off) the reaction rate steadily increases, and the PO selectivity steadily decreases, as a function of temperature. This behavior is fundamentally different than the behavior observed in response to light (Fig. 1, A and B), in which we see sharp drops in the reaction rate and a sharp increase in the selectivity at ~550 mW/cm^2.

The studies discussed advance a number of critical concepts. Although we focused on Cu nanostructures, the discussed mechanisms are universal, and similar principles could be used in the design of various metal nanomaterials with photo-switchable oxidation states. For example, core-shell nanoparticles containing a plasmonic core (such as Au, Ag, or Cu) and a shell of another metal could lend themselves to similar LSPR-mediated photo-induced switching of the oxidation states of surface atoms. Controlling the oxidation state of functioning catalysts is critical for the control of reactant conversion rates and product selectivity. Second, direct epoxidation of propylene without expensive sacrificial agents is one of the most important processes for which no viable heterogeneous catalyst exists. Although the findings reported here may pave the way toward the discovery of viable heterogeneous propylene epoxidation catalysts, hurdles related to efficient and scalable harvesting of light (including abundant solar light) represent considerable challenges.

References and Notes

1. R. L. Cropley *et al.*, *J. Am. Chem. Soc.* **127**, 6069 (2005).
2. A. K. Santra, J. J. Cowell, R. M. Lambert, *Catal. Lett.* **67**, 87 (2000).
3. J. J. Cowell, A. K. Santra, R. M. Lambert, *J. Am. Chem. Soc.* **122**, 2381 (2000).
4. R. M. Lambert, F. J. Williams, R. L. Cropley, A. Palermo, *J. Mol. Catal. Chem.* **228**, 27 (2005).
5. D. Torres, N. Lopez, F. Illas, R. M. Lambert, *Angew. Chem. Int. Ed.* **46**, 2055 (2007).
6. J. R. Monnier, G. W. Hartley, *J. Catal.* **203**, 253 (2001).
7. S. Linic, P. Christopher, D. B. Ingram, *Nat. Mater.* **10**, 911 (2011).
8. P. Christopher, H. Xin, S. Linic, *Nat. Chem.* **3**, 467 (2011).
9. P. Christopher, H. Xin, A. Marimuthu, S. Linic, *Nat. Mater.* **11**, 1044 (2012).
10. K. P. Rice, E. J. Walker Jr., M. P. Stoykovich, A. E. Saunders, *J. Phys. Chem. C* **115**, 1793 (2011).
11. G. H. Chan, J. Zhao, E. M. Hicks, G. C. Schatz, R. P. Van Duyne, *Nano Lett.* **7**, 1947 (2007).
12. E. M. Larsson, C. Langhammer, I. Zorić, B. Kasemo, *Science* **326**, 1091 (2009).
13. D. Seo, G. Park, H. Song, *J. Am. Chem. Soc.* **134**, 1221 (2012).
14. C. Novo, A. M. Funston, P. Mulvaney, *Nat. Nanotechnol.* **3**, 598 (2008).
15. M. Hara *et al.*, *Chem. Commun. Camb.* 3, 357 (1998).
16. S. K. Cushing *et al.*, *J. Am. Chem. Soc.* **134**, 15033 (2012).
17. P. Christopher, D. B. Ingram, S. Linic, *J. Phys. Chem. C* **114**, 9173 (2010).
18. D. B. Ingram, S. Linic, *J. Am. Chem. Soc.* **133**, 5202 (2011).
19. D. B. Ingram, P. Christopher, J. L. Bauer, S. Linic, *ACS Catal.* **1**, 1441 (2011).
20. K. Awazu *et al.*, *J. Am. Chem. Soc.* **130**, 1676 (2008).
21. U. Kreibig, M. Vollmer, *Optical Properties of Metal Clusters* (Springer, New York, ed. 1, 1995).
22. B. N. J. Persson, *Surf. Sci.* **281**, 153 (1993).
23. U. Kreibig, *Appl. Phys. B* **93**, 79 (2008).
24. H. Hövel, S. Fritz, A. Hilger, U. Kreibig, M. Vollmer, *Phys. Rev. B Condens. Matter* **48**, 18178 (1993).
25. K. Watanabe, D. Menzel, N. Nilius, H.-J. Freund, *Chem. Rev.* **106**, 4301 (2006).
26. L. Brus, *Acc. Chem. Res.* **41**, 1742 (2008).
27. A. M. Michaels, L. Jiang, *J. Phys. Chem. B* **104**, 11965 (2000).
28. A. Furube, L. Du, K. Hara, R. Katoh, M. Tachiya, *J. Am. Chem. Soc.* **129**, 14852 (2007).
29. Y. Tian, T. Tatsuma, *Chem. Commun. (Camb.)* (16): 1810 (2004).

