Note

An Approach to Comparing the Functional Group Tolerance of Reactions

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An Approach to Comparing the Functional Group Tolerance of Reactions

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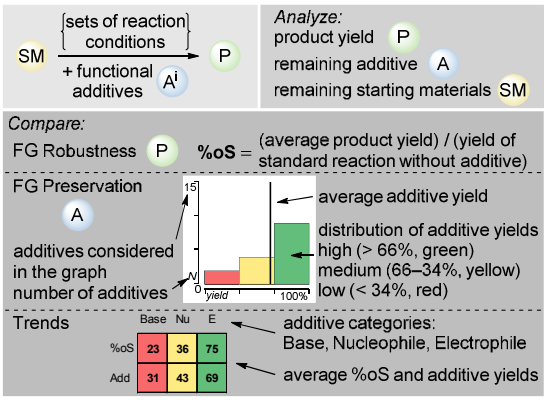
Supporting Information Placeholder

ABSTRACT: Herein, we describe an approach to quantifying and comparing functional group tolerance of synthetic reactions. Additive-based reaction screening is utilized as a tool for the objective comparison of reaction conditions as demonstrated in four case studies. This contributes to an understanding of factors limiting a reaction's FG tolerance and the identification of truly mild reactions.

The availability of complex, functionalized molecules is dependent on high yielding, mild and selective synthetic methods. In the development of such methods and in their application, there has always been an interest in comparing reactions to each other. Identifying the underlying factors limiting a chemical reaction by comparison is crucial for developing improved protocols. Given a synthetic problem, protocols for each transformation are selected based on an assessment of various factors such as presented functional group (FG) tolerance, documentation and overall confidence in the expected outcome.[1] Finally, the value of newly published synthetic methods is generally expressed relative to previously published methodology. Currently, reactions are compared in vague terms like mildness and FG tolerance.[2] The FG tolerance of a reaction is traditionally evaluated by preparing derivatives of the standard substrates, carrying single or multiple FGs in addition to the FGs required for the desired reaction. The scope presentation is commonly determined by availability of starting materials, a bias regarding the likely success of any given prospective scope entry, and possibly the omission of failed substrates. Consequently, the FG tolerance is often assessed in a non-systematic and non-standardized, subjective way.[3] Moreover, the intramolecular assessment is limited as the results can only reflect a superposition of the general tolerance of an FG with electronic and steric changes to the intrinsic reactivity,[4] aggregate effects[5] and FG interactions specific to individual structures. Thus, an objective comparison of synthetic protocols is difficult based on the scope presentations alone. Herein, we propose that an in-depth yet facile comparative analysis of additive-based intermolecular reaction screening allows for an objective comparison of synthetic protocols aiding the rational development of truly mild methods, and the application of a reaction to challenging substrates.

Additive-based intermolecular reaction screening (Scheme 1), formalized as the Robustness Screen, allows a discrete evaluation of interdependent aspects underlying functional group tolerance.[1b,6,7] Equimolar amounts of additives, each containing an FG, are added to the reaction under the conditions in question, one at a time, with practical restraints in terms of reaction scale. The yields of the product, remaining additive and starting materials are determined by GC analysis, using single-point batch calibration. Due to the intermolecular nature of this setup, the reactivity at the reactive site remains constant and the fate of the FGs in a reaction can be followed separately from the course of the desired reaction. The average yield of the standard product over a set of additives reflects the actual robustness of the reaction and, conversely, the amount of recovered functional additives reflects the FG preservation of the reaction conditions.

Scheme 1. Additive-based reaction screening and the metrics for comparing FG robustness and preservation.



