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Employing a robustness screen: rapid assessment of rhodium(III)-catalysed C–H activation reactions

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This paper is dedicated to Professor Paul A. Wender, a great scientist, teacher and mentor

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ABSTRACT

Following the discovery of new synthetic methodology, an assessment of its potential utility in real synthetic problems is highly desirable to facilitate its application. Herein, we describe an assessment of two contemporary rhodium catalysed C–H activation methodologies using our recently reported 'robustness screen'. The results of this screen provide an evaluation of the tolerance of each reaction to specific chemical functionalities and structural motifs, as well as the stability of these functionalities and motifs to the reaction conditions. The results of this screen provide valuable data that can be directly applied in the design of synthetic routes, and thus can facilitate the application of the evaluated reactions.

1. Introduction

Contrary to the rapid publication of new scientific breakthroughs, the application of new knowledge is often slow, and we believe this to be particularly true of synthetic organic methodology. Whilst new synthetic methodologies often report to provide more widely applicable, increasingly efficient and more environmentally benign reactions, or provide routes to previously inaccessible chemical motifs, employing such methodologies with any regularity to 'real' synthetic problems often takes several years.[1,2] In our initial disclosure of this robustness screen methodology we proposed that the lack of information regarding the utility of a given reaction outside the idealised conditions of the seminal report contributes significantly to the delay in its application.[3]

It would be of significant benefit to the synthetic chemistry community should information relating to the application of new methodologies to real synthetic problems be available at the time of the initial publication, though generally this is not the case. Currently, this information is typically developed over a number of years as the reaction is gradually implemented within total syntheses, follow up methodological papers are published, or personal experience is developed. Moreover, even when this information has evolved, it is often fragmented and difficult to locate. In an attempt to both reduce the time period between the discovery and application of new synthetic methodology, and to facilitate the rapid location of relevant information, we recently reported a conceptually simple method to assess the potential utility of new synthetic methodology. The assessment is rapid, experimentally simple, and when appropriate could readily be reported alongside substrate scope in new synthetic methodologies.

It should be noted that this screen should in no way be considered a substitute for the traditional substrate scope. As a consequence of the intentional decoupling of the 'additives' functionality from the reactive centre (vide infra), a limitation of this method is that it is not possible to assess the direct steric/electronic impact of a given functionality on the reaction centre (e.g., an *ortho* substituent on an aromatic ring), unlike the traditional scope. This screen is a fast and simple method to generate additional information of use to synthetic chemists applying the given methodology, about the likely tolerance of the reaction conditions assessed to the functionalities/chemical motifs investigated, and whether these additives are stable to the reaction conditions. Furthermore, like results obtained within a traditional substrate scope, a 'failed' reaction does not preclude the possibility of optimisation

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to tolerate the specific functionality. Unlike a traditional scope, we propose by having a standardised set of additives screened, omission of unfavourable results would be discouraged and consequently more information relating to the reaction would be available: this is highly beneficial. For additional discussion on these points see Ref. 3.

The metal catalysed direct functionalisation of C–H bonds has emerged over the past decade as a highly promising tool for organic synthesis.[4,5] This contemporary approach enabling the direct coupling of C–H bonds without the need for pre-functionalisation represents a significant step forward in synthetic organic chemistry, enabling not only more efficient transformations due to avoidance of pre-functionalisation, but also opening up new disconnection pathways. Consequently, the application of methodology employing a C–H activation strategy to real synthetic problems is highly desirable. To facilitate the application of such methodologies, we herein provide an assessment of two reactions previously reported within our group: a rhodium catalysed[5] tetrahydroisoquinolinone formation,[6] and the direct *ortho*-bromination of arenes.[7] Using the methods previously described in our robustness screen we simultaneously assess both the tolerance of these reactions to chemical functionality, and the tolerance of the specific chemical motifs to the reaction conditions.[3]