Acknowledgments: We gratefully acknowledge support from the U.S. Department of Energy, Office of Basic Energy Science, Division of Chemical Sciences (FG-02-05ER15686) and National Science Foundation (CBET-0966700, CBET-1132777 and CHE-1111770). S.L. acknowledges the DuPont Young Professor grant by the DuPont corporation and the Camille Dreyfus Teacher-Scholar Award from the Camille & Henry Dreyfus Foundation. We also acknowledge H. Xin for discussions and insight. We declare no competing financial interests.

Supplementary Materials

www.sciencemag.org/cgi/content/full/339/6127/1590/DC1
Materials and Methods
Figs. S1 to S6
References (*30*, *31*)

17 October 2012; accepted 3 January 2013
10.1126/science.1231631

Photoredox Activation for the Direct β-Arylation of Ketones and Aldehydes

Michael T. Pirnot, Danica A. Rankic, David B. C. Martin, David W. C. MacMillan*

The direct β-activation of saturated aldehydes and ketones has long been an elusive transformation. We found that photoredox catalysis in combination with organocatalysis can lead to the transient generation of 5π-electron β-enaminyl radicals from ketones and aldehydes that rapidly couple with cyano-substituted aryl rings at the carbonyl β-position. This mode of activation is suitable for a broad range of carbonyl β-functionalization reactions and is amenable to enantioselective catalysis.

Within the field of organic chemistry, the carbonyl moiety is central to many broadly used synthetic modifications and fragment coupling steps, including Grignard reactions, Wittig olefinations, and reductive aminations. The carbonyl system is also a preeminent activation handle for proximal bond constructions such as α-C=O oxidations, alkylations, arylations, and halogenations (*1*, *2*). However, transformations that allow the direct β-functionalization of saturated ketones and aldehydes remain effectively unknown (*3*, *4*). Herein, we describe a catalysis activation mode that arises from the combination of photoredox and amine catalysis to enable the direct arylation of cyclic and acyclic carbonyls at the β-methylene position (Fig. 1).

Historically, β-carbonyl activation has been limited to the addition of soft nucleophiles to α,β-unsaturated carbonyls. Although the study of such reactivity has delivered many useful transformations, this chemistry requires substrates that are not as widely available or require an additional preoxidation step from a saturated precursor (*5*–*9*). Previous studies in transition metal catalysis have shown that direct β-functionalization of esters or amides is possible through the use of palladium catalysis, albeit with only a few examples known to date (*10*–*13*). A direct aldehyde or ketone β-coupling mechanism would obviate the need for preactivated substrates.

Over the past 4 years, visible light–mediated photoredox catalysis has become a rapidly blossoming research area within the organic and organometallic communities (*14*–*17*). Through a series of photoinduced electron transfer (PET) events, this general strategy allows for the development of bond constructions that are often elusive or currently impossible via classical two-electron pathways. In addition, photoredox catalysis provides an alternative means of generating reactive radical intermediates without operational complexity and toxic precursors (often found with high-energy photochemistry and/or reagent-based radical production).

