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A robustness screen for the rapid assessment of chemical reactions

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In contrast to the rapidity with which scientific information is published, the application of new knowledge often remains slow, and we believe this to be particularly true of newly developed synthetic organic chemistry methodology. Consequently, methods to assess and identify robust chemical reactions are desirable, and would directly facilitate the application of newly reported synthetic methodology to complex synthetic problems. Here, we describe a simple process for assessing the likely scope and limitations of a chemical reaction beyond the idealized reaction conditions initially reported. Using simple methods and common analytical techniques we demonstrate a rapid assessment of an established chemical reaction, and also propose a simplified analysis that may be reported alongside new synthetic methodology.

Newly reported synthetic chemistry methodologies strive to provide widely applicable transformations that are more efficient, are more environmentally benign, or provide routes to previously inaccessible chemical motifs[1–7]. It is desirable that new reactions are robust and, once reported, incorporated into the synthetic organic chemists' repertoire of useful reactions as quickly as possible. The importance of developing robust synthetic methodology for the preparation of drug-like molecules, and the subsequent implications for drug development, have recently been reported[8]. We believe a major hurdle to the application of a new chemical methodology to real synthetic problems[9–12] is a lack of information regarding its application beyond the idealized conditions of the seminal report. Two major considerations in this respect are the functional group tolerance of a reaction and the stability of specific chemical motifs under reaction conditions.

The utility of new chemical methodology, including its tolerance to chemical functionality, is typically demonstrated within the substrate scope of a methodological paper. Consider a typical palladium-catalysed cross-coupling reaction of an arylbromide and an arylboronic acid (Fig. 1)[13]. Once reaction conditions are established, the nature and position of R and R′ will be varied and, typically, successful results will be reported. Alternatively, the preparation of natural products or biologically active molecules[14,15], or the derivatization of prepared products[16,17], is often reported alongside new methodology to demonstrate its potential. Substrate scope in particular is a critical element of new methodological papers, often providing information beyond functional group tolerance, particularly with regard to mechanism. Despite the utility of these methods, they have inherent limitations in terms of assessing a reaction for application to non-idealized synthetic problems. Within substrate scope, functional group tolerance is typically incorporated into an assessment of the steric and electronic limitations of the methodology and is not assessed discretely: indeed, the non-reactive functional group (consider R or R′) typically influences the reactive centre. We suggest that the non-reactive functionality is generally constrained within a small substrate, and that its influence on the reaction may not necessarily be extrapolated to larger or more flexible substrates. The preparation of natural products or the derivatization of compounds prepared within a report invariably provides little information with which to facilitate an assessment of the application of the methodology in a broader context. Naturally, the molecules prepared tend to be selected to highlight the strengths of the new methodology, and the derivatization of products has a tendency towards simple transformations.

Taking into account the limitations of the current methods, we propose that a lack of understanding regarding the application of a given reaction to non-idealized synthetic problems can result in a reluctance to apply new methodology. Confidence in the utility of a new reaction develops over time—often over a number of years—as the reaction is gradually applied within total syntheses, follow-up methodological papers are published, or personal experience is developed. Unfortunately, even when this information has evolved, it is often widely dispersed, fragmented and difficult to locate. To address this problem, both the tolerance of a reaction to chemical functionality and of the chemical functionality to the reaction conditions must be established when appropriate, and reported in an easily accessible manner, preferably alongside the new methodology. This will facilitate more rapid incorporation of the given reaction into the synthetic chemists' toolbox. It should be noted that, to the best of our knowledge, no discrete method for assessing the stability of chemical functionality or motifs, including heterocycles (of particular importance within the pharmaceutical and agrochemical industries), has been reported.

