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Intermolecular Reaction Screening as a Tool for Reaction Evaluation

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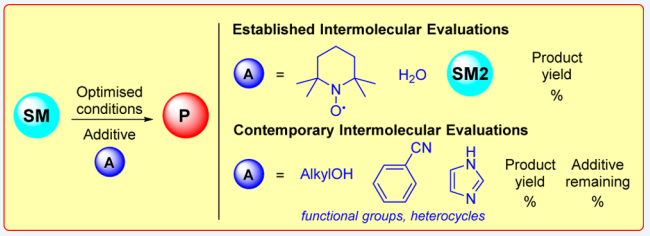
CONSPECTUS: Synthetic organic chemistry underpins many scientific disciplines. The development of new synthetic methods proceeds with the ultimate intention of providing access to novel structural motifs or providing safer, increasingly efficient, or more economical chemical reactions. To facilitate the identification and application of new methods in solving real synthetic problems, this Account will highlight the benefits of providing a fuller picture of both the scope and limitations of new reactions, with a primary focus on the evaluation of functional group tolerance and stability of a reaction using intermolecular screens.



This Account will begin with a discussion on reaction evaluation, specifically considering the suitability of a given reaction for application in target-oriented synthesis. A comparison of desirable and essential criteria when choosing a reaction is given, and a short discussion on the value of negative and qualitative data is provided. The concept of intermolecular reaction screening will be introduced, and a direct comparison with a traditional substrate scope highlights the benefits and limitations of each and thus the complementary nature of these approaches.

In recent years, a number of ad hoc applications of intermolecular screens to evaluate the functional group tolerance of a reaction or the stability of functional groups to a given set of reaction conditions have been reported, and will be discussed. More recently, we have developed a formal high-throughput intermolecular screening protocol that can be utilized to rapidly evaluate new chemical reactions. This simple and rapid protocol enables a much broader evaluation of a reaction in terms of functional group tolerance and the stability of chemical motifs to the reaction conditions than is feasible with a typical reaction scope. The development, evaluation, and application of this method within our group will be discussed in detail, with both the potential benefits and limitations highlighted and discussed.

In addition, we will discuss more recent applications of intermolecular screens from both industrial and academic groups. Modifications in protocols and applications will be highlighted, including problem based evaluations, assessment of biomolecule compatibility, establishment of relative rate data, and the identification of new reactivity. Such screens have been applied in diverse chemistries including C−H functionalization reactions, frustrated Lewis-pair-catalyzed hydrogenations, heterogeneous catalysis, photoredox catalysis, enantioselective organocatalysis, and polymer science. We feel that the application of intermolecular screens to such a diversity of reactions highlights the practical simplicity of such screens. A summary of the applications and potential utility of intermolecular reaction evaluation is provided.

■ INTRODUCTION

Reaction Evaluation

In target-oriented synthesis, potentially useful chemical reactions are evaluated on personally defined criteria. While practicality, cost, and yield may be specific requirements, broadly we seek reactions that we are confident (for new methods this can stem from either the reputation of the authors or the detail of a report) will provide access to our target compound in the quantity and purity that we require (Table 1). Although what is "required" from a reaction can widely vary, compromising on "desirable" criteria is commonplace.

Selecting suitable protocols to transform a novel compound is not trivial, particularly when we consider new synthetic methods. We are often forced to make qualitative judgments based on the data available from a single substrate scope, and if we are lucky, from an occasional application. Although our ability to predict the outcome of a reaction precisely is typically very poor and reactions often fail, in the absence of an effective alternative,[1] this is the dominant practice of synthetic chemists.

Table 1. Common Criteria for Evaluating the Potential Application of Chemical Reactions

desirable	essential
• excellent yield	• adequate reactivity
• excellent selectivity	• adequate substrate stability
• experimentally simple (including purification)	• adequate functional group tolerance
• short reaction time	• product is isolable
• commercial starting materials	
• high-efficiency (cost, atom economy, etc.)	

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An increase in relevant data, quantitative or qualitative, would clearly facilitate our judgments. Although quantitative data may intuitively seem more valuable, it is worth highlighting that qualitative data is an integral part of reaction evaluation and scientific reporting. An absolute value for a reaction yield is widely accepted as a crucial part of a synthetic report, yet is clearly a qualitative representation dependent on multiple factors, many of which, including the "hands" of the chemist, are clearly unquantifiable. Matter-of-factly, we accept reported yields as a qualitative indication of the *likely* outcome of an experiment: very good, good, or poor. Rightly, despite the qualitative nature of the reaction yield, this data is considered both integral to a scientific report and extremely useful when evaluating a given reaction.

Here it is also important to highlight the value of negative data when selecting an appropriate reaction. Although the value of demonstrating that a reaction is tolerant of a given functionality is clear, defining which functional groups and chemical motifs are unstable to reaction conditions or inhibit reaction is just as valuable when evaluating the utility of a reaction. While this is broadly understood, it is poorly reflected in the literature, with substrate scopes having a tendency to be comprised of reactions that give typically good to excellent yields. An occasional moderate yield or failed reaction may be reported, though we tacitly accept that many more substrates are prepared, tested, and left out because they simply did not work. The inclusion of such "negative" data would be of great use in facilitating the application and further development of new protocols.