Recently, using the concept of "accelerated serendipity," our laboratory discovered a unique bond construction that enables the direct arylation of α-methylene amines via visible light photoredox catalysis (*18*). On the basis of mechanistic insights gained from this arylation protocol, we hypothesized that photoredox and amine catalysis might be used in conjunction to enable the direct β-functionalization of carbonyls. A prospective mechanism for this dual-catalysis β-aldehyde or ketone arylation is shown in Fig. 2. It is well known that tris-cyclometalated Ir(III) complexes, such as tris(2-phenylpyridinato-C^2,N)iridium(III) [Ir(ppy)$_3$] (**1**), have a strong absorption cross section in the visible range, allowing them to accept a photon from a variety of light sources to populate the *Ir(ppy)$_3$ (**3**) metal-to-ligand charge transfer excited state (*19*). Given that *Ir(ppy)$_3$ (**3**) is a strong reductant [oxidation potential ($E_{1/2}^{ox}$) = −1.73 V versus saturated calomel electrode (SCE) in CH_3CN] (*19*, *20*), we proposed that this high-energy

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

*Corresponding author. E-mail: dmacmill@princeton.edu

intermediate would undergo single-electron transfer (SET) with 1,4-dicyanobenzene (**4**) [reduction potential $E_{1/2}^{red} = -1.61$ V versus SCE in CH_3CN] (*21*) to afford the arene radical anion **5** and oxidized photocatalyst $Ir^{IV}(ppy)_3$ (**6**). Concurrent with this photoredox step, we hypothesized that amine catalyst **2** should condense with aldehyde substrate **7** to form the electron-rich enamine **8**. At this juncture we hoped that the photoredox and organocatalytic cycles would merge, as the electron-deficient $Ir^{IV}(ppy)_3$ (**6**) intermediate ($E_{1/2}^{red} = +0.77$ V versus SCE in CH_3CN) (*19*, *20*) should readily accept an electron via SET from the electron-rich enamine **8** to generate the corresponding radical cation **9** (and thereby complete the photoredox cycle) (*22*). As a key mechanistic consideration, we hypothesized that formation of the enaminyl radical cation **9** would sufficiently weaken the allylic C–H bonds (at the original carbonyl β-position) so as to allow deprotonation and formation of the β-enamine radical **10**, which represents the critical 5πe⁻ activation mode. We assumed that intermolecular coupling of radical anion **5** and β-radical **10** would then forge a new sp^3-sp^3 carbon-carbon bond and that the resulting cyclohexadienyl anion **11** would undergo rapid β,δ-elimination of cyanide to regain aromaticity. Hydrolysis of the resulting enamine would then complete the organocatalytic cycle while delivering the desired β-aryl aldehyde product **12**.

This dual-catalysis design plan has several key features. First, a stabilized radical, such as radical anion **5**, would be sufficiently electron-rich to avoid direct reaction with enamine **8**, thus avoiding bond formation at the α-carbonyl position. Similarly, electron-deficient arenes, such as 1,4-dicyanobenzene, are capable of forming radical anion intermediates that have relatively long lifetimes, thereby increasing the propensity for selective radical-radical bond formation with the β-enaminyl radical **10** (*23*). Moreover, such radical anion species do not typically engage in homocoupling—a step that would lead to a net loss in reaction efficiency. We also recognized from an early stage that the requisite amine catalyst must be sufficiently electron-rich to chemically enable three critical steps: (i) enamine formation, (ii) enamine oxidation, and (iii) nucleophilic radical coupling of the key 5πe⁻ activated intermediate **10**. With respect to the key deprotonation step (**9** to **10**), we recognized that an alternative mechanism might be encountered wherein the nitrogen-centered radical cation **9** could undergo proton loss at the α-methylene position on the catalyst framework to generate an α-amino radical (not shown). However, initial density functional theory calculations to investigate this chemoselectivity issue suggested that the proposed allylic C–H bond functionalization has a significantly lower energy of activation than the corresponding α-aminium radical deprotonation step (*24*–*26*).