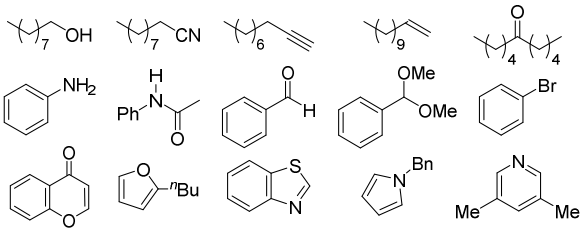
The following limitations apply for the additive-based screening. Firstly, the accuracy of the yields is limited to ca. ± 5% by the setup. Moreover, the results are not meant to approximate the behavior of a specific substrate carrying that same functionality, as intramolecular influences are not accounted for. Conversely, general information on the reactivity of functional groups is gained. Finally, a selection of additives for such a screening will always be arbitrary and incomplete. Extrapolation to moieties not present in the screening can be problematic, so care must be taken when drawing general conclusions (the same is true for traditional scope presentations). Therefore, to avoid overinterpretation of the individual results, we evaluate the results using the average reduction in product yield by all additives, indicated as %oS (percent of the standard yield), and histograms with three categories for high (100%...67%), medium (66%...34%) and low (33%...0%) additive recovery (Scheme 1). A vertical line in the graphs indicates the average additive yield. This enables a qualitative comparison of multiple reaction conditions. For an intuitive of reactivity trends, the results can also be evaluated according to subgroups of additives. To demonstrate this, we grouped the additives into nucleophiles, electrophiles and bases and quote the average relative yield (%oS) and additive recovery for each category. Further second tier studies, such as control reactions, additive pooling, or separating individual parameters making up the reaction conditions, can

be added to this analysis to deepen mechanistic insight regarding the factors limiting functional group tolerance. During the preparation of this manuscript, the use of additive-based reaction screening for the optimization of functional group-tolerant reactions was published.[7]

We conducted four case studies to investigate if the relative FG tolerance of two protocols for the same transformation can be meaningfully compared using additive-based reaction screening. The case studies were selected with an interest in mild transformations in mind. While habitually the term mildness is used to describe reaction parameters, we propose that a separate consideration of FG preservation and robustness for different protocols of the same transformation provides an approach for a more quantitative description of mildness. We argue that for practical purposes the outcome of a reaction reflects its mildness. Considering non-mildness is associated with decomposition and side-reactions, the stability of any functionalities is in fact a measure for the reaction's relative mildness.

Initially, a set of 41 additives representative of FGs, heterocycles and protecting groups was assembled. To facilitate operation and uptake of the method, we further selected a truncated set of 15 additives that should reproduce the trends of the full set (Scheme 2). Since case studies 1 and 2 confirmed this assumption (see SI), we performed the last two case studies with the truncated set and compared all results on the basis of these 15 additives. The reaction conditions in the case studies are generally taken from the original method publication with minor adaptions. However, yield and additive recovery may be influenced in different ways by the presence of excess reagents.

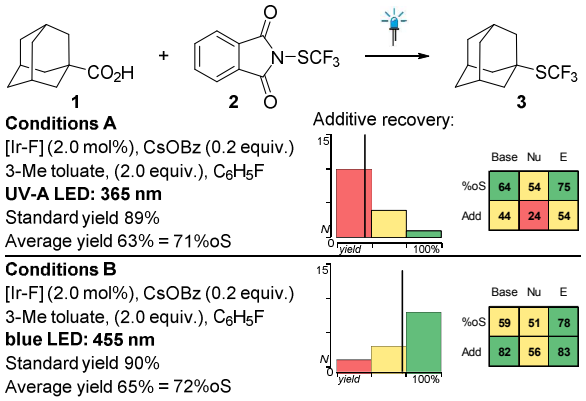
Scheme 2. Truncated 15 additive set.



For the first case study, we investigated a photoredox-catalyzed decarboxylative trifluoromethylthiolation. Harnessing the energy from light is a highly-regarded strategy in the context of green chemistry.[8] Photocatalytic processes have gained prominence recently due to their ability to generate radicals, oxidants and/or reductants in a selective manner in catalytic amounts.[9] Thus, in contrast to radical generation using (super)stoichiometric amounts of oxidants or reductants, photocatalysis is often claimed to be milder and more FG tolerant.[9d] Our group reported a protocol for the visible-light-promoted decarboxylative di- and trifluoromethylthiolation of alkyl carboxylic acids in 2016.[10] The photocatalyst used in this transformation ($[Ir(dF(CF_3)ppy_2)(dtbbpy)]PF_6$ = [Ir-F]) has an absorption maximum at 380 nm and can be excited both by UV-A and blue visible light. We investigated the effect of the light source (3 W 365 nm LED vs. 5 W 455 nm LED) on the robustness and FG preservation in this transformation using additive-based reaction screening (Scheme 3).