A substrate scope arguably provides the most valuable information about a newly reported method, particularly with regard to the steric, electronic, and functional group tolerance of a reaction. It therefore follows that a more diverse and larger substrate scope could be of great value. Unfortunately, substrate accessibility and what can reasonably be expected in terms of exploring an essentially unlimited number of possible substrates, results in a scope being naturally limited in size. In recent times, a number of reports have explored the use of intermolecular additives as an alternative approach to provide information on the functional group tolerance of a given reaction, without recourse to the labor intensive evaluation of endless substrates. In these studies, the influence of this secondary functionality on an optimized reaction is reported (Figure 1).

While such an approach has often been used in the community in an ad hoc manner, broader and more systematic evaluations have recently become more prominent, and the development of formal protocols has been reported. Should we also consider widely established intermolecular reaction evaluations such as stoichiometric competition or inhibition experiments (e.g., radical inhibitors, H_2O), uncountable examples have been reported over the years. However, herein we will focus on recent applications that primarily evaluate functional group tolerance. For a general comparison of intermolecular screens and a traditional substrate scope see Table 2.

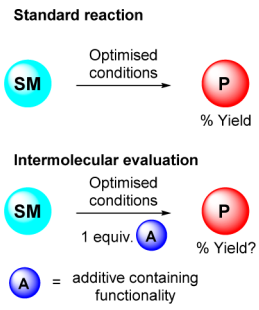

Figure 1. Concept of intermolecular reaction evaluation.

In 2009 Fox reported an "inhibition study" in which the yields of a number of three-component cycloaddition reactions performed in the presence of one molar equivalent of a series of different functional groups were given (Scheme 1).[2]

In 2011, Enthaler reported a number of studies on metal-catalyzed reductions of sulfoxides (Scheme 2).[3−5] The selectivity of these reactions was evaluated using intermolecular competition experiments, the authors reporting both the yield of the reaction and the reactivity of the additive.

In 2011, Stephan explored this concept in more detail while studying a frustrated Lewis-pair (FLP) mediated hydrogenation of imines.[6] Having optimized the reaction, the impact of introducing one molar equivalent of a number of additives was reported. Steps to validate these results were taken, subjecting imines bearing functionality that the screen indicated would either have no influence (imine **3**) or inhibit the reaction (imine **4**) to the reaction conditions (Scheme 3). Importantly, both the positive and negative control reactions were reported to provide a good correlation, though the actual yields were not given.

Stephan proposed that bimolecular approaches to evaluate functional group tolerance are valid, and highlights the expeditious nature of such a screen and the potential for automation. However, it is importantly noted that such an approach does not provide a comprehensive evaluation of a given method, especially when considering the electronic influence of a substituent on the reaction. A similar approach by Fu reported the influence of additives on the yield of a palladium-catalyzed dehydrohalogenation of alkyl bromides.[7]

In 2012, we began developing and evaluating a systematic intermolecular screen for the *high-throughput* evaluation of synthetic methodology.[8−10] We were inspired by high-throughput protocols for reaction discovery[11−13] and a desire to facilitate the application of new methodology to solve "real" synthetic problems. As discussed earlier, we proposed that providing more information about the functional group tolerance of a reaction, or lack thereof, would be highly beneficial.

Key considerations for the design of our protocol included the following:

- How can we rapidly evaluate the tolerance of a reaction to a greater range of chemical functionality than would be practical in a substrate scope?
- Can we simultaneously provide a discrete evaluation of the stability of chemical functionality to reaction conditions?
- Practically, the protocol must be simple, cheap, and rapid to perform.

Our ultimate goal was to encourage the undertaking of a screen and presentation of results as part of the seminal publication. Furthermore, by formalizing the process, we hoped that both positive and negative results would be reported, providing a better overview of new methods.

The basis of our "robustness screen" was identical to the methods discussed above: we sought to evaluate the impact of

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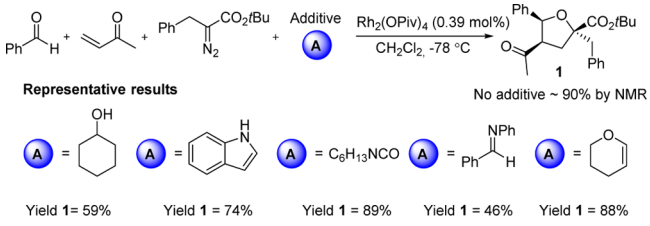
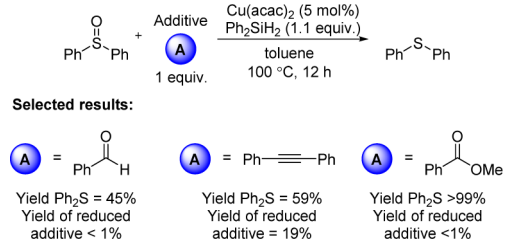
Table 2. Simple Comparison of a Traditional Substrate Scope and an Intermolecular Reaction Evaluation