With these considerations in mind, we first examined this β-carbonyl arylation reaction with octanal, 1,4-dicyanobenzene, and a variety of amine catalysts, photocatalysts, and weak light sources. To our delight, we found that the use of $Ir(ppy)_3$ (**1**) and *N*-isopropylbenzylamine (*i*-PrBnNH) (**13**) in the presence of a 26-W fluorescent light bulb while using 1,4-diazobicyclo[2.2.2]nonane (DABCO) as a base provided the respective β-aryl aldehyde adduct in 86% yield, without formation of any α-amine arylation adducts. Control experiments established the importance of both the organocatalyst and the photocatalyst, as no desired reaction was observed in the absence of light, $Ir(ppy)_3$, or *i*-PrBnNH (*26*). The fact that $Ir(ppy)_3$ was found to be the optimal photocatalyst is readily appreciated given its matched redox potentials for both the reduction of 1,4-dicyanobenzene and oxidation of the amine catalyst–derived enamine.

Having identified the optimal conditions for this β-arylation reaction, we next examined the

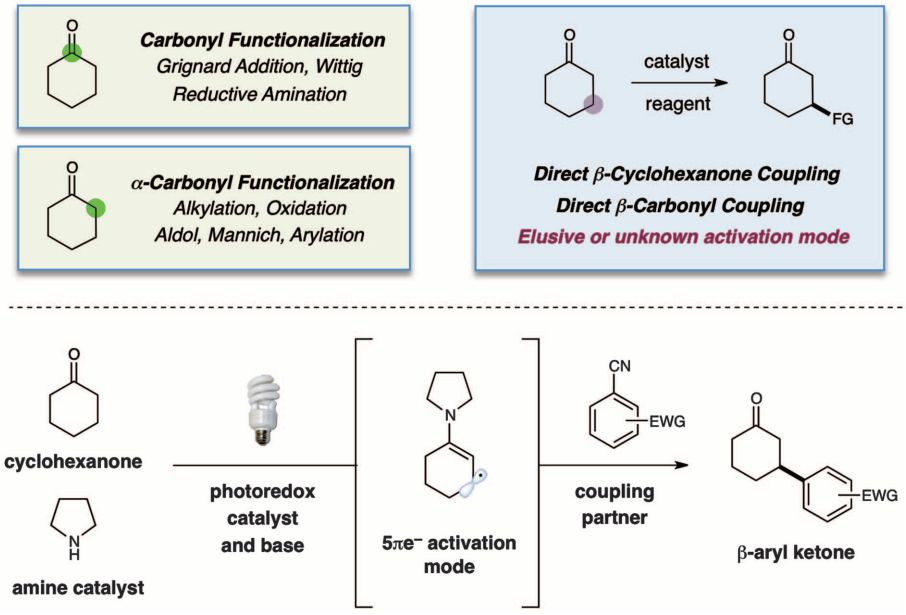

Fig. 1. Proposed activation mode for direct β-arylation of carbonyls—an elusive transformation.

