesium Chloride.* To a round-bottom flask was added LiCl (265 mg, 6.25 mmol). The flask was heated (120 °C) under vacuum (~1 mm Hg) for 20 min and purged several times with argon followed by the addition of Mg turnings (304 mg, 12.5 mmol) and dry THF (10 mL). To the resulting mixture 3-iodotoluene (0.65 mL, 5 mmol) was added dropwise at rt (*Caution! As the reaction is exothermic, an ice bath was used to cool the mixture if the temperature exceeded 50 °C!*). After addition of the substrate the reaction mixture was stirred for 1 h at rt. The conversion of the reaction was determined by GC. The resulting solution of Grignard reagent was then decanted and transferred to a dry round-bottom flask under argon. The concentration (0.5 M) of active Grignard reagent was determined by titration with I_2.

Procedure for the Real-Time IR Monitored Preparation of m-Methylphenylmagnesium Chloride in Flow. The aryl iodide (1.0 equiv., 0.7 mmol), was dissolved in a 1 mL of THF and loaded into a 1 mL PTFE sample loop. The second 1 mL PTFE loop was filled with a 0.8 M THF solution of *i*PrMgCl.LiCl. The reagent mixtures were pumped at a flow rate of 0.2 mL/min. The reaction streams were combined at the T-piece and then directed into a 10 mL reaction coil at rt. A flow DiComp probe of the ReactIR FD was placed immediately after the coil for real-time IR measurements. IR spectra were recorded every 30 s. A back-pressure regulator (75 psi) was placed at the end of the setup. The reaction stream was then directed to a flask filled with a saturated aqueous solution of NH_4Cl.

Preparation of 0.5 M Toluene/THF (1 equiv) solution of m-Methylphenylmagnesium Chloride. To an oven-dried round-bottom flask were added Mg turnings (304 mg, 12.5 mmol), THF (0.4 mL, 5 mmol), and dry toluene (5 mL) under an Ar atmosphere. To the resulting mixture 3-iodotoluene (0.65 mL, 5 mmol) was added dropwise at rt. (*As the reaction is exothermic, an ice bath was used to cool the mixture, if the temperature exceeded 50 °C!*). After addition of the substrate, the reaction mixture was stirred for 2 h at rt. Subsequently, an additional 5 mL of dry toluene was added. Different solutions of *m*-methylphenylmagnesium chloride were prepared by adding dry THF. The IR spectra of

0.5 M *m*-methylphenylmagnesium chloride solution (in toluene) with 1, 2, 4, and 10 equiv of THF are shown in Figure 10.

4.3. General Procedure for the LiCl-Mediated I/Mg Exchange Reaction Using Aryl Iodides 1−7. *Procedure for Real-Time IR-Monitored Preparation of Grignard Reagents in Flow and Their Addition to Aldehydes/Ketones.* Two flow streams were pumped by the Vapourtec R4/R2+: stream 1 containing a solution of *i*PrMgCl·LiCl (1.1 equiv solved in 1 mL THF) loaded into a 1 mL PEEK loop and stream 2 containing aryl iodide **1**−**7** (1 equiv dissolved in 1 mL of THF). The mixtures were pumped (flow rate 0.2 mL/min) and mixed at a T-piece before entering the reactor (10 mL) at room temperature. The combined streams were directed to the IR flow cell of the ReactIR-FD via a PTFE coil. The mixture was then united with a third solvent stream (flow rate 0.4 mL/min) of the aldehyde or ketone (1.1 equif in 2 mL THF) via a second T-piece. The installation of two back pressure regulators (2 × 75 psi) before the second T-piece was used to ensure unidirectional flow through the PTFE coil (10 mL). On exiting the PTFE coil, the product flow stream was directed directly into a flask filled with a saturated aqueous solution of NH_4Cl. The suspension was transferred to a separating funnel. The organic phase was separated and the aqueous phase washed with CH_2Cl_2 (2×). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude material purified by flash column chromatography to afford the desired alcohols **11**−**20**.