Reaction parameter evaluated	Traditional Substrate Scope	High-Throughput Intermolecular screen
Sterics	Readily assessed	No information
Electronics	Readily assessed	No information
Functional group tolerance	Limited by ease of substrate accessibility and resources required	Simple and expeditious
Functional group stability	Limited by ease of substrate accessibility and resources required – no discrete evaluation	Simple, expeditious & discrete
Predictive potential for real synthetic problems	Qualitative	Qualitative

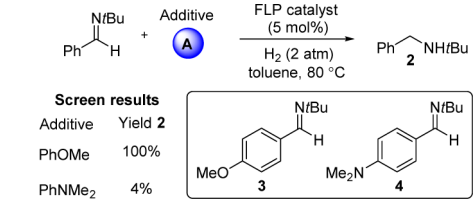
Scheme 1. A Rhodium-Catalyzed Cycloaddition Reaction Developed by Fox Was Evaluated Using an Intermolecular Additive Screen[2]



Scheme 2. Enthaler Highlights the Benefits of Evaluating the Stability of an Additive to the Reaction Conditions[5]



Scheme 3. A Preliminary Assessment of Functional Group Tolerance Using Intermolecular Additives by Stephan[6]



an intermolecular additive on an optimized reaction. Following the defined reaction time, the yield, the conversion of the reaction, and the amount of additive remaining were determined (Figure 2). Respectively, these measurements demonstrate the impact of the additive on the reaction

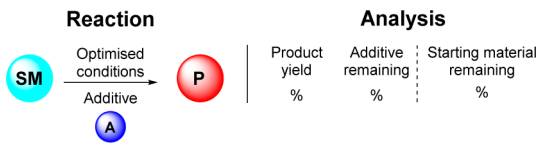


Figure 2. General concept of a robustness screen.[8]

(poisoning or retardation of rate) and the stability of the additive to the reaction conditions.

Employing basic parallel synthesis techniques, batch reaction preparation, and standard GC analysis, we demonstrated that ~40 additives can be evaluated in 1 week without any specialist equipment.[9,10] Validation of the experimental protocols demonstrated that reactions can be performed reproducibly on a 0.100 mmol scale and that single-point batch calibration of the gas chromatograph for all products, starting materials, and additives is sufficiently accurate for practical purposes. GC analysis is the time-limiting factor excluding reaction time, and therefore more rapid analytical techniques would further expedite such screens. For a more in depth discussion, see ref 10.

For the development of our method, we evaluated the seminal conditions reported for the Buchwald–Hartwig amination reaction, screening nearly 40 additives (Figure 3A). By selecting an established and well-explored reaction, we were able to undertake a preliminary evaluation of the data generated against literature precedent. To further evaluate the results, we prepared substrates containing a secondary functional group that had been evaluated in the intermolecular screen. A comparison of robustness of screen results and the reactions employing these bifunctional substrates gave a qualitatively valid correlation (Figure 3B). Reactions I–III, which were predicted to perform very well or very poorly, showed an excellent correlation. The yields of reactions V and VI with motifs that demonstrate moderate/poor stability in the screen were logically lower than directly predicted, as unlike in the screen, the product is also unstable to the reaction conditions.

Although this screen provides what we propose to be both valid and useful data, it is important to be critical and clarify the characteristic limitations of such an approach. A crucial consideration is the validity of the data generated and whether extrapolating the results to more complex substrates is reasonable. While we feel the data generated from our initial evaluation of the Buchwald–Hartwig reaction correlates well with both the published literature and the experimental evaluation, clearly the absolute values from the screen are not likely to reflect a precise outcome for any given reaction. In addition, the intermolecular nature of this screen precludes the evaluation of steric and electronic parameters, though these aspects of a reaction are typically demonstrated in a substrate scope.

We suggest that our initial validation is indicative of a good qualitative guide to functional group tolerance and stability. Naturally, chemical "common sense" must be maintained when making extrapolations from the data. For example, as