The average yield of the desired reaction in the presence of the additives is nearly identical for both conditions, indicating a similar robustness, regardless of the choice of irradiation wavelength. The FG preservation is independent from the robustness of the reaction, though, as evidenced by a pronounced difference of the yields of recovered additives. Visualized in the histograms, most of the additives have a low (< 34%) recovery under UV-A irradiation, while the opposite is true for visible light irradiation whereby most additives are observed to have high (> 66%) recovery. Consequently, the latter protocol can be regarded as milder. Among the additives not preserved even under irradiation with visible light are mainly electron-rich, oxidation sensitive compounds (thus, mostly in the "nucleophile" group). In order to assess the relevance of the results from the additive-based screening to intramolecular reactions, four functionalities were incorporated in a substrate each, which was subjected to the reaction. Reasonable agreements with the screening results were found (see SI). We performed further experiments demonstrating how the separate analysis of robustness and FG preservation can aid the understanding of the limitations of a reaction.

Scheme 3. Case study 1: Decarboxylative trifluoromethylthiolation.



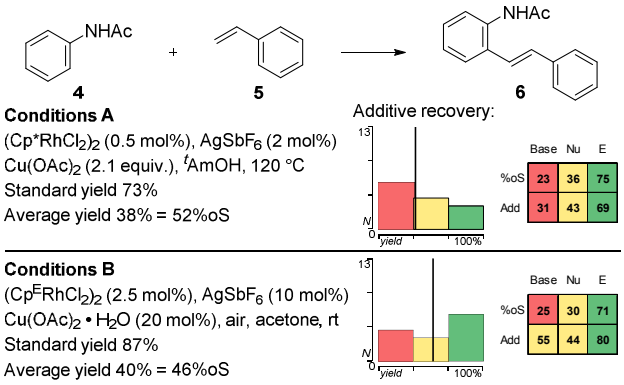
Focusing on a key step in photocatalysis, our group recently employed luminescence quenching as a probe for the interaction of the excited photocatalyst with a reagent in a mechanism-based screening approach.[11] Such interactions might be linked with decomposition, competing side reactions or inhibition of the desired reaction, but they could also not have any effect on the outcome of a reaction at all, i.e. in case of non-productive quenching. Of the full 41 additive set, 14 additives were found to quench the emission of the excited photocatalyst (see SI). In some instances, catalyst quenching by an additive can be linked with a decreased yield of the trifluoromethylthiolation reaction. In cases where additive decomposition was observed under the reaction conditions (recovery < 67%), a separate assessment was made, irradiating a solution of the additive in the absence of the photocatalyst and other reagents. Thus, the influence of the light source on the FG preservation as one reaction parameter can be isolated and a more general statement on the stability of FGs towards irradiation can be made independent of a reaction. All except four additives were preserved almost quantitatively after irradiation with blue light. Conversely, 14 additives were at least partially decomposed (< 67% recovery) upon irradiation with 365 nm UV-A light (see SI). Thus, by the comparative analysis, we found that the irradiation with blue light results in milder reaction conditions than the UV-A irradiation.

We performed the second case study on a rhodium-catalyzed oxidative C–H olefination of acetanilides (Scheme 4). The functionalization of C–H bonds has been an intense field of study and a wide variety of catalytic systems have been identified that enable such transformations.[12] Initially, the focus was on the identification of novel catalytic systems enabling the cleavage of otherwise inert C–H bonds and, as such, harsh reaction conditions were

often required. More recently, there has been a strong interest in developing milder transformations on C–H bonds to enable applications to complex molecule synthesis and late stage functionalization.[13] In 2010, our group presented the Cp*Rh^{III}-catalyzed (Cp* = pentamethylcyclopentadienyl) olefination of acetanilides under conditions that would not be described mild, with $Cu(OAc)_2$ as a stoichiometric oxidant at 120 °C.[14a] Five years later, Tanaka presented a protocol for this transformation with the modified ligand Cp^E (where two –Me groups of Cp* are changed for $–CO_2Et$) on rhodium.[14b] This method proceeds at room temperature with $Cu(OAc)_2$ in catalytic amounts and air as terminal oxidant and might consequently be judged as being milder. On the other hand, the Cp^{E}Rh-catalyst is present in higher amounts and likely a stronger Lewis acid due to the electron-poorer ligand. The presence of oxygen might also induce undesired reactivity.

