analysis of the structure of more complex polyatomic compounds (*26–29*). Whereas the discussed scaling behavior is generic to all alkali metal atoms, the derived $\overline{d} \approx A_s^2/n^{*2}\mu_s^2$ scaling suggests considerable variations of the dipole moments among different atomic species. In particular, cesium, with a smaller noninteger part of the *s*-wave quantum defect (*30*) and a larger *s*-wave scattering length (*31*), might possess a dipole moment of ~15D (larger by an order of magnitude) for the same electronic state discussed above. By the same mechanism described here, we can expect that the molecular electronic states of the so-called trilobite molecules (*9*) admix a small amount of *s*-wave character, possibly making such molecules accessible to a standard two-photon association process. These trilobite molecules are predicted to have much larger permanent dipole moments (on the order of 1 kD), presenting extreme sensitivity to external fields.

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Fig. S1
References (*32–34*)

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Discovery of an α-Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity

Andrew McNally, Christopher K. Prier, David W. C. MacMillan*

Serendipity has long been a welcome yet elusive phenomenon in the advancement of chemistry. We sought to exploit serendipity as a means of rapidly identifying unanticipated chemical transformations. By using a high-throughput, automated workflow and evaluating a large number of random reactions, we have discovered a photoredox-catalyzed C–H arylation reaction for the construction of benzylic amines, an important structural motif within pharmaceutical compounds that is not readily accessed via simple substrates. The mechanism directly couples tertiary amines with cyanoaromatics by using mild and operationally trivial conditions.

Accidental or serendipitous discoveries have led to important breakthroughs in the chemical sciences. With regard to bond-forming reactions, such fundamental synthetic transformations as Friedel-Crafts, Wittig olefination, and Brown hydroboration reactions were found when the objectives of the initial experiments were not in accord with the observed outcomes (*1*).

Recently, we questioned whether serendipity could be forced or simulated to occur on a predictable basis in the realm of reaction discovery, thereby providing a reliable platform to access valuable transformations or unexpected pathways. Herein, we describe the successful execution of these ideals and describe a fundamentally distinct C–H functionalization-arylation reaction that we expect will be of broad use to practitioners of chemical synthesis and, in particular, medicinal chemistry.

Assuming that serendipity is governed by probability (and thereafter manageable by statistics), performing a large number of random chemical reactions must increase the chances of realizing a serendipitous outcome. However, the volume of reactions required to achieve serendipity in a repetitive fashion is likely unsuitable for traditional laboratory protocols that use singular experiments. Indeed, several combinatorial strategies have previously been used to identify singular

Merck Center for Catalysis, Department of Chemistry, Princeton University, Princeton, NJ 08544, USA.

*To whom correspondence should be addressed. E-mail: dmacmill@princeton.edu

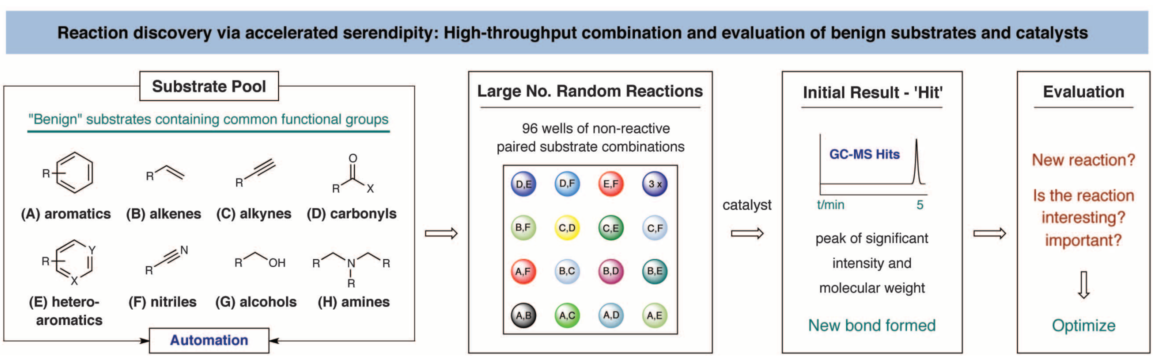

Fig. 1. Approach to reaction discovery without preconceived design via the concept of accelerated serendipity. R indicates a generic organic substituent; X and Y, heteroatoms.