We present a facile methodology that can be applied to new and existing chemical transformations, which in contrast to established methods can simultaneously provide a fast and discrete assessment of the functional group tolerance of the reaction and the stability of

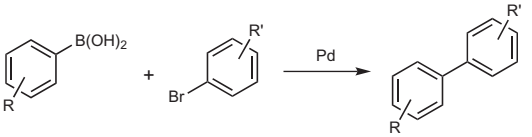

Figure 1 | A typical palladium-catalysed Suzuki–Miyaura cross-coupling. The scope of this reaction would traditionally be investigated by assessing the nature of R and R′ in terms of their electronic influence (that is, electron-donating functional groups (OMe, NMe_2) and electron-withdrawing functional groups (CO_2Me, NO_2)) and their steric influence by varying the position of a given substituent (*ortho*, *meta* or *para*) on the reactive centre.

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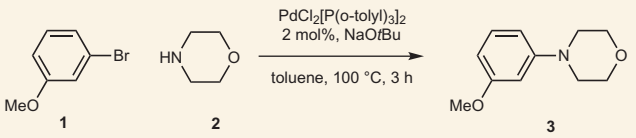
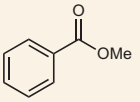
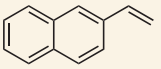
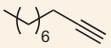
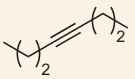
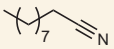
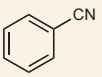
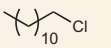
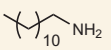
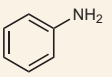
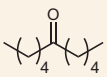
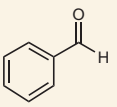
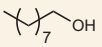
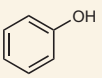
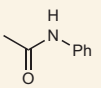
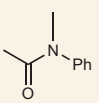
Table 1 | Examining functional group compatibility.



Entry	Additive	Yield of 3 (%)*	Additive remaining (%)*	SM remaining (%)*	Entry	Additive	Yield of 3 (%)*	Additive remaining (%)*	SM remaining (%)*
A0	None	89†	-		A9		49 –	60 –	0
A1		86 ✓	97 ✓	0	A10		75 ✓	100 ✓	0
A2		0 x	100 ✓	100	A11		82 ✓	99 ✓	0
A3		79 ✓	100 ✓	0	A12		20 x	95 ✓	75
A4		84 ✓	100 ✓	0	A13		82 ✓	85 ✓	0
A5		23 x	90 ✓	61	A14		0 x	100 ✓	100
A6		37 –	49 –	0	A15		21 x	0 x	0
A7		3 x	0 x	0	A16		17 x	100 ✓	65
A8		9 x	96 ✓	82	A17		80 ✓	83 ✓	0

The standard reaction is undertaken in the presence of one molar equivalent of the given additive. The yield of 3, and the additive and starting material remaining after reaction is given. Colour coding should help the ready assessment of the data: green '✓' (above 66%), yellow '–' (34–66%), red 'x' (below 34%). *GC yield. †Isolated yields. SM is starting material.

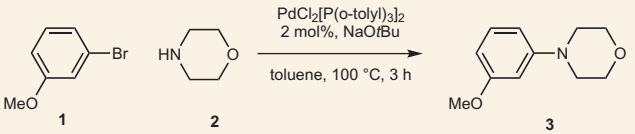
these chemical motifs to the reaction conditions. Our method intentionally decouples the functional group from the reactive centre, although, as a consequence, it is not feasible to simultaneously assess the direct steric/electronic impact of a given functionality on the reaction centre. We therefore propose this method to be highly complementary to the traditional substrate scope, and the data obtained should be reported alongside the traditional substrate scope. This approach will provide data that directly correlate to both the likely tolerance and limitations of a chemical transformation. It should be noted that as with a traditional substrate scope, a static set of reaction conditions is assessed, and as such, a negative result in the screen does not preclude that a given functionality/chemical motif may be compatible if reaction conditions are optimized.

