# Visible-light enabled C(sp$^3$)–C(sp$^2$) cross-electrophile coupling via synergistic nickel and halogen-atom transfer (XAT) catalysis

Girish Suresh Yedase,[a] Avishek Kumar Jha[a] and Veera Reddy Yatham[a]*

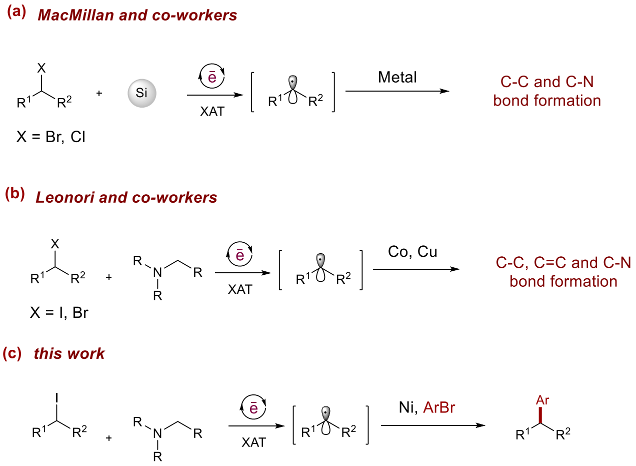
[a]School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India.

*Correspondence to: reddy@iisertvm.ac.in

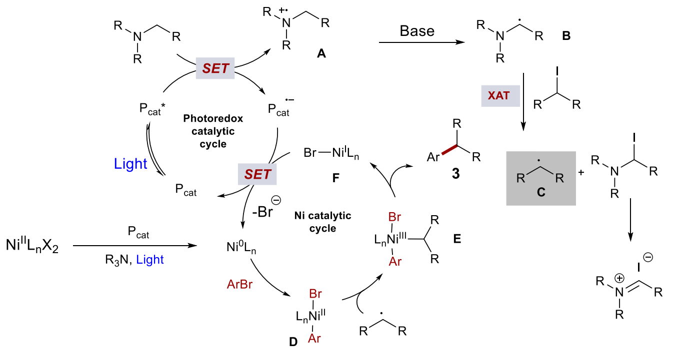
**ABSTRACT:** We herein report the first visible-light-mediated cross-coupling of unactivated alkyl iodides with aryl bromides through synergistic nickel and halogen atom transfer (XAT) catalysis. This simple protocol operates under mild reaction conditions and tolerates variety of functional groups affording C(sp$^3$)–C(sp$^2$) cross-coupling products in good to moderate yields.

In the past 10 years, visible light photocatalysis has emerged as one of the fastest growing fields in organic synthesis to construct variety of C–C or C–X (X= N, O, S, B) bonds.[1] Unique reactions that are previously inaccessible under thermal conditions can be accessed through this photocatalysis. Recently, also photocatalysis has been successfully merged with metal-based catalysis for the development of cross coupling reactions. Initially this concept was familiarized by Sanford[2a] and Glorius,[2b] in which photocatalyst was employed to promote single electron transfer (SET) process for generating carbon radical entities that can be recombined with the metal-based catalysts (Pd, Au) for the subsequent cross coupling reactions. Next, simultaneously MacMillan and Molander group independently demonstrated that synergistic dual Ni and photoredox catalysis could be used in cross coupling reactions of alkyl radicals and benzyl radicals (through SET oxidation events) with arylbromides.[3a-b] These reports confirmed not only the potential of cheap and available transition metals in dual catalysis, but also the ability of Ni complexes to promote efficiently SET processes,[3c-d] thus making them particularly interesting catalyst in further transformations.