chemical reactions (*2–11*); however, the use of substrate-tagging methods or large collections of substrate mixtures does not emulate the representative constituents of a traditional chemical reaction. On this basis, we posited that an automated, high-throughput method of reaction setup and execution, along with a rapid gas chromatography–mass spectrometry (GC-MS) assay using National Institute of Standards and Technology (NIST) mass spectral library software, might allow about 1000 random transformations to be performed and analyzed on a daily basis (by one experimentalist) (Fig. 1). Although we recognized that it is presently impossible to calculate the minimum number of experiments that must be performed to achieve "chance discoveries" on a regular basis, we presumed that 1000 daily experiments would be a substantial starting point.

Substrate pools were created of molecules containing common functional groups that would be considered nonreactive or benign in one-to-one combinations (see figs. S2 and S3 for substrate pools). As a critical design element, we identified that such a process must be free from any preconceived bias as to which chemical reaction is discovered or the mechanism by which it may happen. As such, we sought to minimize substrate combinations that are likely to participate in established reaction pathways. A Chemspeed (ChemSpeed Technologies, Basel, Switzerland) robotic system was used to arrange all of the pairwise combinations into 96-well plates (for example, a pool of 19 substrates equates to 171 different combinations) before a catalyst system was added (i.e., catalyst, ligand, additive, solvent, etc.). This screening platform was then used in a repetitive fashion to examine a range of catalyst systems. Our analysis method to detect potential coupling products had its basis in a GC-MS assay where peaks of substantial intensity and molecular weight were an indication of possible coupling between the two reactants, with the NIST mass spectral library providing an indication of possible structure. A critical evaluation stage was used to determine whether a reaction is mechanistically unanticipated and might furthermore show potential as an interesting or useful chemical transformation. Initially, transition metal complexes derived from Pd, Ru, Au, Fe, etc., were examined. New catalysts were identified for three existing transformations: $AuCl_3$ catalyzed indole alkylation with styrene, $FeCl_3$ catalyzed alkyne dimerization, and $Ru_3(CO)_{12}$ catalyzed styrene hydroesterification with MeOH, where Me is a methyl group (fig. S8) (*12*). However, in order to exploit the full potential of serendipity and discover unanticipated chemical reactions, we recognized that implementing this discovery process in a relatively uncharted area of synthetic methodology might statistically aid in the pursuit of this goal (Fig. 2A). In this context, photoredox catalysis was selected as a target area, given that it is a relatively young and emerging field in organic synthesis that has recently delivered a variety of powerful bond-forming processes (*13*).

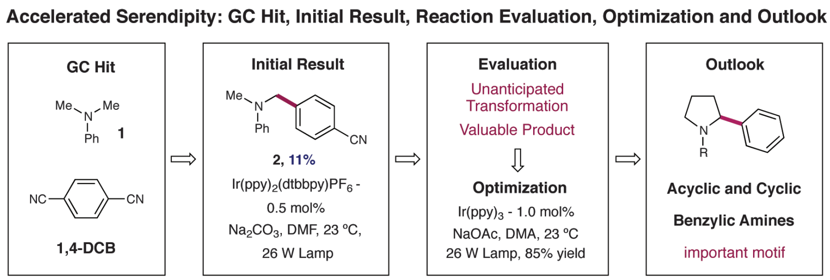

Fig. 2. Discovery of a new photoredox amine C–H arylation reaction. Ph phenyl group; DMF, *N*,*N*-dimethylformamide; DMA, *N*,*N*-dimethylacetamide.