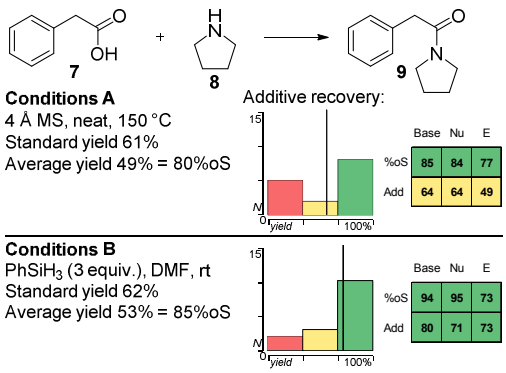
While the average yield of the desired reaction across the additives is very similar with both protocols, indicating a similar robustness, a marked increase in FG preservation is found for the Cp^{E}Rh^{III}-catalyzed version. Nevertheless, the oxidative nature of the conditions and the occurrence of side reactions in the presence of certain FGs is common to both protocols, limiting the overall FG preservation. The analysis by additive type clearly reveals an intolerance of the Rh-catalyzed olefination to basic additives, which deactivate the catalyst, whereas electrophiles are well-tolerated. Competitive rhodium-catalyzed side reactions include C–H activation at other arenes carrying carbonyl derivatives and olefination with the alkyne or alkene additives. Copper can promote the oxidative dimerization of heterocycles and alkynes, which is observed under these conditions. As the rhodium- and copper-promoted side reactions occur less under conditions B, these conditions result in more chemoselective reactions.

Scheme 4. Case study 2: Rhodium-catalyzed oxidative C–H olefination.



In the third case study, we compared two amidation reactions (Scheme 5). The formation of amide bonds is a commonly employed transformations in organic chemistry.[15] The direct formation of amides from free amines and carboxylic acids is problematic proceeding at temperatures well over 100 °C with some means of water removal.[16a] Stoichiometric reagents have been developed to activate the carboxylic acid and allow reactions to proceed at lower temperatures.[15] We compared the thermal amidation under neat conditions at 150 °C in the presence of molecular sieves[16a] with a silane-mediated coupling taking place at room temperature.[16b] The decrease in reaction temperature and the introduction of a solvent are expected to increase the mildness of the transformation, yet the addition of a reagent might also compromise the FG preservation.

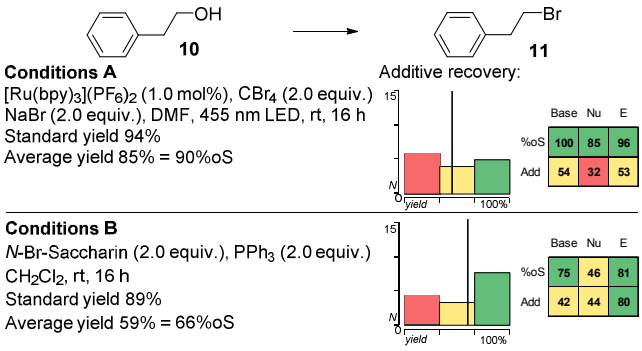
Scheme 5. Case study 3: Amidation of phenylacetic acid.



The results showed a higher FG preservation with the silane-mediated protocol. The intrinsic reactivities of the amine and the carboxylic acid limit the overall preservation even in the "milder" method equally with nucleophilic and electrophilic additives. Nevertheless, the results from the thermal conditions demonstrate that even under high temperatures and solvent-free conditions there is no huge decrease in preservation in the absence of other factors. The average yield of the amidation reaction across all additives is nearly the same for both protocols, indicating a similar robustness.

Finally, a fourth case study concerned the conversion of alcohols to bromides (Scheme 6).[17a] We compared a photocatalytic protocol reported by Stephenson[17b] with a variation of the classical Appel reaction conditions.[17c] Analyzing the reaction parameters, the uncatalyzed protocol might be judged as less mild than the photocatalytic protocol due to the use of both the strong oxidant *N*-bromosaccharin and the base PPh_3. In the catalytic version, the reactive Vilsmeier–Haack reagent is only generated in small quantities at any given time.

Scheme 6. Case study 4: Appel bromination.



In contrast to this judgement, the results indicate a slightly higher FG preservation in the uncatalyzed protocol. However, the average yield of the desired product across all additives is higher using the photocatalytic protocol, indicating an exceptional robustness towards FGs. Possibly, the lower preservation is a result of an overall excess of the Vilsmeier–Haack reagent during the course of the reaction, indicated by the low preservation of electron-rich arenes and other nucleophilic additives. Both protocols tend to display a low preservation of oxidation-sensitive functional groups. This case study highlights how the effect of reaction conditions on the preservation of FGs cannot easily be predicted from the reaction conditions alone.