2. Results and discussion

Our goal is to demonstrate the application of the semi-quantitative robustness screen as previously reported, as well as providing a rapid assessment of contemporary C–H activation synthetic methodologies. The robustness screen itself is conceptually and experimentally very simple: a standard reaction is undertaken in the presence of 1 molar equivalent of a given functional group or structural motif, termed an 'additive', and the reaction then analysed by an appropriate method (LC-MS, HPLC, GC). We have employed gas chromatography (GC) analysis to enable determination of the yield of the reaction product, and both the starting material and the additive remaining after the predetermined reaction time. This allows determination of the tolerance of the reaction to the given functionality, whether the additive either inhibits product formation or retards the rate of reaction, and of the stability of the additive to the reaction conditions.

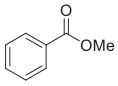
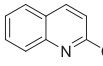
For an initial assessment of a given reaction we have proposed 20 common functional groups/chemical motifs. Additives were selected to cover a range of typical properties, e.g., basic, ligating, unsaturated etc., though it is important to note that the additives were not evaluated with regard to possible influence on reactivity, or their stability to the reaction conditions. In addition, commercial availability and sufficient difference in retention times to allow for batch analysis (vide infra) using GC analysis were additional prerequisites. We feel that a more critical selection process for the additives 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. The 20 functional groups/chemical motifs are split into two 'groups', with Group A containing common functional groups, and Group B, common heterocyclic motifs (Table 1).

2.1. Application of the robustness screen to a tetrahydroisoquinolinone formation reaction

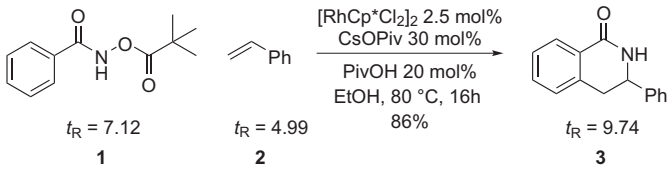
The robustness screen was first applied to our recently reported preparation of tetrahydroisoquinolinone **3** from hydroxamic ester **1** and styrene **2** (Scheme 1). This reaction has also been reported by Fagnou using similar reaction conditions.[6,8]

Prior to experimentation, GC (or selected alternative) analysis of the starting materials and the product of the reaction are required

Table 1
Chemical functionalities and structural motifs to be evaluated using the robustness screen

Group A - Functional Groups	Retention time[a] (min)	Group B - Heterocycles	Retention time[a] (min)
	4.69		5.02
	5.59		5.25
	5.66		5.58
	5.84		5.73
	6.22		5.84
	6.50		6.05
	6.58		6.36
	7.03		7.01
	7.46		7.22
	7.53		7.48

[a]Retention times are for GC analysis using method A: Initial temperature 50 °C, hold 3 min, increment 40 °C/min, final temperature 280 °C, hold 3 min.



Scheme 1. Tetrahydroisoquinolinone formation to be evaluated using the robustness screen. t_R is retention time for GC method A.

to establish any signal overlap with the additives or the analytical standard (mesitylene, retention time 5.55 min). Should signal overlap be detected, a change in the analytical method, or exclusion/substitution of the given additive from the screen can be undertaken if deemed necessary.

Using GC analysis, a batch calibration technique (see Experimental section for details) inspired by Hartwig's analysis of complex mixtures[9] was employed for the simultaneous calibration of all Group A additives, the starting material and the product against the analytical standard. This was then repeated for Group B additives. This technique allows for a rapid semi-quantitative analysis of all components of the screen. Only two GC experiments are performed, one for each group of additives. The relative ratios of the additives, starting material and product to the standard were subsequently determined and used as 'single point' calibrations for further analysis (see Experimental section for GC traces). Although absolute values cannot be determined, this semi-quantitative analysis provides a valuable measure of how a reaction proceeds in the presence of a given additive, and the stability of the additive to the reaction conditions.