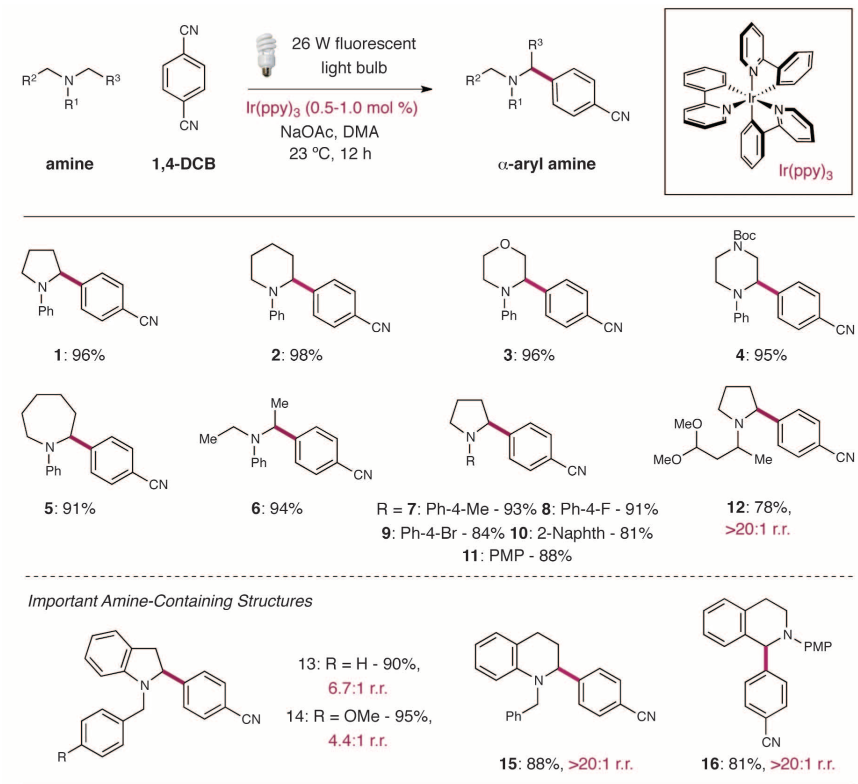

Fig. 3. Photoredox C–H arylation: amine scope. R, generic alkyl or aryl substituent. Data reported as **entry**, % isolated yield, regiomeric ratio (r.r., determined by ^{1}H nuclear magnetic resonance analysis). 2.5 to 3.0 equivalents of amine used (see fig. S6 for stoichiometry effects).

Substrate pools were exposed to a series of inorganic photoredox catalysts in the presence of a household 26-W fluorescent lamp (all performed on a Chemspeed robotic platform). The use of GC-MS analysis revealed a reaction hit for the combination of *N*,*N*-dimethylaniline and 1,4-dicyanobenzene (1,4-DCB) with $Ir(ppy)_2(dtbbpy)PF_6$ (where dtbbpy is 4,4′-di-*t*-butyl-2,2′-bipyridine and ppy indicates 2-phenylpyridine) as a photocatalyst (Fig. 2B). Investigation into the reaction mixture revealed the formation of an unusual α-amino cyanobenzene coupling product, **2**, that formed in 11% yield (*14*). In evaluating the observed outcome, we found that the discovery was, indeed, a new example of a photoredox catalyzed process. Photolytic methods for the α-functionalization of amines typically require the use of high-energy light (and therefore the availability of specialized equipment for reaction setup) (*15–19*). Additionally, we recognized the value of the benzylic amine product **2**. More specifically, α-aryl amines are a prominent structural class found among medicinal agents, with 8 of the 100 top-selling pharmaceuticals containing this motif (and a vast array of others being simple derivatives thereof) (*20*). Given the potential utility of such a transform, optimization was undertaken, and improvements in efficiency were made with changes to the solvent, base, and most notably the photocatalyst, with the commercial $Ir(ppy)_3$ system providing the desired α-arylation adduct **2** in 85% yield. With this highly efficient process in hand, our attention turned to the full exploitation of this α-amine C–H arylation reaction as a mild and operationally trivial means of forming benzylic amines (*21–26*).