Alkyl radicals are powerful synthetic intermediates in organic chemistry for the construction of carbon–carbon and carbon-heteroatom bonds.[4-6] The generation of alkyl radicals through homolytic cleavage of alkyl C–X (X= Cl, Br, I) bonds is the first and most apparent way due to alkyl halides are being ubiquitous starting materials for the synthesis of functionalized molecules. In early days, metal-based reagents (Sn, Mn) were employed for the generation of alkyl radicals from alkyl halides through halogen atom transfer (XAT).[7] Significant efforts have been made for replacing toxic metals with other compounds such as silicon reagents,[8] trialkylborane-O$_2$ system[9] and cyanoborohydride anion.[10] Photoinduced electron transfer is the alternative method to generate alkyl radicals from activated alkyl halides.[11] However direct reduction of unactivated alkyl halides by an excited-state photocatalyst is difficult due to their high reduction potentials ($E_{red}$ ~ -2.0 V *vs* SCE). Which necessitate the use of a strongly reducing photocatalyst.[13] Another method to generate alkyl radicals from alkyl halides is visible light induced halogen atom transfer (XAT) process,[13-14] because the energy of C–X bonds is low (bond dissociation energies range from 50 -70 kcal mol$^{-1}$). Recently, MacMillan and co-workers reported visible light induced generation of alkyl radicals from unactivated alkyl halides (R–Br, R–Cl) through halogen atom transfer (XAT) with silicon reagents and further cross-coupling reactions in presence of metal catalyst (Scheme 1, a).[13a-d] Very recently, Leonori and co-workers demonstrated that the generated α-aminoalkyl radicals in photoredox catalysis undergo in situ halogen atom transfer (XAT) with unactivated alkyl iodides and bromides to generate the desired alkyl radicals. The generated alkyl radical through this XAT process further participated in C–C, C=C and C–N bond formation reactions in the presence of suitable metal catalyst (Scheme 1, b).[14]

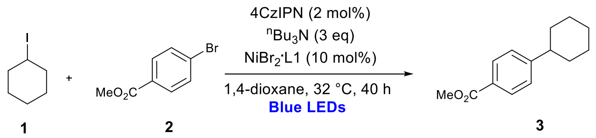


**Scheme 1**. Photoinduced cross-coupling reactions via synergistic metal and halogen-atom transfer (XAT) catalysis.

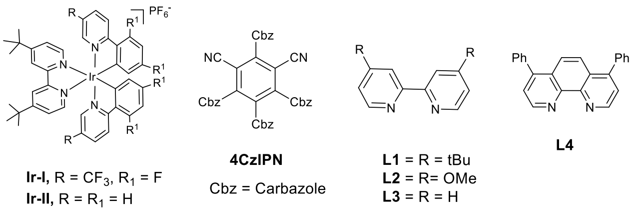


**Scheme 2**. Mechanistic Hypothesis

Inspired by the reports of Leonori and co-workers we assumed that the generated alkyl radical through XAT process from alkyl iodides under photocatalysis could be trapped by the in situ generated $L_nArNi^{II}Br$ complex which eventually lead to cross-coupling product after reductive elimination (Scheme 1, c). A detailed description of our mechanistic hypothesis for the new cross electrophile coupling is proposed in Scheme 2. We believed that upon initial irradiation with visible light, the photocatalyst ($P_{cat}$) is photoexcited to $P_{cat}$*. Next the oxidation of alkyl amine by the photoexcited photocatalyst ($P_{cat}$*) via a SET event would then generate an amino radical cation (**A**), which further converted to $\alpha$-amino radical **(B)** upon loss of proton. During this process the photocatalyst turned to corresponding radical anion of the photocatalyst ($P_{cat}^{\bullet-}$) species. It's known that the $\alpha$-amino radical is capable of abstracting iodine atom from alkyl iodides which eventually leads to carbon radical (**C**).[14] Simultaneously, with this photoredox cycle, we assumed that oxidative addition of the $L_nNi^0$ species (generated in situ from $Ni^{II}$) with an aryl bromide (ArBr) would produce the $ArL_nNi^{II}Br$ intermediate (**D**). Further interception of the generated alkyl radical (**C**) with $ArL_nNi^{II}Br$ (D) species generates the $Ni^{III}$ adduct (**E**). Subsequent reductive elimination of the $Ni^{III}$ adduct would be affording the desired C(sp$^3$)–C(sp$^2$) cross-coupling product **3** and expelling the $LnNi^IBr$ (**F**). Final, SET between the radical anion of the photocatalyst ($P_{cat}^{\bullet-}$) species and the $L_nNi^IBr$ complex (**F**) would regenerate the both photocatalyst ($P_{cat}$) and $L_nNi^0$ complex. With this mechanistic hypothesis in hand, we first examined the proposed cross-coupling by using iodocyclohexane (**1**), Methyl 4-bromobenzoate (**2**) and optimization of reaction was carried with a variety of Ni-complexes, photocatalysts, amines and solvents.