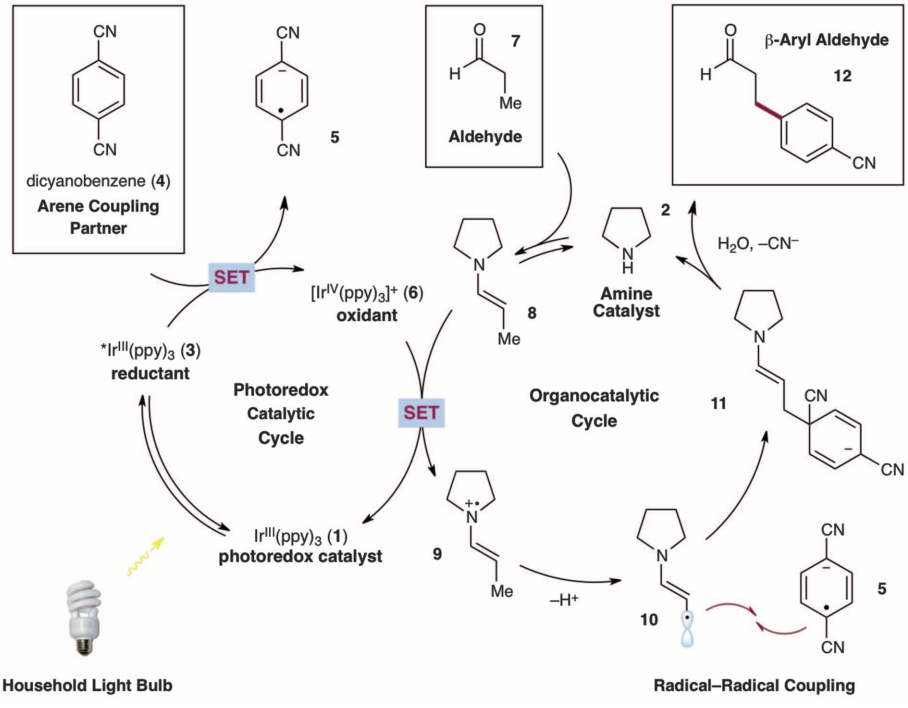

Fig. 2. Photoredox C–H β-arylation: Proposed mechanistic pathway (Me, methyl).

scope of the aldehydic coupling partner. As shown in Fig. 3, a broad array of alkanals can serve as competent substrates. For example, functional groups as diverse as ethers, alkenes, alkynes, arenes, and carbamates are readily tolerated (Fig. 3, entries 17 to 22; 63 to 88% yield). We found that β-aryl– and β-amino–substituted aldehydes are also suitable substrates (entries 20 to 22; 63 to 88% yield). Perhaps most remarkable is the capacity of this activation mode to enable bond formations at highly sterically congested centers, as highlighted with the β,β′-disubstituted aldehydes (entries 23 to 25). In each case, quaternary carbon-containing β-aryl products are forged with excellent levels of efficiency (entries 23 to 25; 70 to 74% yield). These results are consistent with an early transition state in the critical radical-radical coupling (Fig. 2, **5** + **10**), which in turn would minimize the impact of nonbonding interactions. We recognized from an early stage that our transformation might allow direct β-arylation of propionaldehyde, thereby delivering a one-step approach to the production of hydrocinnamaldehyde equivalents. As revealed in entry 26, this strategy was indeed found to be feasible (78% yield).

As might be expected, the electronic nature of the β-enaminyl radical **10** plays a critical role in the efficiency of the arylation step. For example, β-aryl aldehyde substrates that are electron-rich in nature, such as *p*-methoxyphenyl (entry 20) and *N*-methylindolyl (entry 21), readily undergo β-aryl coupling. In contrast, the use of 3-(*p*-cyanophenyl) propionaldehyde (the product of entry 26) results only in the recovery of starting materials, presumably due to the low nucleophilicity of the corresponding β-enaminyl radical. These results provide a mechanistic basis as to why mono-arylation adducts are selectively observed in this study, given the electron deficiency of the β-aryl products formed.

We next examined the scope of the aromatic coupling component in this synergistic catalysis protocol. As further shown in Fig. 3, a range of cyanobenzene and cyanoheteroaromatics have