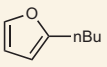
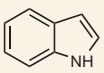
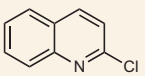
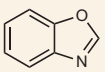
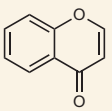
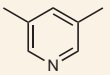
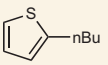
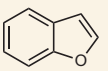
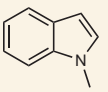
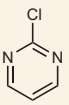
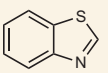
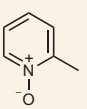
Our approach is conceptually very simple. A standard reaction is undertaken in the presence of one molar equivalent of an 'additive' with a given chemical functionality or structural motif. Reactions are analysed using gas chromatography (GC), providing a quantitative assessment of the yield and therefore the tolerance of the reaction to the given functionality, and of the stability of the additive to the reaction conditions. We propose that the intermolecular introduction of a secondary functionality is more likely to parallel the behaviour of the larger or more flexible substrates typically encountered in the synthesis of complex molecules, rather than constraining the functionality within small bifunctional molecules as is typical within reaction scope investigations.

Results

To demonstrate our analytical methodology, we selected the widely applied Buchwald–Hartwig reaction. Using the seminal catalyst system independently reported by both Buchwald and Hartwig—$PdCl_2[P(o\text{-tolyl})_3]_2$ (refs 18,19)—we investigated the reaction of 3-bromoanisole 1 and morpholine 2 (Table 1). In the absence of

Table 2 | Examining heterocycle compatibility.



Entry	Additive	Yield of 3 (%)*	Additive remaining (%)*	SM remaining (%)*
B0	None	89†	–	
B1		82 ✓	100 ✓	0
B2		0 x	0 x	96
B3		11 x	100 ✓	75
B4		70 ✓	83 ✓	0
B5		0 x	81 ✓	99
B6		76 ✓	70 ✓	5
B7		10 x	0 x	36
B8		61 –	28 x	13
B9		75 ✓	51 –	0
B10		8 x	85 ✓	79
B11		77 ✓	85 ✓	0
B12		81 ✓	87 ✓	0
B13		83 ✓	100 ✓	0
B14		4 x	0 x	87
B15		8 x	70 ✓	66
B16		54 –	81 ✓	0

The standard reaction is undertaken in the presence of one molar equivalent of the given additive. The yield of **3**, and the additive and starting material remaining after reaction is given. Colour coding should help the ready assessment of the data: green '✓' (above 66%), yellow '–' (34–66%), red 'x' (below 34%). *GC yield. †Isolated yield. SM is starting material.

any additive, the reaction was determined to proceed to give **3** in 89% yield (Table 1, entry A0; Table 2, entry B0).

The reaction was then repeated in the presence of various additives, and the yield of product **3** as well as the amount of additive and starting material remaining after the reaction were determined. Measuring the remaining starting material is critical so as to determine whether the additive merely retards the rate of reaction, or is detrimental to the formation of the product. The additives were divided into two groups: 'functional groups' **A** and 'heterocycles' **B**, with the results reported in Tables 1 and 2, respectively. The additives were selected to cover a broad range of common functionalities and chemical motifs, and are all available commercially. It should be noted that the additives were not evaluated with regard to possible influence on reactivity or stability to the reaction conditions. We feel that a more critical selection process should be avoided as it could potentially lead to a bias in the screen, with additives likely to work being chosen in preference to those predicted to fail.

Before undertaking experimentation, GC calibration of starting material **2**, product **3** and the additives was undertaken. We have successfully demonstrated a batch calibration technique inspired by Hartwigs' analysis of complex mixtures applied in the high-throughput discovery of new chemical reactivity[20] (see also ref. 21). This allows for the simultaneous calibration of multiple compounds, significantly reducing analysis time (Supplementary Section S3). To minimize experimental time, reactions were run in parallel: the standard reaction was prepared on scale, and subsequently distributed to reaction vessels containing a given additive. After the predetermined reaction time, the reactions were directly analysed using GC. It is critical that this method is simple and fast so as to maximize its utility and encourage uptake within the synthetic organic