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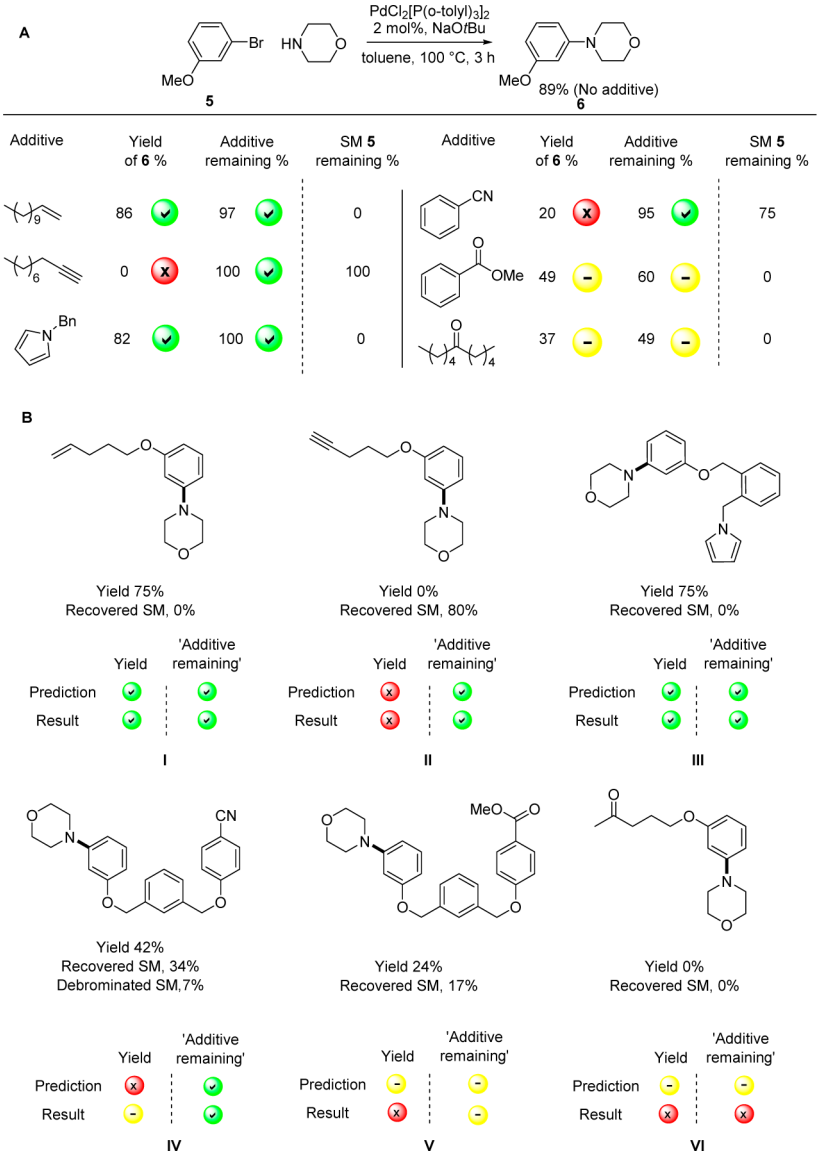
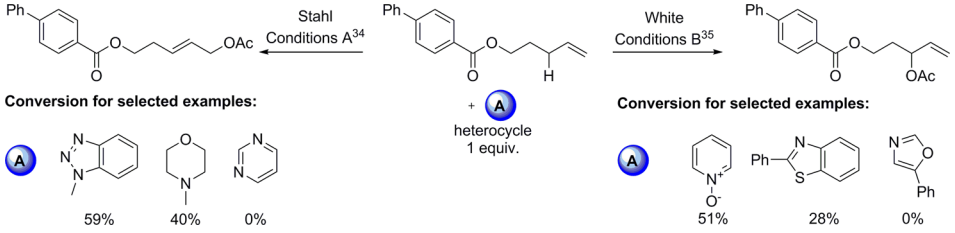


Figure 3. (A) Selected results from an intermolecular evaluation of additives for a Buchwald–Hartwig amination reaction. Color-coding was used to provide a rapid qualitative assessment: red 0–33%, yellow 34–66%, green 67–100%. (B) The reaction of bifunctional substrates was undertaken to evaluate the screen results.[8]

Scheme 4. In Work Towards Overcoming Reaction Inhibition, an Intermolecular Screen Was Used to Evaluate the Tolerance of Complementary C–H Acetoxylation Protocols[a] to Lewis-Basic Heterocycles[14]



[a]Conditions A: $Pd(OAc)_2$ (10 mol %), 4,5-diazafluorenone (10 mol %), *p*-benzoquinone, NaOAc, AcOH, 1,4-dioxane, 60 °C, 48 h. Conditions B: $Pd(OAc)_2$/$PhS(O)C_2H_4S(O)Ph$ (10 mol %), *p*-benzoquinone, AcOH, 1,4-dioxane, 45 °C, 48 h.

demonstrated in our study (Figure 3, reaction IV) altering the electronics of a given functionality (CN) will more likely result in a greater deviation from the screen's predicted outcome. A more complete assessment of intermolecular screens for establishing functional group tolerance can only be established by further comparisons of data generated in screens and genuine synthetic applications of reactions.

A team from Novartis headed by Malik, in collaboration with Houk and Du Bois, reported an alternative application of intermolecular additive screening.[14] Rather than simply

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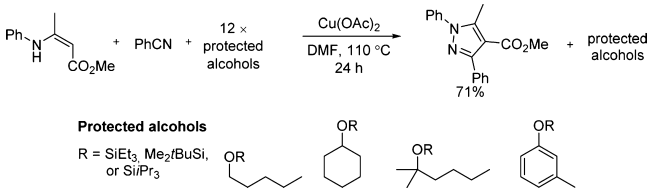
assessing the functional group tolerance of a reaction, they attempted to develop solutions for the inhibition of allylic C−H acetoxylation in the presence of Lewis basic heterocycles. An initial evaluation of the impact of various heterocycles on the conversion of complementary C−H acetoxylation chemistries reported by Stahl[15] and White[16] was undertaken (Scheme 4).