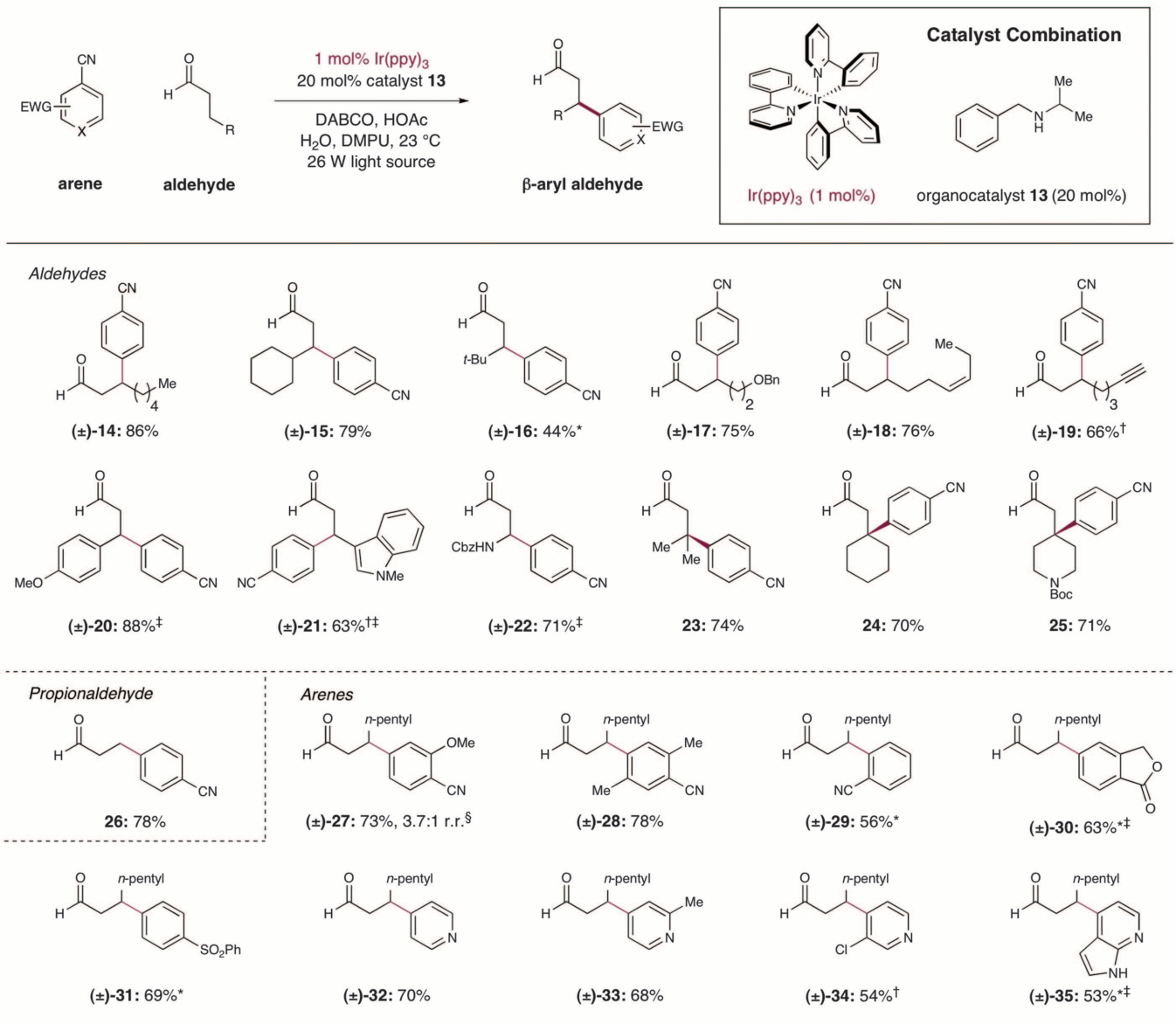

Fig. 3. Photoredox C–H β-arylation: aldehyde and arene scope. For each entry number (in boldface), data are reported as percent isolated yield. R = generic alkyl or aryl substituent; X = CH, C, or N; DMPU, 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one; DABCO, 1,4-diazabicyclo[2.2.2]octane; Me, methyl; Bn, benzyl; *t*-Bu, *tert*-butyl; Boc, *tert*-butyl carbamoyl; Cbz, benzyl carbamoyl. *See supplementary materials for experimental details. †1.0 equiv of Na_2CO_3 added. ‡Product isolated as β-aryl alcohol. §Regiomeric ratio (r.r., determined by ^1H nuclear magnetic resonance analysis; see supplementary materials). Major isomer is shown; minor isomer is 3-methoxy-4-alkylbenzonitrile.