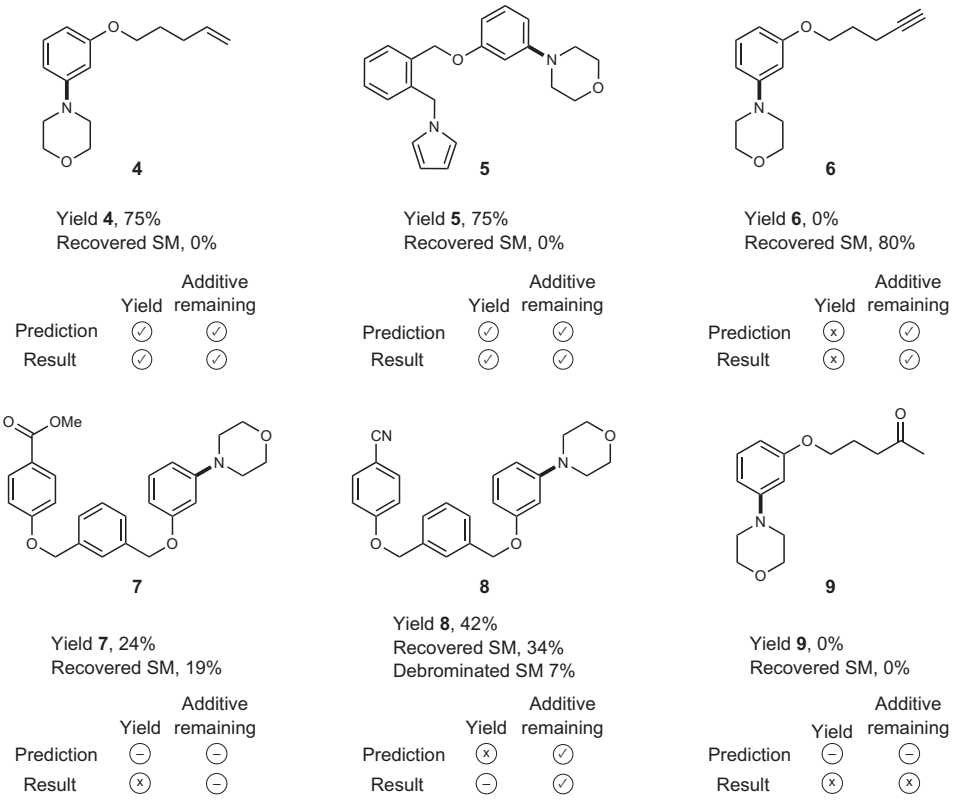


Figure 2 | Results of the preparation of multifunctional substrates to validate the predictions of the robustness screen. Reaction conditions were identical to those used in the screen. Yields are for isolated compounds. SM, starting material. '✓' (above 66%), '–' (34–66%), and '✗' (below 34%).

community, and, as such, it should be noted that experimentation and analysis of all additives was undertaken in one week.

Discussion

The data generated from this screen are simple, easy to interpret, and of significant value. Consideration of group **A** clearly demonstrates that aliphatic and aromatic alcohols and amines are not well tolerated by the reaction conditions. The secondary amide, terminal alkyne, aromatic aldehyde and aromatic nitrile are also not tolerated. In contrast, reactions in the presence of one equivalent of an internal alkyne, terminal alkene, styrene, aliphatic nitrile, tertiary amide, aryl or aliphatic chloride proceed in excellent yield, and importantly the additive is not significantly degraded. The reaction conditions are moderately tolerant of both aromatic esters and aliphatic ketones, although the stability of the additive is only moderate. In the same manner, analysis of group **B** demonstrates which heterocycles (i) inhibit reactivity and (ii) are stable to the reaction conditions. Although these results do not provide definitive information on the success of a specific reaction as specific electronic, steric and conformational effects cannot be considered, it provides an overview of which structural motifs are likely to be tolerated by the reaction conditions and which structural motifs are stable to the reaction conditions. This information can be applied in the assessment of whether the reaction is likely to be suitable for a given substrate, and in the design of synthetic routes.