Validation studies that compared the yields from the intermolecular screen and bifunctional substrates indicated a qualitative correlation. Surprisingly, a discrete evaluation of heterocycle stability to the reaction conditions was not considered. Based on the presumption that reaction inhibition was a consequence of the Lewis-basic nature of the heterocycle, strategies to "block" the basic site were investigated. Using a pyridine-containing substrate as a model, the introduction of Lewis acids demonstrated only limited potential. Alternatively, it was shown that formation of the N-oxide restored significant reactivity, though unfortunately this solution is not readily extended to other heterocycles.

We have also investigated the use of intermolecular screening to evaluate the stability of protecting groups to a given set of reaction conditions.[17] While established protecting group texts are indispensible, evaluating protecting group stability for contemporary synthetic methods is not addressed. Having prepared a number of silyl-protected alcohols, acetals, ketals, and protected amines, we investigated the stability of the protecting groups during a $Cu(OAc)_2$-catalyzed pyrazole formation. The stability of the individual protecting groups was evaluated discretely, though "one-pot" experiments demonstrated that the relative stabilities of up to 12 protecting groups could be determined in a single experiment (Scheme 5).

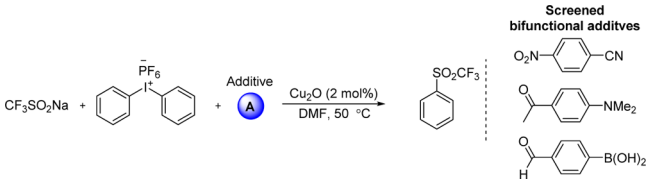
Scheme 5. Evaluating the Stability of up to 12 Different Protecting Groups in a Single Experiment Has Been Demonstrated[17]



Several examples of intermolecular reaction evaluation of functional group tolerance and stability have recently been reported, often with modifications or extensions to the methods discussed so far. Peters and Fu reported an intermolecular evaluation of a light induced copper-catalyzed N-arylation of indole and related heterocycles (Scheme 6A).[18] A number of functional groups, including several potentially competitive nucleophilic species were evaluated. In addition, the stereochemical integrity of *cis* and *trans* double bonds to the reaction conditions was reported; using an intermolecular screen to evaluate the stereochemical integrity of stereodefined species is potentially a very useful tool. More recently, the same team evaluated a related O-arylation of phenols (Scheme 6B).[19]

An example from the pharmaceutical company AbbVie has also been reported.[20] Describing a Cu_2O mediated coupling of CF_3SO_2Na and aryliodonium salts, a notably systematic investigation of electronic and steric parameters was undertaken in the substrate scope. A significant intermolecular screening of functional group tolerance to provide a broader overview of the reaction utility was then undertaken, with both yield and the additive remaining after reaction reported. Interestingly, they employed bifunctional additives to further expedite the screening process (Scheme 7). While this is potentially beneficial, should a bifunctional additive prove inhibitory, further experiments would be required to identify the disruptive functionality. Furthermore, the mutual influence of the conjugated functionalities must be considered.

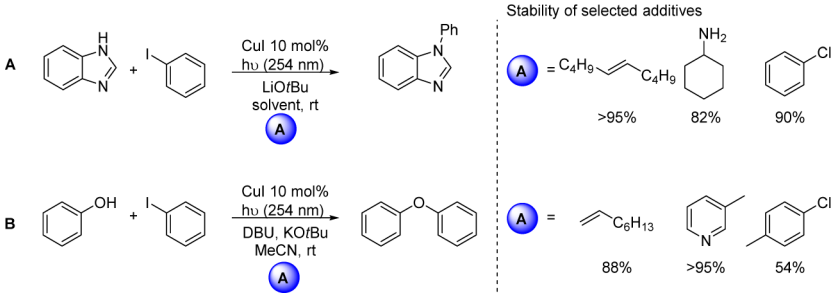
Scheme 7. A Number of Bifunctional Additives Were Screened in the Evaluation of a Copper-Catalyzed Arylation of Sodium Trifluoromethanesulfinate[20]



Yoshida and co-workers have demonstrated that investigating several additives containing different functionalities in a single experiment is also feasible.[21] While exploring the functional group tolerance of an electrooxidative C−H functionalization of naphthalene with imidazoles, they evaluated up to three additives in a single reaction, reporting the additive remaining after reaction and the yield of the product (Scheme 8). As with bifunctional additives, additional experiments may be required to identify inhibitory functional groups.

A report from the group of Buchwald[22] clearly recognizes the importance of "negative" results. Describing a new catalyst system for the palladium-catalyzed fluorination of (hetero)-aryltriflates, an intermolecular screen focused on evaluating the tolerance of the reaction to industrially relevant nitrogen containing heterocycles (Scheme 9) was undertaken. It is noteworthy that the results are reported despite the majority of the heterocycles significantly inhibiting the reaction.