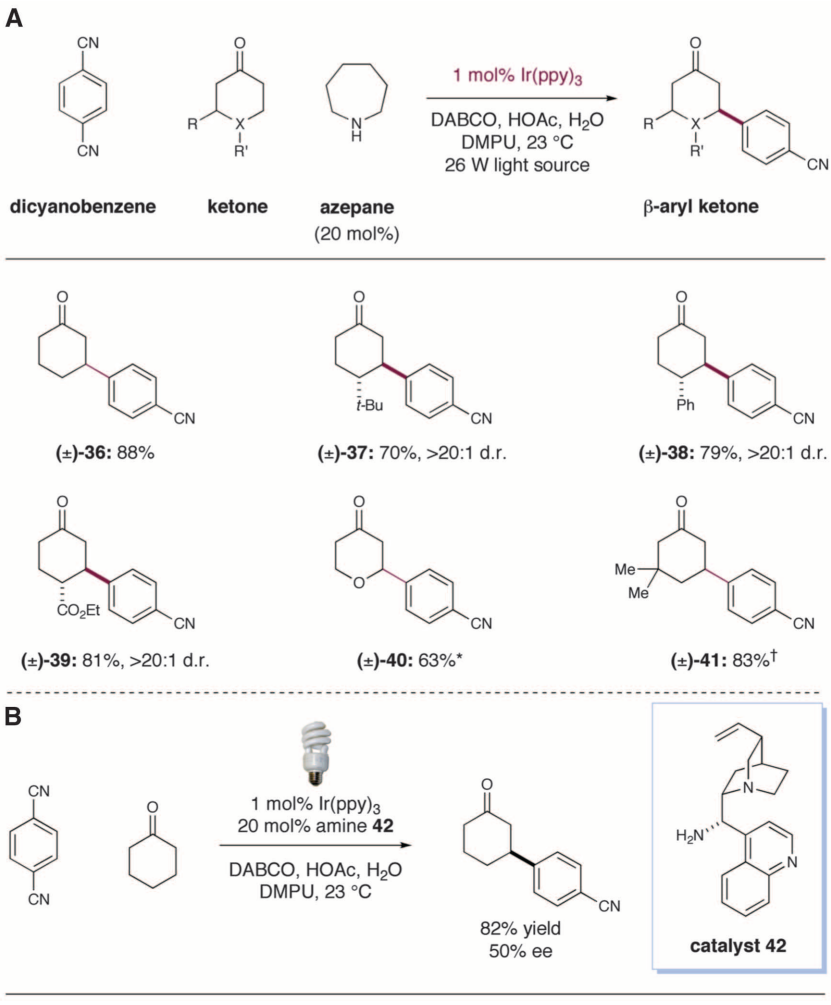

Fig. 4. (**A**) Direct β-arylation of ketones. For each entry number, data are reported as percent isolated yield; for entries 37 to 39, diastereomeric ratio (d.r.) was determined by ^{1}H nuclear magnetic resonance analysis. R = hydrogen or methyl; R′ = hydrogen, generic alkyl, or aryl substituent; X = CH or O. (**B**) Enantioselective β-arylation of cyclohexanone (ee, enantiomeric excess). *20 mol % piperidine used as the organocatalyst. †40 mol % azepane used as the organocatalyst.

been found to be suitable substrates (Fig. 3, entries 27 to 35; 53 to 78% yield). Sterically hindered arenes, such as 2,5-dimethylterephthalonitrile, readily undergo addition to the activated 5πe$^-$ species **10** (entry 28, 78% yield). Moreover, cyanoaromatics that incorporate substituents at the ortho, meta, and para sites are readily tolerated (entries 27 to 30, 33, and 34; 54 to 78% yield). Although cyano-substitution appears to be essential for the arene coupling partner, superior yields are obtained when electron-withdrawing groups, such as esters and sulfones, are incorporated at the ortho and para positions (entries 29 to 31; 56 to 69% yield). With respect to heteroaromatic systems, a broad range of cyano-substituted pyridines with both electron-donating and electron-withdrawing substituents undergo β-coupling with good levels of efficiency (entries 32 to 35; 53 to 70% yield). Moreover, 7-azaindole, an important biological isostere for indole in medicinal chemistry, readily participates in this transform (entry 35). The formation of cyanide is an unfortunate drawback of this protocol but can be easily washed away with an aqueous work-up.