4.4. LiCl−Mediated Br/Mg Exchange Reactions Using Aryl Bromides 21−25. *Procedure for Real-Time IR Monitored Preparation of Grignard Reagents in Flow and Their Addition to Aldehydes/Ketones.* Two flow streams were pumped by the Vapourtec R4/R2+: stream 1 containing a solution of *i*PrMgCl·LiCl (1.1 equiv solved in 1 mL THF) loaded into a 1 mL PEEK loop and stream 2 containing aryl bromide **20**−**25** (1 equiv solved in 1 mL THF). The mixtures were pumped (flow rate 0.1 mL/min) and mixed at a T-piece before entering the reactors (2 × 10 mL) at room temperature. The combined streams were directed to the IR flow cell of the ReactIR-FD via a PTFE coil. The mixture was then united with a third solvent stream (flow rate 0.2 mL/min) of the aldehyde or ketone (1.1 equiv in 2 mL THF) via a second T-piece. The installation of two back pressure regulators (2 × 75 PSI) before the second T-piece was used to ensure unidirectional flow through the PTFE coil (5 mL). On exiting the PTFE coil, the product flow stream was directed directly into a flask filled with a saturated aqueous solution of NH_4Cl. The suspension was transferred to a separating funnel. The organic phase was separated and the aqueous phase washed with CH_2Cl_2 (2×). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude material purified by flash column chromatography to afford the desired alcohols **26**−**30**.

5. ANALYTICAL DATA

***m*-Tolyl(*p*-tolyl)methanol (11):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.16 (m, 7H), (7.12, br d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 2.47 (br s, 1H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 141.2, 138.1, 137.2, 129.2, 128.3, 127.2, 126.6, 123.7, 76.1, 21.6, 21.2; ESI-HRMS [M − H$^+$] calculated for $C_{15}H_{15}O$: 211.1117, found: 211.1121.

Phenyl(*m*-tolyl)methanol (12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.34 (m, 4H), 7.33−7.22 (m, 3H), 7.20 (br d, J = 7.5 Hz, 1H), 7.12 (br d, J = 7.2 Hz, 1H), 5.79 (s, 1H), 2.44 (br s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.9, 138.2, 128.5, 128.45, 128.4, 127.5, 127.3, 126.6, 123.7, 76.3, 21.6; ESI-HRMS [M − H$^+$] calculated for $C_{14}H_{13}O$: 197.0961, found: 197.0964.

Furan-2-yl(*p*-tolyl)methanol (13): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 0.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 6.32 (dd, J = 3.1 Hz, 1.8 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 5.78 (s, 1H), 2.61 (br s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 142.5, 138.1, 137.9, 129.2, 126.7, 110.3, 107.3, 70.1, 21.2; ESI-HRMS [M − H$^+$] calculated for $C_{12}H_{11}O_2$: 187.0754, found: 187.0757.

1-Phenyl-1-(*m*-tolyl)ethanol (14): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7−44 (m, 2H), 7.38−7.32 (m, 2H), 7.31−7.28 (m, 1H), 7.28−7.26 (m, 1H), 7.25−7.22 (m, 2H), 7.13−7.07 (m, 1H), 2.37 (s, 3H), 2.38 (br s, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 148.1, 137.8, 128.3, 128.2, 127.8, 127.0, 126.6, 126.0, 123.1, 76.3, 31.0, 21.7; ESI-HRMS [M − H$^+$] calculated for $C_{15}H_{15}O$: 211.1117, found: 211.1114.

1-(*m*-Tolyl)cyclohexanol (15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 2.41 (s, 3H), 1.93−1.74 (m, 7H), 1.74−1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 137.8, 128.2, 127.5, 125.5, 121.7, 73.2, 39.0, 25.7, 22.3, 21.7; EI-MS [M$^{+\bullet}$] calculated for $C_{13}H_{18}O$: 190.1352, found: 190.1360.

***p*-Tolyl(4-(trifluoromethyl)phenyl)methanol (16):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.79 (s, 1H), 2.78 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.8, 140.4, 138.0, 129.5, 126.8, 126.7, 125.5, 125.4, 75.7, 21.2; ESI-HRMS [M − H$^+$] calculated for $C_{15}H_{12}F_3O$: 265.0835, found: 265.0836.