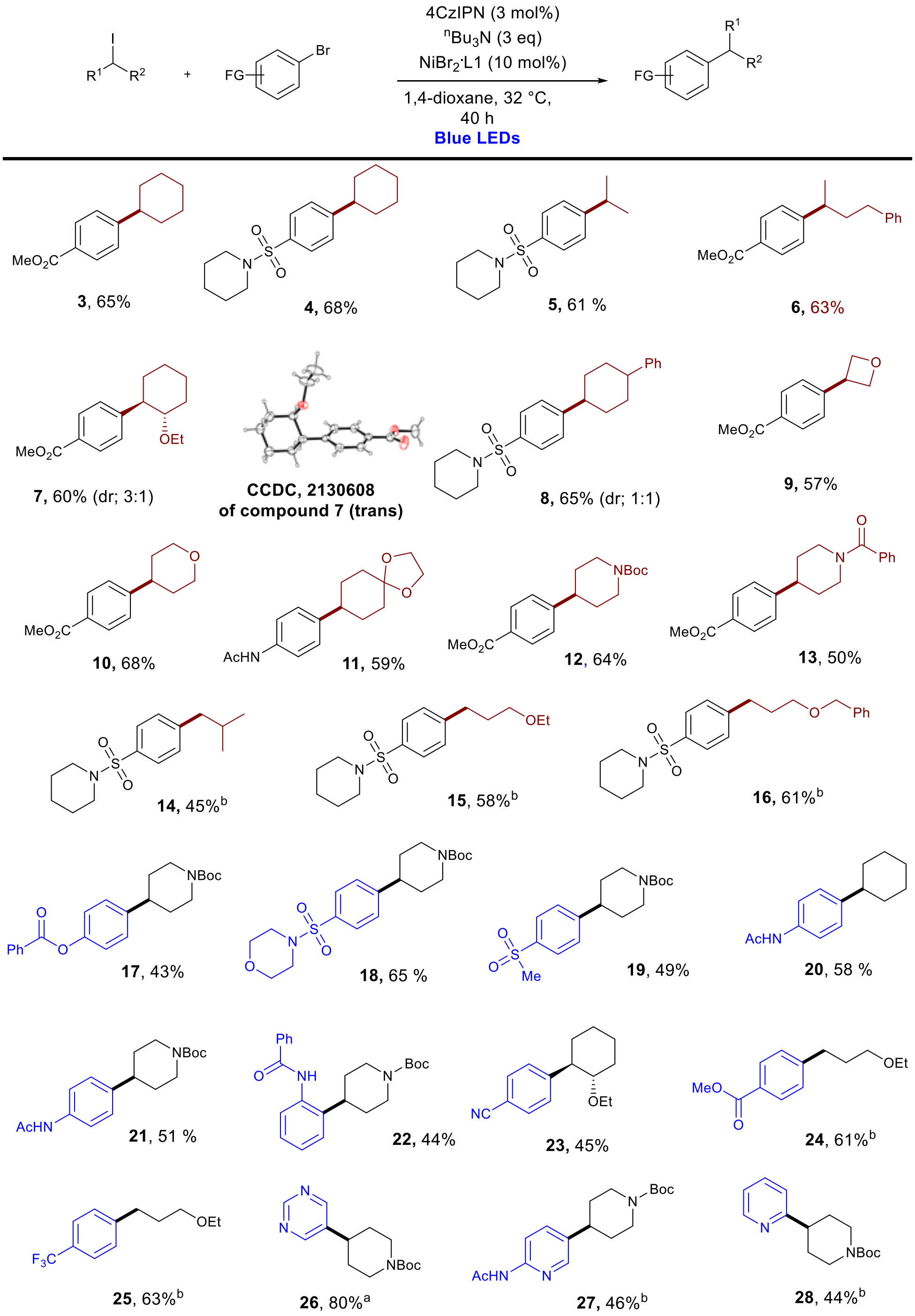


| *Entry* | *Deviation from standard conditions* | **3a**(%)[b] |
|---|---|---|
| 1 | **None** | ***70 (65%)***[c] |
| 2 | **$NiBr_2$·glyme** (10 mol%), **L1** (12 mol%) instead of **$NiBr_2$·L1** (10 mol%) | 50-65 |
| 3 | **$NiBr_2$·$H_2O$** (10 mol%), **L1** (12 mol%) instead of **$NiBr_2$·L1** (10 mol%) | 30 |
| 4 | **$NiBr_2$·L2** instead of **$NiBr_2$·L1** | *67* |
| 5 | **$NiBr_2$·L3** instead of **$NiBr_2$·L1** | *30* |
| 6 | **$NiBr_2$·L4** instead of **$NiBr_2$·L1** | *42* |
| 7 | **Ir-I** instead of **4CzIPN** | 50 |
| 8 | **Ir-II** instead of **4CzIPN** | 40 |
| 9 | **$Et_3N$** instead of **$^nBu_3N$** | 44 |
| 10 | **DIPEA** instead of **$^nBu_3N$** | 30 |
| 11 | **2,2,6,6-Tetramethylpiperidine** instead of **$^nBu_3N$** | 0 |
| 12 | **DABCO** instead of **$^nBu_3N$** | 0 |
| 13 | **$CH_3CN$** instead of **1,4-dioxane** | 54 |
| 14 | **THF** instead of **1,4-dioxane** | 64 |
| 15 | **EtOAc** instead of **1,4-dioxane** | 56 |
| 16 | **DMF** instead of **1,4-dioxane** | 28 |
| 17 | **without** $^nBu_3N$, 4CzIPN, $NiBr_2$·L1, L1 | 0 |
| 18 | **without** Blue Led's | 0 |



**Scheme 3**. [a]**1a** (0.25 mmol), **2a** (0.2 mmol), 4CzIPN (2 mol%), $^nBu_3N$ (3.0 eq), $NiBr_2$·dttbpy (10 mol%), 1,4-dioxane (2 ml) at 32 °C, 40 h [b] NMR yields using benzylalcohol as an internal standard. [c]Isolated yield.

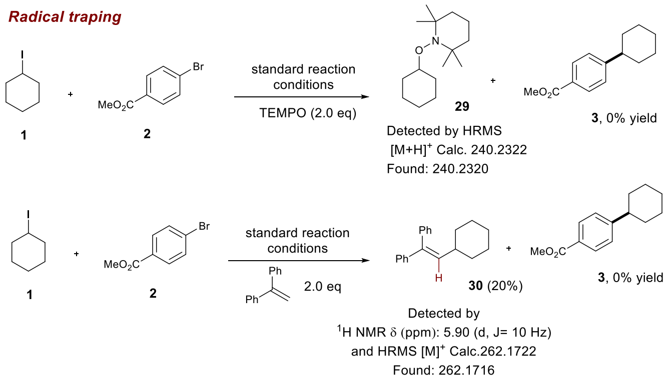