Given that enamine formation is a central step in the formation of the 5πe$^-$ intermediate **10**, we presumed that ketones should also be amenable to this β-coupling reaction, provided that a suitable amine catalyst could be identified. As shown in Fig. 4, the seven-membered azepane system was found to be an exceptional catalyst for the β-functionalization of a myriad of cyclohexanone derivatives (Fig. 4A, entries 36 to 41; 63 to 88% yield). As was the case with aldehydes, this photoredox arylation protocol is tolerant of significant steric variation on the cyclohexyl ring (entries 37, 38, 39, and 41; 70 to 83% yield). Moreover, useful levels of trans-diastereocontrol are accomplished with ketone substrates bearing substituents at the 4-position (entries 37 to 39; >20:1 d.r., 70 to 81% yield). Heteroatom-containing ketones also serve as competent coupling partners (entry 40, 63% yield). The addition of increased quantities of water was required with ketone substrates to avoid the production of bis-3,5-β,β′-arylation products, presumably due to the need for a fast enamine hydrolysis step after the initial arylation. Preliminary studies have revealed that cinchona-derived organocatalysts, such as amine **42**, effect the β-arylation of cyclohexanone with promising levels of enantioselectivity (Fig. 4B, 82% yield, 50% ee). This result clearly demonstrates that this activation mode is amenable to asymmetric catalysis, and work on this topic is ongoing.

References and Notes

1. D. A. Evans, G. Helmchen, M. Rüping, *Asymmetric Synthesis—The Essentials* (Wiley-VCH, Weinheim, Germany, 2006).
2. S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **107**, 5471 (2007).
3. A one-pot two-step oxidation, iminium-catalyzed β-functionalization process has been reported (*4*).
4. S.-L. Zhang *et al.*, *Nat. Commun.* **2**, 211 (2011).
5. R. Itooka, Y. Iguchi, N. Miyaura, *J. Org. Chem.* **68**, 6000 (2003).
6. F. López, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **126**, 12784 (2004).
7. N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **124**, 7894 (2002).
8. A high-energy light promoted example of β-functionalization with preformed ketone enamines has been reported (*9*).
9. M. Kawanisi, K. Kamogawa, T. Okada, H. Nozaki, *Tetrahedron* **24**, 6557 (1968).
10. M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **131**, 9886 (2009).
11. A. Renaudat, L. Jean-Gerard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **49**, 7261 (2010).
12. Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **133**, 12984 (2011).
13. M. V. Leskinen, K.-T. Yip, A. Valkonen, P. M. Pihko, *J. Am. Chem. Soc.* **134**, 5750 (2012).
14. D. A. Nicewicz, D. W. C. MacMillan, *Science* **322**, 77 (2008).
15. M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **130**, 12886 (2008).
16. J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc. Collect. Czech. Chem. Commun.* **76**, 859 (2011).
17. A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **334**, 1114 (2011).
18. L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura, F. Barigelletti, *Top. Curr. Chem.* **281**, 143 (2007).
19. I. M. Dixon *et al.*, *Chem. Soc. Rev.* **29**, 385 (2000).
20. Y. Mori, W. Sakaguchi, H. Hayashi, *J. Phys. Chem. A* **104**, 4896 (2000).
21. V. P. Renaud, S. Schubert, *Angew. Chem.* **102**, 416 (1990).
22. D. Mangion, D. R. Arnold, *Acc. Chem. Res.* **35**, 297 (2002).
23. All calculations were performed with Gaussian 09 (*25*).
24. M. J. Frisch *et al.*, Gaussian 09, Rev. B.01 (Gaussian Inc., Wallingford, CT, 2010).
25. See supplementary materials on *Science* Online.

Acknowledgments: Supported by National Institute of General Medical Sciences grant R01 GM103558-01 and gifts from Merck, Amgen, Abbott, and Bristol-Myers Squibb.

Supplementary Materials

www.sciencemag.org/cgi/content/full/339/6127/1593/DC1
Materials and Methods
Supplementary Text
Fig. S1
Table S1
NMR Spectra
References (*27*–*37*)

20 November 2012; accepted 17 January 2013
10.1126/science.1232993