Structural scope exploration began with five-membered pyrrolidine, six-membered piperidine, morpholine, *N*-Boc (where Boc is tert-butoxycarbonyl) piperazine, and seven-membered azepane rings, all of which provided excellent results (Fig. 3, entries 1 to 5). Acyclic amines also functioned efficiently in this protocol (entry 6). Variation of the *N*-aryl group was tolerated, including methyl and halogen substituents as well as *N*-naphthyl–substituted amines (entries 7 to 10). A *p*-methoxyphenyl (PMP) substituent, which serves as a well-established protecting group for the nitrogen atom (*27*), can also be used (entry 11). Moreover, we have developed an alternative, nonaryl protecting group in the form of dimethoxy butane (DMB) that can be successfully used in the photoredox arylation (entry 12) and easily removed thereafter by using acidic conditions [supporting online material (SOM)] (*28*). Privileged cyclic amine structures from medicinal chemistry were also subjected to this arylation reaction, such as protected indolines and tetrahydroquinolines, and there is a distinct preference for arylation at the ring position as opposed to the acyclic benzylic site (entries 13 to 15). However, the situation is altered by using PMP-protected tetrahydroisoquinoline with arylation at the cyclic benzylic position as the only detectable outcome (entry 16).

The scope of the aryl ring component in this α-amine arylation protocol has also been studied (Fig. 4). We found that benzonitriles substituted with esters, amides, phosphonate esters, and electron-deficient tetrazoles are suitable substrates (entries 1 to 4). The cyano group also proved effective as a coupling handle in the challenging steric environment of 2,6-disubstituted aryl rings to generate bis-ortho-substituted products (entry 5). Furthermore, the site specificity of the coupling process can be further exploited through the use of 1,2-dicyanobenzene, efficiently forming the corresponding ortho-substituted isomer (entry 6). In recognizing the electron-poor nature of the arene nucleus as an essential feature for reactivity, our attention turned to electron-deficient heteroaromatics as coupling partners. These moieties are among the most widespread constituents of pharmaceutical compounds (*29*). Our initial results in this area appear to be extremely encouraging. Cyano-substituted pyridines smoothly undergo coupling with the amine substrate, albeit with lower efficiency in the ortho case (entries 7 to 9). Azaindoles, an important biological isostere for indoles (*29*), are also amenable to this arylation strategy (entry 10).

We have also identified that five-membered heterocycles are suitable substrates. For instance, a triazole was found to undergo coupling in moderate yield (entry 11). Furthermore, for certain classes of five-membered heteroaromatics, a simple chloride can function equivalently to