To our delight, we found that the combination of 4CzIPN and $NiBr_2·L1$ (L1 = 4,4'-di-tert-butyl-2,2'-bipyridyl), in the presence of 3.0 equivalents of $^nBu_3N$ upon continuous irradiation with blue led's achieved the desired cross coupling product in 65% isolated yield (Scheme 3, entry 1). Deviations from this standard condition did not improve the yield of the product. Also, it was observed that the yields of the reaction were less reproducible and varied about 15% upon weighing nickel precursor ($NiBr_2$·glyme) and ligand separately (Scheme 3, entry 2). Employing different $NiBr_2$·ligands ($NiBr_2$·**L2-L4**), metal based photocatalysts (**Ir-1**, **Ir-2**) and amines ($Et_3N$, DIPEA) afford the cross-coupling product in moderate yields (Scheme 3, entries 4-10), while employing 2,2,6,6-Tetramethylpiperidine (TMP) and DABCO did not led to any product (Scheme 3, entries 11-12). Screening of different solvents such as $CH_3CN$, THF and EtOAc afford slightly reduced yield (Scheme 3, entries 13-15), while in case of DMF observed sluggish yield (Scheme 3, entry 16). Control experiments have confirmed that all reaction parameters such as light, photo catalyst, Ni and ligand were necessary to proceed the reaction (Scheme 3, entries 17-18).



**Scheme 4.** Visible light mediated cross-coupling of unactivated alkyl iodides with aryl bromides through synergistic nickel and halogen atom transfer (XAT) catalysis. Reaction conditions as given in Scheme 1 (entry 1). Isolated yields, average of at least two independent runs. [a]35 h reaction time. [b]48 h reaction time.