In four case studies, we quantify and compare aspects of FG tolerance and demonstrate the utility of additive-based reaction screening for comparing sets of reaction conditions. Change in reaction yield by the additives reflects the FG-robustness and the amount of recovered additive reflects the FG-preservation. While habitually, reaction parameters are related to a method's mildness, we found that the actual preservation of FGs is sometimes not readily predictable. Importantly, FG robustness and preservation are independent aspects as demonstrated by protocols with a high robustness, yet low preservation or vice versa. Thus, the additive-based reaction screening is a tool for the objective comparison of reaction conditions, revealing such underlying trends. This analysis contributes to an understanding of factors limiting a reaction's FG tolerance and aids a targeted development of truly mild reactions. Nevertheless, the fundamental limitation of additive-based reaction screening in predicting the reactivity of specific molecules has to be kept in mind – and, naturally, that the same limitation applies to traditional scope presentations.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out under an atmosphere of argon in flame-dried glassware. The solvents used were purified by distillation over standard drying agents and were stored over molecular sieves or transferred under argon. Blue LEDs (5 W, λ_{max} = 455 nm) and UV-A LEDs (3 W, λ_{max} = 365 nm) were used for blue and UV-A light irradiation, respectively (see the SI for emission spectra). In each case, the light source was placed ~5 cm from the reaction vessel. A custom made "light box" was used with 6 LEDs arranged around the reaction vessels (see Figure S2 in the SI). A fan attached to the apparatus was used to maintain the temperature inside the "box" at no more than 9 °C above room temperature. Photocatalysts $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ (**[Ir-F]**, $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-3-trifluoromethylpyridine)[18] and $[Ru(bpy)_3]_2(PF_6)_2$ (bpy = 2,2′-bipyridine)[19] were prepared according to literature procedures. (9*H*-Fluoren-9-yl)methyl (1-phenylethyl)carbamate (**PG4**),[6d] trifluoromethylthiophthalimide (**2**),[20] *N*-bromosaccharin[21] and $(Cp^ERhCl_2)_2$[22] were prepared following literature procedures. All other chemicals were used as purchased without any further purification. Flash chromatography was performed on Merck silica gel (40–63 mesh) using standard techniques. NMR spectra were recorded on a Bruker ARX-300, AV-300, AV-400 MHz or on a Varian Associated, Varian 600 unity plus spectrometer. Chemicals shifts (δ) are quoted in ppm downfield of tetramethylsilane. The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.13 ppm). ^{19}F NMR spectra are not calibrated by an internal reference. Coupling constants (J) are quoted in Hz. GC-MS spectra were recorded on an Agilent Technologies 7890A GC system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, film: 0.25 µm). The major signals are quoted in m/z with the relative intensity in parentheses. The method indicated as '50_40' starts with the injection temperature T_0 (50 °C); after holding this temperature for 3 min, the column is heated by 40 °C/min to temperature T_1 (290 °C or 320 °C) and this temperature is held for an additional time t. GC-FID analysis was undertaken on an Agilent Technologies 6890A equipped with an HP-5 quartz column (0.32 mm x 30 m, film: 0.25 µm) using flame ionisation detection. Method: initial temperature 50 °C, hold 3 min, increment 40 °C/min, final temperature 280 °C, hold 3 min. ESI mass spectra were recorded on a Bruker Daltonics MicroTof spectrometer. Luminescence quenching experiments were conducted using a Jasco FP-8300 spectrofluorometer. The following parameters were employed: excitation bandwidth = 5 nm, data interval = 0.2 nm, scan speed = 500 nm/min, response time = 0.2 sec. The samples were measured in Hellma fluorescence QS quartz cuvettes (chamber volume = 1.4 mL, $H \times W \times D$ = 46 mm × 12.5 mm, 12.5 mm) fitted with a PTFE stopper.

General Procedure for the Addtive-Based Screening. The protocol requires carrying out the desired transformation under the standard reaction conditions in the presence of equimolar amounts of a single functionalized additive. After a predetermined reaction time, the yield of the product and the remaining additive and starting materials are determined by GC-FID analysis. Calibration of the additives and products of the reaction was done using a single point batch calibration. In this study, we evaluate four additive sets described previously[6a] and a fifth set consisting of representative protecting groups not contained in the other four sets. Case studies 1 and 2 were carried out with all 41 additives. In case studies 3 and 4 we used a truncated set consisting of 15 additives (Scheme S2). Notes: (1) change in volume of the stock solution due to addition of liquid starting materials was not accounted for, hence a control reaction (no additive) was carried out to determine the maximum yield of the reaction in the screen. (2) dodecylamine (**A9**), *N*-methylimidazole (**B2**), acetanilide (**C7**), 2-picoline-*N*-oxide (**D5**) and 2-(9*H*-fluoren-9-yl)methyl (1-phenylethyl)carbamate (**PG4**) should be filtered through Celite® when preparing samples for GC analysis.