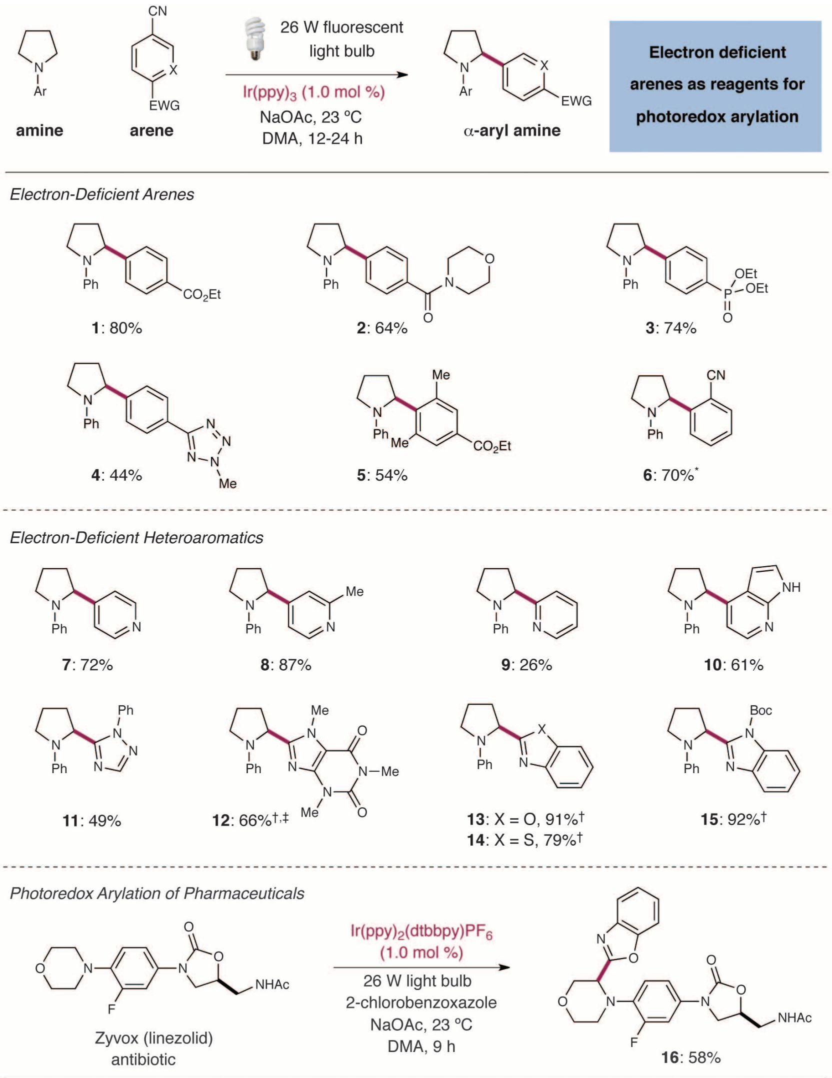

Fig. 4. Photoredox C–H arylation: arene and heteroarene scope. Ar, generic aryl group; X, CH or heteroatom; EWG, electron-withdrawing functional group. Data reported as **entry**, % isolated yield. 3.0 equivalents of amine used (see fig. S6 for stoichiometry effects). *Run with 5 mol % catalyst. †Leaving group is a chloride; photocatalyst is $Ir(ppy)_2(dtbbpy)PF_6$. ‡Reaction time is 72 hours.

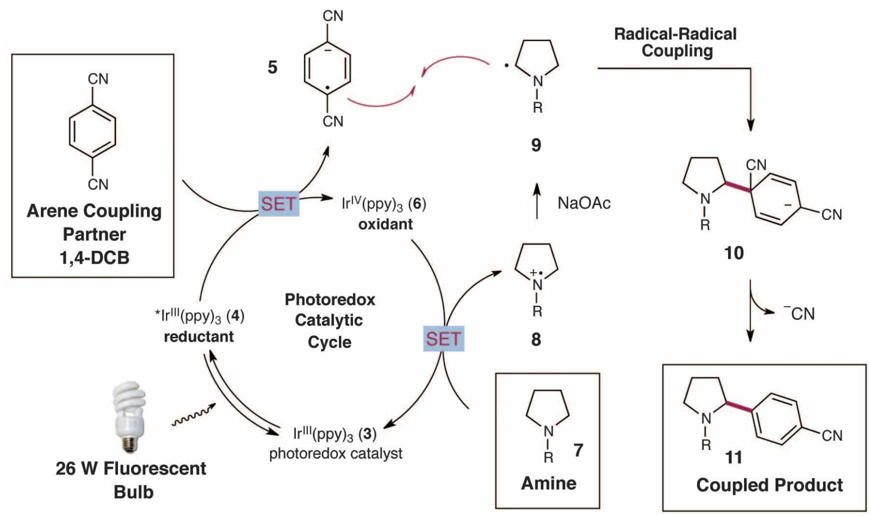

Fig. 5. Photoredox C–H arylation: proposed mechanistic pathway. R, generic alkyl or aryl substituent; SET, single-electron transfer.

CN^- as a suitable leaving group. This enables arylation of amines with chloro-substituted caffeine, benzoxazole, benzothiazole, and *N*-Boc benzimidazole (entries 12 to 15). Lastly, the direct derivatization of pharmaceutical agents has been demonstrated by using linezolid, an antibiotic that undergoes direct heteroarylation in 58% yield (entry 16). This result further demonstrates the capacity of druglike molecules to readily participate in this C–H functionalization reaction.