Having established the optimal reaction conditions for this C(sp$^3$)-C(sp$^2$) cross-coupling we focused our attention on the scope of the alkyl iodides with different functionality (Scheme 4.) Simple cyclic, acyclic secondary alkyl iodides, substituted 2-ethoxy and 4-phenyl iodocyclohexane gave corresponding C(sp$^3$)–C(sp$^2$) cross-coupling products (**3**-**8**) with different aryl bromides in good yields (60-65%). Different oxygen containing cyclic secondary iodoalkanes are well tolerated in our dual catalysis and give the coupling products (**9-11**) in moderate to good yields (57-68%). Protected *N*-heterocyclic systems such as 4-iodo-*N*-Boc-piperidine and 4-iodo-*N*-Benzoyl-piperidine are also readily tolerated (**12, 13,** 50-64%). Variety of primary alkyl iodides containing different functionalities such as ether, benzyloxy afford the corresponding cross-coupling products (**14-16**) in good yields (45-61%). As shown in Scheme 4, a wide range of aryl bromides are amenable to this dual-catalysis strategy. Many aryl bromides that contain different functional groups such as phenolic ester, sulfonamide, sulfonyl, acetamide, benzamide, nitrile, ester and trifluoromethyl group are well tolerated, afford cross-coupling products in good yields (**17**-**25**, 43-63% yield) with different iodoalkanes. Heteroaromatics, in the form of differentially substituted bromopyridines, are also efficient coupling partners to produce corresponding products (**26** to **28**) in moderate to good yields (44 to 80%).

This novel synergistic photoredox-nickel and halogen-atom transfer (XAT) catalysis prompted us to conduct preliminary mechanistic studies (Scheme 5). As anticipated, light/dark experiments revealed that light is necessary (See, SI). When a radical scavenger such as TEMPO (2,2,6,6-tetramethyl-1- piperidinyloxy) or ethene-1,1-diyldibenzene was present, the reaction was inhibited (Scheme 5). Furthermore, 1-(cyclohexyloxy)-2,2,6,6-tetramethyl piperidine (**29**), (2-cyclohexylethene-1,1-diyl)dibenzene (**30**), were detected by high-resolution mass Spectrometry and $^1$H NMR spectrum (Scheme 5). These two experiments point to a radical pathway.



**Scheme 5.** Preliminary Mechanistic Studies

Furthermore Stern-Volmer luminescence quenching experiments of 4CzIPN were carried out with tributyl amine, iodocyclohexane and aryl bromide (Figure 1). The excited state of 4CzIPN (+1.35 V vs SCE)[15] was quenched by the tributyl amine (+0.8 V vs SCE) but not aryl bromide (**2**) or iodocyclo hexane (**1**). Also, the excited 4CzIPN was effectively quenched by 2,2,6,6-Tetramethylpiperidine (TMP) (see, SI), but unable to generate α-aminoalkyl radical, does not promoted the desired reactivity. This experiment might rule out the possibility of involvement of Ni-source for the generation of alkyl radial from iodoalkanes in our cross-coupling reactions.

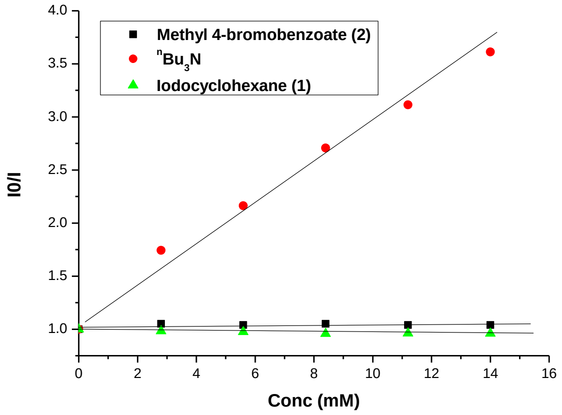


**Figure 1. Stern-Volmer Plot**

In conclusion, we have developed a new protocol in synthetic organic chemistry that leads to C(sp$^3$)–C(sp$^2$) bond formation via synergistic nickel and halogen-atom transfer (XAT) catalysis. This reaction operates under mild reaction conditions and tolerates a variety of unactivated Iodo alkanes and aryl bromides containing different functional groups. Preliminary mechanistic studies suggested that the canonical photoredox catalytic cycle might be operative. Related XAT coupling reactions employing iodoalkanes are ongoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare

## Acknowledgements

Financial support by the Science and Engineering Research Board (SERB), Government of India (File Number: SRG/2021/000834) is greatly acknowledged. G.S.Y thanks MHRD (for PMRF), A. K. J thanks IISER-TVM (for Institute fellowship). Authors thank Alex A. for collecting the X-ray data of **7** (trans). The authors thanks to IISER Thiruvananthapuram for the facilities.