To give support to the conclusions of our analysis we prepared a number of multifunctional substrates in which the secondary functionality should not have direct steric or electronic influence on the arylbromide moiety. Reaction of the corresponding bromides with morpholine using standard conditions was undertaken, and the results are given below in Fig. 2.

Compounds **4** and **5** were obtained in 75% and 81% yields, respectively, which correlate well with the yields of 86% and 82% obtained in the screen (Table 1, entry A1; Table 2, entry B1). Failure to synthesize **6** using the standard conditions also correlates strongly with the robustness screen, as the terminal alkyne was shown to completely inhibit reactivity (Table 1, entry A2). The recovery of the starting material in 80% yield also demonstrates the stability of the functionality to the reaction conditions, as predicted by the screen. Compound **7** was synthesized in 24% yield, in comparison to the 49% predicted in the robustness screen (Table 1, entry A9). The combined sum of the product yield and the starting material of 43% is representative of the stability of the functionality to the reaction conditions, and is comparable with the 60% shown in the screen. Compound **8** was synthesized in 42% yield (compared with the 20% observed in the screen; Table 1, entry A12), with a total yield of 83%, comparable to the 95% observed in the screen. These examples demonstrate that the behaviour of substrates that are not predicted to show excellent reactivity and stability, or complete inhibition of the reaction, are more difficult to predict using the robustness screen, although the results obtained correlate to a significant degree with the those obtained in the screen. The failure to isolate compound **9** is attributed to polymerization of the starting material and product under the reaction conditions. The mass balance of the reaction was 16%, with significant amounts of insoluble material also observed. Analysis of the crude reaction product suggests some product formation and that starting material remained, although no clean material was isolated. This result further demonstrates the complexity of predicting the behaviour of substrates that display intermediate reactivity and/or stability. Overall, we have shown that the robustness screen correlates very well with results for the reaction of the corresponding multifunctional substrates when these substrates are expected to show excellent reactivity/stability, or complete inhibition of reaction. Using the screen to predict the behaviour of substrates that show intermediate

reactivity/stability is more challenging, although typically the correlation between the robustness screen and the results shown in Fig. 2 is significant.

We have provided an extensive and quantitative demonstration of this methodology as applied to the initial reaction conditions reported for the Buchwald–Hartwig coupling reaction. This extended analysis is critical to demonstrate the utility of the methodology, and provides a comprehensive assessment of the investigated reaction in a short time period. However, we understand that the application of a quantitative analysis may, in some instances, be considered unnecessary or too time-consuming, and consequently we propose a shorter qualitative analysis to be applied and reported alongside the reaction scope of new methodologies, as appropriate (Supplementary Section S6). Two batches of ten additives, divided into 'functional groups' and 'heterocycles', can be investigated. Batch calibration solutions can be prepared, analysed once, and then utilized for multiple investigations. Using a standard for comparison, a semi-quantitative analysis can be undertaken using any appropriate analytical technique (HPLC, GC, GC-MS, LC-MS). We propose that, by using this method, experimentation and analysis can be completed in less than two days, excluding reaction time, providing valuable data.

This short analysis provides data typically obtained over a significant time period from multiple sources. The discrete evaluation of chemical motifs and functionality with respect to a chemical reaction is highly complementary to the information generated in a typical reaction scope, and should be reported concurrently. Importantly, we also envisage that the retrospective application of this methodology will be of particular use in an industrial environment where the preparation of structurally similar analogues is commonplace. This method can be tailored readily to assess a chemical reaction with respect to specific functionality or motifs within a project, determining the suitability of the reaction before the preparation of complex molecules that may prove either intrinsically unstable to the reaction conditions, or inhibit reactivity. We strongly believe that this method will facilitate the application of new and existing chemical reactions within both academic and industrial environments.

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Author contributions

F.G. and K.D.C. conceived the concept and experiments. K.D.C. performed all experiments. Both authors discussed the results and co-wrote the paper.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to F.G.

Competing financial interests

The authors declare no competing financial interests.