Scheme 6. Light Induced Arylations of Heteroatoms Have Been Evaluated Using an Intermolecular Additive Screen[18,19]



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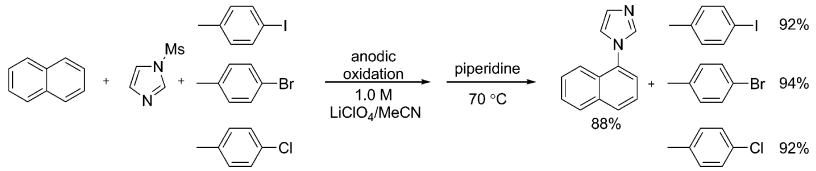
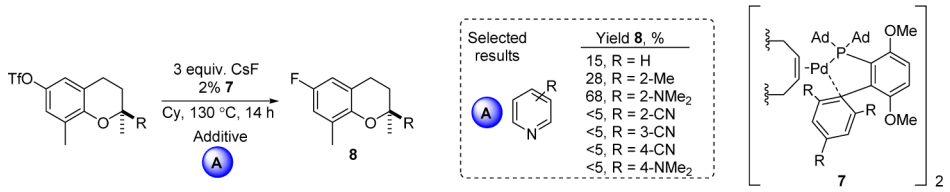
Scheme 8. Yoshida Evaluates the Tolerance of Several Additives in a Single Experiment[21]

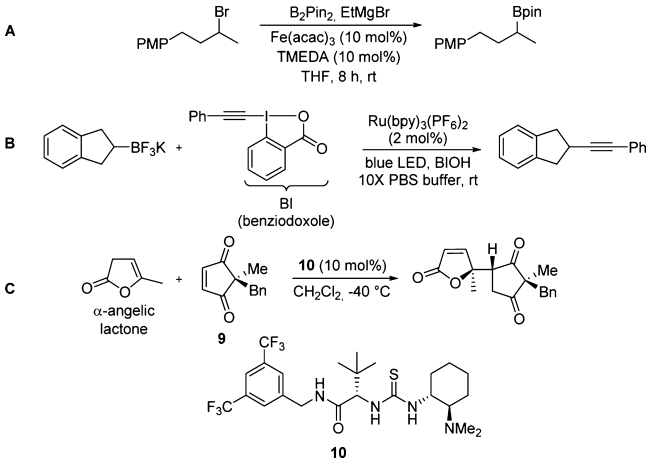


Scheme 9. Buchwald Employs a Targeted Screen to Evaluate the Reactions' Tolerance to Nitrogen Containing Heterocycles[22]



Silas Cook has reported an iron-catalyzed borylation of alkyl electrophiles, which we feel represents a near ideal example in terms of reaction evaluation (Scheme 10A).[23] Pleasingly, the significant substrate scope (41 substrates) appears to include examples irrespective of the yield of the reaction, and an intermolecular screen has been employed to rapidly *further* evaluate and define limits of the reaction, with both positive and negative results reported. The impact of several common functional groups and heterocycles were reported, as was the stability of the additive to the reaction conditions.

Scheme 10. Diversity of Reactions That Have Been Shown To Be Suitable for Evaluation Using Intermolecular Screens Is Significant[23,24,27]

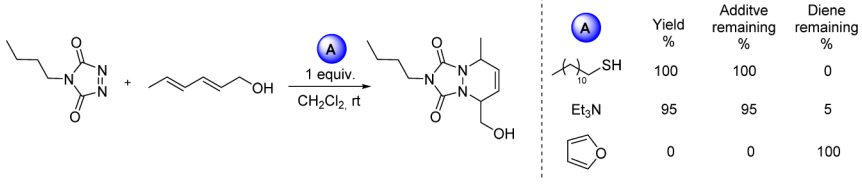


A recent protocol developed by Chen for the visible-light induced deboronative alkynylation of alkyl trifluoroborates used an intermolecular screen to demonstrate potential for application in chemical biology and related fields.[24] Although the optimized protocol employed a solvent system of CH_2Cl_2/H_2O (1:1), they focused their study on evaluating the impact of amino acids, glycosides, nucleosides, proteins, and bacterial cell lysates when the reaction was undertaken in an aqueous buffer solution (Scheme 10B). A related visible-light induced decarboxylative coupling of *N*-acyloxyphthalimides with alkylsulfones was also evaluated for biomolecule compatibility.[25] Jacobi von Wangelin has employed an intermolecular evaluation for a metal free carbonylation reaction using photoredox catalysis.[26]

Mukherjee reported the first application of a "robustness screen" applied to an organocatalytic reaction, and the only application to an enantioselective reaction to date.[27] Studying a desymmetrization of a substituted cyclopentene-1,3-dione **9** catalyzed by a bifunctional thiourea derivative **10**, they undertook an evaluation of the reaction using an intermolecular approach (Scheme 10C). Numerous potentially competitive electrophiles and carbon nucleophiles were shown not to react and had little influence on the yield and enantioselectivity, though primary, secondary, and tertiary amines all inhibited the reaction. We feel that successfully predicting that the reaction would demonstrate such high chemoselectivity would have been unlikely.