General Procedure for the Decarboxylative Trifluoromethylthiolation. To a 10 mL Schlenk tube was added cesium benzoate (0.2 equiv.) and trifluoromethylthiolation reagent **2** (2.0 equiv.) in a glove-box. The vial was removed from the glovebox and carboxylic acid **1** (1.0 equiv. = 0.1 mmol), $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ (2.0 mol%), fluorobenzene (0.05 M), 3-methyl toluate (2.0 equiv.) and the corresponding additive (1.0 equiv.) were added. The solution was degassed using three freeze–pump–thaw cycles. The mixture was stirred under irradiation from UV-A LEDs (λ_{max} = 365 nm, Conditions A), or blue LEDs (λ_{max} = 455 nm, Conditions B). After 4 hours, the reaction outcome was analyzed using GC-FID with mesitylene as internal standard.[10]

General Procedure for the Additive Stability Screening under 365 nm / 465 nm Irradiation. To a 10 mL Schlenk tube was added the additive (0.1 mmol) and fluorobenzene (2 mL, 0.05 M). The solution was degassed using three freeze–pump–thaw cycles. The mixture was stirred under irradiation from UV-A LEDs (λ_{max} = 365 nm, Conditions A) or blue LEDs (λ_{max} = 455 nm, Conditions B). After 4 hours, the remaining additive was quantified using GC-FID with mesitylene as internal standard.

General Procedure for Luminescence Quenching Studies. All samples used in the luminescence quenching studies were prepared under oxygen-free conditions. The photocatalyst and potential quenchers were weighed into vials and placed inside a glovebox (a common glovebag can alternatively be used) under a positive pressure of argon. Fluorobenzene was degassed by argon sparging for one hour and also placed inside along with micropipettes and their tips, cuvettes, empty vials, waste containers and parafilm. Each photocatalyst and substrate sample was then dissolved in fluorobenzene. For each measurement, the appropriate amount of the photocatalyst and substrate were added to a cuvette and diluted to 1 mL with fluorobenzene using micropipettes. A photocatalyst concentration of 10 µM was used throughout the screening studies along with substrate concentrations of 25 mM, which equates to 2500 equivalents of each potential quencher relative to the photocatalyst. The cuvette was then capped with a PTFE stopper and sealed further with parafilm before being removed from the glovebox and transferred to the fluorescence

spectrometer. After the measurements, the sealed cuvette was brought back into the glovebox, emptied, cleaned with fluorobenzene and dried under a stream of argon before preparation of the next sample. The luminescence emission spectrum of the photocatalyst excited at 420 nm was measured six times (three different samples measured twice each) and an average was taken as the standard reference spectrum. The samples containing potential quenchers were each measured twice and an average was taken. The emission intensity (I) at a pre-defined wavelength was noted and compared with that of the photocatalyst in isolation (I_0). The amount of decrease in the emission intensity was then quantified as a "quenching fraction" (F) defined by the following formula:

$$F(\%) = 100\left(1 - \frac{I}{I_0}\right)\%$$

The structure of the photocatalyst **[Ir-F]** employed in this study and the emission wavelength used to calculate the quenching percentage (F) as well as UV/vis absorption spectra and extinction coefficients at 455 nm and 365 nm for the selected photocatalyst can be found in the Supporting Information.

General Procedure for the Cp*Rh-Catalyzed Oxidative Olefination (Conditions A). To a flame-dried, Ar-filled Schlenk-flask equipped with a magnetic stirring bar was added $AgSbF_6$ (2.0 mol%) and $Cu(OAc)_2$ (2.1 equiv.) in a glove box. 1 mL of a stock solution containing acetanilide (1.0 equiv. = 0.20 mmol) and $(Cp^*RhCl_2)_2$ (0.5 mol%) in ^{t}AmOH (1 mL/equiv.) was added under a stream of argon, followed by styrene (1.5 equiv.) and the corresponding additive (1.0 equiv.) in quick succession and shaking the flask gently after each addition. The flask was sealed and the reaction was stirred at 120 °C for 15 h. The reactions were analyzed by GC-FID using mesitylene as internal standard.