Our proposed mechanistic explanation for the C–H arylation process is described in Fig. 5. Triscyclometalated Ir(III) complexes, such as $Ir(ppy)_3$ (**3**), are reversibly promoted to their excited state form [$^*Ir(ppy)_3$ (**4**)] upon absorption of a photon from the 26-W light source (*30*). $^*Ir^{III}(ppy)_3$ (**4**) is a powerful reductant [oxidation potential ($E_{1/2ox}$) = –1.73 V versus saturated calomel electrode (SCE) in CH_3CN] (*30*, *31*) and, upon encountering 1,4-DCB ($E_{1/2red}$ = –1.61 V versus SCE in CH_3CN) (*32*), could donate an electron to form the corresponding arene radical anion **5** (*33–35*). The resultant $Ir^{IV}(ppy)_3$ (**6**) is a strong oxidant ($E_{1/2red}$ = +0.77 V versus SCE in CH_3CN) (*30*, *31*) and would be capable of undergoing a single-electron transfer event with amine **7**, generating amine radical cation **8**, as well as re-forming $Ir^{III}(ppy)_3$ (**3**) and thereby completing the photoredox cycle. The C–H bonds adjacent to the nitrogen atom in **8** are weakened by about 40 kcal/mol and so could undergo deprotonation by NaOAc (where OAc is an acetoxy group) to give α-amino radical **9** (*19*, *36*). A radical-radical coupling reaction could then unite intermediates **5** and **9**, representing the key bond-forming step (*15–19*, *37–43*). Elimination of CN^- from **10** would then form the aromatized benzylic amine product **11**.

In summary, the concept of accelerated serendipity has been successfully executed, resulting in the discovery of a photoredox amine C–H arylation reaction. Requiring only commercially available materials, mild conditions, and operationally trivial reaction protocols, we anticipate this carbon-carbon bond-forming protocol will be widely used in the synthesis of benzylic and heterobenzylic amines.

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Pelagic Fishing at 42,000 Years Before the Present and the Maritime Skills of Modern Humans

Sue O'Connor,[1] Rintaro Ono,[2] Chris Clarkson[3]

By 50,000 years ago, it is clear that modern humans were capable of long-distance sea travel as they colonized Australia. However, evidence for advanced maritime skills, and for fishing in particular, is rare before the terminal Pleistocene/early Holocene. Here we report remains of a variety of pelagic and other fish species dating to 42,000 years before the present from Jerimalai shelter in East Timor, as well as the earliest definite evidence for fishhook manufacture in the world. Capturing pelagic fish such as tuna requires high levels of planning and complex maritime technology. The evidence implies that the inhabitants were fishing in the deep sea.

Although humans were able to travel hundreds of kilometers over the ocean by 50,000 years ago (ka), as required for the colonization of Australia, global evidence for fishing is rare before about 12 ka (*1*, *2*). Middle Stone Age sites in southern Africa, such as Klaises River Mouth Main Cave, Pinnacle Point, and Ysterfontein 1, contain evidence of shellfish predation and the remains of marine mammals such as seals, but evidence of fishing before the Holocene is absent or exceptionally rare (*1*, *3*, *4*). Whether this reflects real behavioral changes or the loss of coastal archaeological sites as sea level rose is unknown. A record of early marine fishing is found at Blombos Cave dating between ~140 and 50 ka, but the fish represented are shallow-water species and would not have required boats or complex technology for their capture (*5*).

At Jerimalai shelter in East Timor, evidence exists for systematic pelagic fishing from 42 ka, showing the high level of maritime capacity

[1]Department of Archaeology and Natural History, College of Asia and the Pacific, Australian National University, Canberra, Australian Capital Territory 0200, Australia. [2]Department of Maritime Civilizations, School of Marine Science and Technology, Tokai University, Shizuoka 424-8610, Japan. [3]School of Social Science, University of Queensland, St Lucia, Queensland 4072, Australia.