Winne and Du Prez evaluated the chemoselectivity and functional group tolerance of hetero-Diels–Alder reactions employing triazolinedione dienophiles (Scheme 11). This transformation was applied in the synthesis of polyurethane and poly(methyl acrylate) derivatives that demonstrated polymer-network healing, reshaping, and recycling.[28] The reaction typically showed complete tolerance to a wide range of additives including nucleophilic and electrophilic species, with furan proving the only additive to have a significant impact on the reaction.

Scheme 11. A Hetero-Diels–Alder Reaction Employed in the Preparation of Dynamic Polymer Systems Was Evaluated Using an Intermolecular Additive Screen[28]



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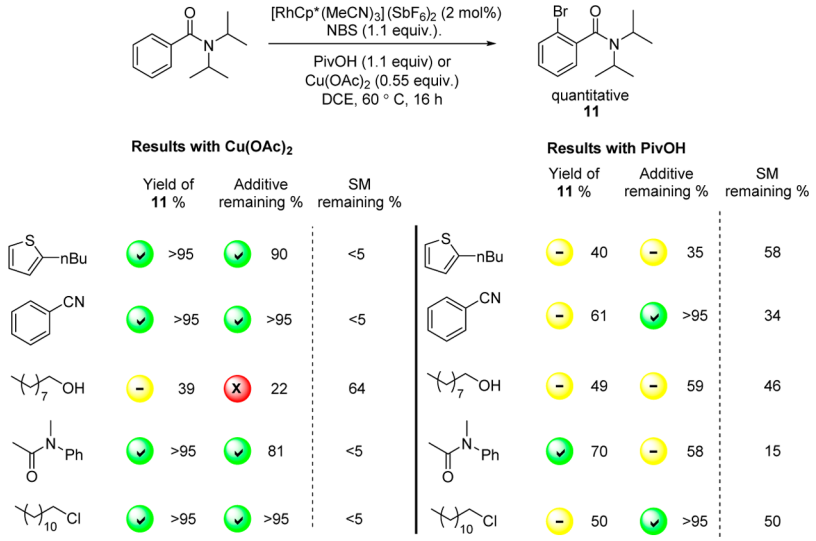


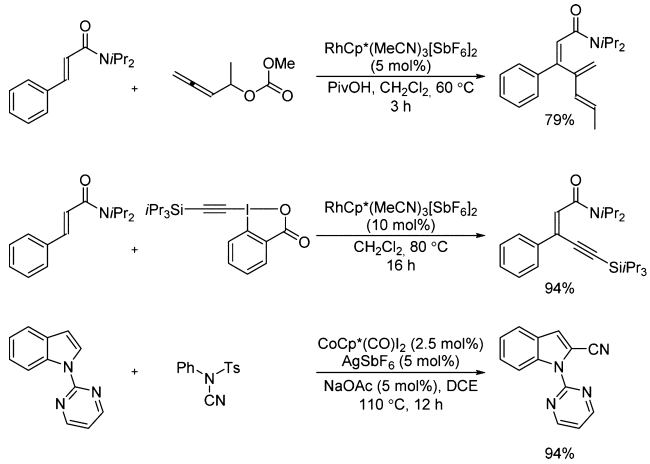
Figure 4. A comparison of the influence of basic and acid additives on the functional group tolerance of RhCp*-catalyzed *ortho*-bromination of benzamides.[9]

The works discussed demonstrate the diversity of reaction types for which an intermolecular approach to reaction evaluation can potentially be of great value. As discussed, we feel it is important that *all* of the data obtained using such methods should be reported, not only to facilitate understanding, development, and application of new methodologies but also to continue to evaluate and define the limitations of intermolecular screens. Consequently, we strongly discourage the "preselection" of additives that are likely to be tolerated, though we do see significant value in evaluating "families" of additives, for example, nitrogen containing heterocycles or common electrophiles. For our own studies, we defined a set of 20 additives, including heterocycles and other common functional groups, that we evaluate irrespective of the reaction.[9,10] Although this additive set is naturally limited, we feel that having a defined set prevents us from subconsciously or otherwise, preselecting functionality that we believe will be tolerated by a given reaction, biasing the screen.

The evaluation of C−H activation protocols has been the most active area for assessment within our group.[9,10,29−34] Our first report compared two sets of reaction conditions established for RhCp*-catalyzed *ortho*-bromination of benzamides and related systems.[9] As well as providing for the first time a broader picture of the functional group tolerance of a RhCp*-catalyzed C−H activation protocol, we identified notable differences between conditions employing PivOH compared with those employing $Cu(OAc)_2$ (Figure 4). Of particular note was that the presence of $Cu(OAc)_2$ inhibited the direct reaction of thiophene with NBS, enabling the selective functionalization of the benzamide. In comparison, the same reaction in the presence of PivOH resulted in significant bromination of the thiophene. Several other examples in which either the stability of the additive or the efficiency of the reaction were increased were identified. In our minds, these outcomes were neither intuitive nor predictable.