General Procedure for the Cp^{E}Rh-Catalyzed Oxidative Olefination (Conditions B). To an oven-dried, air-filled Schlenk-flask equipped with a magnetic stirring bar was added $AgSbF_6$ (10 mol%) and $Cu(OAc)_2 \cdot H_2O$ (20 mol%) under air. 1 mL of a stock solution containing acetanilide (2.0 equiv.) and $(Cp^ERhCl_2)_2$ (2.5 mol%) in acetone (1 mL/equiv.) was added, followed by styrene (1.0 equiv.= 0.2 mmol) and the corresponding additive (1.0 equiv.) in quick succession and shaking the flask gently after each addition. The flask was sealed and the reaction was stirred at room temperature for 15 h. The reactions were analyzed by GC-FID using mesitylene as internal standard.

General Procedure for the Thermal Amidation of Phenyl Acetic Acid (Conditions A). 4 Å molsieves were activated under vacuum by heating with a heat gun at 600 °C for ca. half an hour and subsequently stored under argon. To an oven-dried, Ar-filled Schlenk-flask were added activated 4 Å molsieves (ca. 10 mg), phenyl acetic acid (1.0 equiv. = 0.20 mmol), the corresponding additive (1.0 equiv.) and pyrrolidine (2.0 equiv.). The flask was sealed and the reaction was heated to 150 °C for 2.5 h. The reaction was analyzed by GC-FID the internal standard mesitylene.

General Procedure for the Silane-Mediated Amidation of Phenyl Acetic Acid (Conditions B). To a flame-dried, Ar-filled Schlenk-flask equipped with a magnetic stirring bar was added the corresponding additive (1.0 equiv.). 1.6 mL of a stock solution containing phenyl acetic acid (1.0 equiv. = 0.20 mmol) and pyrrolidine (1.0 equiv.) in DMF (1.6 mL) was added under a stream of argon. After stirring the mixture for a few seconds, phenyl silane (3.0 equiv.) was added under a stream of argon. The flask was sealed and the reaction was stirred at room temperature for 5 h. The reaction was analyzed by GC-FID using mesitylene as internal standard.

General Procedure for the Photocatalytic Appel Reaction (Conditions A). A flame-dried 10 ml Schlenk flask with magnetic stir bar was charged with tris(2,2′ -bipyridyl)ruthenium(II) dihexafluorophosphate (0.001 mmol, 1.0 mol%), 2-phenylethanol (0.1 mmol, 1.0 equiv.), carbon tetrabromide (0.2 mmol, 2.0 equiv.), the additive (0.1 mmol) and sodium bromide (0.2 mmol, 2.0 equiv.). The flask was purged with a stream of argon, and dry DMF (1.0 ml) was added with a syringe. The mixture was degassed by freeze–pump–thaw (three cycles) and irradiated with light from blue LEDs (455 nm). After 14 h, the amount of formed product and the remaining additive was quantified using GC-FID by adding mesitylene as internal standard.

General Procedure for the PPh_3/NBS-Mediated Appel Reaction (Conditions B). To a mixture of *N*-Bromosaccharin (0.2 mmol, 2.0 equiv.) and PPh_3 (0.2 mmol, 2.0 equiv.) in dry CH_2Cl_2 (1.0 mL, 0.1 M) was added 2-phenylethanol (0.1 mmol, 1.0 equiv.) and the additive (0.1 mmol) at room temperature. After 5 h of stirring, the amount of formed product and the remaining additive was quantified using GC-FID by adding mesitylene as internal standard.

ASSOCIATED CONTENT

Supporting Information

Detailed screening results, screening procedures, results of screening verification experiments and spectra. The Supporting Information is available free of charge on the ACS Publications website.

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‡T.G. and M.T. contributed equally.

Notes

The authors declare no competing financial interests.

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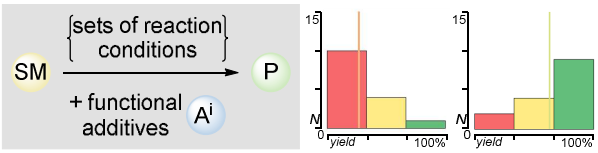
TOC


sets of reaction conditions
SM
P
+ functional additives
A^i
15
N
0
yield
100%
15
N
0
yield
100%