(3-Chlorophenyl)(*p*-tolyl)methanol (17): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.28−7.22 (m, 5H), 7.21−7.15 (m, 2H), 5.74 (s, 1H), 2.49 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 140.5, 137.8, 134.4, 129.8, 129.4, 127.6, 126.7, 124.7, 75.6, 21.2; ESI-HRMS [M − H$^+$] calculated for $C_{14}H_{12}ClO$: 231.0571, found: 231.0575.

(3-Methoxyphenyl)(*p*-tolyl)methanol (18): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.21 (m, 3H), 7.14 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 2.1 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 8.2, 2.0 Hz, 1H), 5.77 (s, 1H), 3.78 (s, 3H), 2.33 (s, 3H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 137.3, 134.7, 129.9, 128.3, 52.7, 21.1, 14.7; ESI-HRMS [M − H$^+$] calculated for $C_{15}H_{15}O_2$: 227.1067, found: 227.1073.

3-(Hydroxy(*p*-tolyl)methyl)benzonitrile (19): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.81 (s, 1H), 2.35 (s, 3H), 2.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 140.1, 138.1, 131.0, 130.9, 130.0, 129.6, 129.2, 126.7, 118.9, 112.3, 75.1, 21.2; ESI-HRMS [M − H$^+$] calculated for $C_{15}H_{12}NO$: 222.0913, found: 222.0916.

Ethyl 4-(hydroxy(*p*-tolyl)methyl)benzoate (20): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.82 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.35 (br s, 1H), 2.33 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 148.9, 140.6, 137.9, 129.9, 129.7, 129.5, 126.8, 126.3, 75.9, 61.1, 21.2, 14.5; EI-MS [M$^{+\bullet}$] calculated for $C_{17}H_{18}O_3$: 270.1250, found: 270.1261.

(3,4-Dichlorophenyl)(*p*-tolyl)methanol (26): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.23−7.13 (m, 5H), 5.69 (s, 1H), 2.57 (br s, 1H), 2.35 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 140.1, 138.1, 132.6, 131.3, 130.4, 129.6, 128.4, 126.7, 125.9, 75.0, 21.2.

***p*-Tolyl(4-(trifluoromethyl)phenyl)methanol (27):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.82 (s, 1H), 2.50 (br s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.8, 140.4, 138.0, 129.6, 126.8, 126.7, 125.5, 125.4, 75.7, 21.2; EI-MS [$M^{+\bullet}$] calculated for $C_{14}H_{13}OCl$: 232.0649, found: 232.0655.

(2-Chlorophenyl)(*p*-tolyl)methanol (28): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.7, 1.4 Hz, 1H), 7.35 (dd, J = 7.9, 1.0 Hz, 1H), 7.33 (dd, J = 7.5, 1.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (td, J = 7.6, 1.6 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 6.17 (s, 1H), 2.55 (br s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.5, 137.6, 132.5, 129.6, 129.3, 128.7, 128.0, 127.1, 127.0, 72.6, 21.2; EI-MS [$M^{+\bullet}$] calculated for $C_{15}H_{13}OF_3$: 266.0913, found: 266.0921.

Pyridin-3-yl(*p*-tolyl)methanol (29): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 1.4 Hz, 1H), 8.30 (dd, J = 4.7, 1.2 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.24−7.16 (m, 3H), 7.12 (d, J = 7.9 Hz, 2H), 5.76 (s, 1H), 5.12 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.8, 140.6, 140.3, 137.6, 134.6, 129.4, 126.6, 123.6, 73.6, 21.2; ESI-HRMS [M + H^+] calculated for $C_{13}H_{14}NO$: 200.1075, found: 200.1066.

Pyridin-2-yl(*p*-tolyl)methanol (30): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1H), 7.61 (td, J = 7.7, 1.7 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.21−7.12 (m, 4H), 5.73 (s, 1H), 5.04 (br s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 147.9, 140.5, 137.6, 136.9, 129.4, 127.1, 122.4, 121.4, 75.0, 21.2; ESI-HRMS [M + H^+] calculated for $C_{13}H_{14}NO$: 200.1075, found: 200.1082.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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