By undertaking numerous screens of C−H activation chemistries catalyzed by RhCp* and CoCp* based catalysts (Scheme 12), we feel that we have established a much broader idea of the limitations of these reactions. In addition, using the same set of additives for each screen has provided a basis for comparison that provides additional insight. While common

Scheme 12. Rhodium and Cobalt-Catalyzed C−H Activation Reactions for Which an Intermolecular Reaction Evaluation Has Been Undertaken[29,33,34]



trends appear across the majority of reactions, unexpected results and surprising inconsistencies between related transformations have been identified. This information is naturally of value to those wishing to apply these chemistries but also provides additional insight into the catalyst system. We are currently looking to exploit this collated data in the development of increasingly functional group tolerant C−H activation protocols.

We recently reported a Pd/C-catalyzed C-3 arylation of thiophenes with aryliodonium salts for which we have undertaken an intermolecular additive screen.[35] In addition to information on the functional group tolerance, we gained significant insight into the reactivity of other heterocycles. Furan, indole, and benzofuran were shown to be productively reactive under these conditions, but because intermolecular screens are effectively competition experiments, we were also able to extrapolate the relative reaction rates from the screen. We then exploited this data to predict and demonstrate the chemo- and regioselective arylation of bis-heterocycle **12** (Scheme 13). This is an excellent example of how additional

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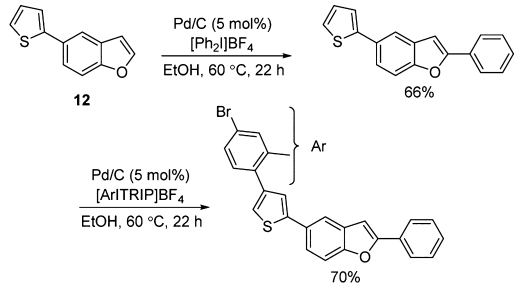
value can be rapidly derived from a high-throughput intermolecular additive screen.

Scheme 13. Relative Rate Data Obtained in an Intermolecular Evaluation Enabled Predictable Chemoselective Arylation of Bis-heterocycles[35]



Throughout this Account, we have attempted to highlight the value we feel can be derived from both qualitative data and negative results. In particular, we have focused on the functional group tolerance of reactions and the stability of chemical functionality, as we believe this is arguably the most important factor to facilitate the application of new synthetic methods. It is crucial that useful synthetic methods are identified quickly and applied to solve real synthetic problems.[36,37] We hope to have presented a guide through recent intermolecular screenings (see Table 2 for a comparison with a traditional substrate scope), highlighting variations, unexpected results, and novel applications (Table 3). The ultimate goal of this Account is to stimulate discussion and consideration of how the value of new synthetic methods can be maximized and how we can encourage more rapid uptake up of new protocols. We believe that more thorough evaluations of new methodologies and the reporting of "negative" results would go someway to addressing this, though unfortunately we must consider how external pressures influence how and what we report. We are hopeful that this Account will at the very least stimulate thought and discourse, which in the long term has a constructive influence on the field.

Table 3. Applications of Intermolecular Additive Screens

	application
all examples	expeditious evaluation of the functional group tolerance of a reaction
all examples	potential mechanistic insight
multiple examples	expeditious evaluation of the stability of chemical functionality
Buchwald[22]	focused evaluation of heterocycle compatibility
Chen[24,25]	focused evaluation of biomolecule compatibility
Enthaler,[3−5] Mukherjee[27]	focused evaluation of chemoselectivity
Glorius[35]	determination and utilization of relative rate data
Glorius[35]	identification of productively reactive substrates (reaction discovery)
Glorius[9]	broad and facile comparisons of reaction conditions
Glorius[17]	evaluating protecting group stability
Malik[14]	problem based evaluations

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The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

Biographies

Karl Collins obtained his Master's degree from the University of Manchester. Under the supervision of Prof. David J. Procter, he remained at Manchester for his doctoral studies, before moving to the Westfälische Wilhelms-Universität Münster for a postdoctoral stay in the group of Prof. Frank Glorius. Karl now works as a Laboratory Leader at Bayer HealthCare, Wuppertal, Germany.

Frank Glorius was educated in chemistry at the Universität Hannover, Stanford University (Prof. Paul A. Wender), Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz), and Harvard University (Prof. David A. Evans). He began his independent research career at the Max-Planck-Institut für Kohlenforschung (Mentor, Prof. Alois Fürstner) in 2001 and was appointed Associate Professor at the Philipps-Universität Marburg in 2004. Since 2007 he has been a Full Professor of Organic Chemistry at the Westfälische Wilhelms-Universität Münster. His research program focuses on the development of new concepts for catalysis and their implementation in organic synthesis.

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