## Notes and references

1. (a) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034. (b) M. D. Kärkäs, J. A. Porco, Jr, C. R. J. Stephenson, *Chem. Rev.* **2016**, *116*, 9683. (c) N. A. Romero, D. A. Nicewicz. *Chem. Rev*. **2016**, *116*, 10075. (d) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem*. **2016**, *81*, 6898.
2. (a) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc*. **2012**, *134*, 9034. (b) B. Sahoo; M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc*. **2013**, *135*, 5505.
3 (a) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437 (b) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433. (d) S. H. Lau, M. A. Borden, T. J. Steiman, L. S. Wang, M. Parasram, A. G. Doyle, *J. Am. Chem. Soc.* **2021**, *143*, 15873. (e) D. K. Kölmel, A. S. Ratnayake, M. E. Flanagan, *Biochem. Biophys. Res. Commun.* **2020**, *533*, 201.
4 Radicals in Organic Synthesis; P. Renaud, M. P. Sibi, Eds.; WileyVCH, 2001.
5 S. Z. Zard, Radical Reactions in Organic Synthesis; Oxford University Press, 2003
6 A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58.
7 (a) H. G. Kuivila, L. W. Menapace. *J. Org. Chem*. **1963**, *28*, 2165−2167. (b) C. Chatgilialoglu, C. Ferreri, Y. Landais, V. I. Timokhin, *Chem. Rev*. **2018**, *118*, 6516. (c) R. S. Herrick, T. R. Herrinton, H. W. Walker, T. L. Brown, *Organometallics* **1985**, *4*, 42
8 C. Chatgilialoglu, *Acc. Chem. Res*. **1992**, *25*, 188.
9 (a) V. Darmency, P. Renaud, Tin-free radical reactions mediated by organoboron compounds. Radicals in synthesis I; Springer-Verlag: Berlin, 2006; pp 71. (b) C. Ollivier, P. Renaud, *Chem. Rev*. **2001**, *101*, 3415.
10 T. Kawamoto, S. Uehara, H. Hirao, T. Fukuyama, H. Matsubara, I. Ryu, *J. Org. Chem*. **2014**, *79*, 3999.
11 (a) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756. (b) M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem. Int. Ed. Engl*. **2011**, *50*, 951. (c) E. Arceo, E. Montroni, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 12064. (d) X. Gu, X. Li, Y. Qu, Q. Yang, P. Li, Y. Yao, *Chem. - Eur. J.* **2013**, *19*, 11878. (e) C. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875. (f) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc*. **2011**, *133*, 4160. For a recent review see (g) T. Constantin, F. Julia, D. Leonori, *Chem. Rev*. **2021**, DOI: 10.1021/acs.chemrev.1c00558.
12 (a) T. Kohlmann, R. Naumann, C. Kerziga, M. Goez, *Photochem. Photobiol. Sci.* **2017**, *16*, 1613. (b) R. Naumann, F. Lehmann, M. Goez, *Angew. Chem. Int. Ed*. **2018**, *57*, 1078. (c) J. L. Kuo, C. Lorenc, J. M. Abuyuan, J. R. Norton, *J. Am. Chem. Soc*. **2018**, *140*, 4512. (d) R. Matsubara, T. Yabuta, U. Idros, M. Hayashi, F. Ema, Y. Kobori, K. Sakata, *J. Org. Chem*. **2018**, *83*, 9381. (e) M. Claros, F. Ungeheuer, F. Franco, V. Martin-Diaconescu, A. Casitas, J. Lloret-Fillol, *Angew. Chem. Int. Ed.* **2019**, *58*, 4869. (f) Y. Shen, J. Cornella, F. Juliá-Hernández, R. Martin, *ACS Catal*. **2017**, *7*, 409. (g) W. Delian, L. Xipan, S. Lei, D. Yuzhen, L. Kangjiang, X. Chengfeng, *Org. Chem. Front.* **2021**, *8*, 6364.
13 (a) N. W. Dow, A. Cabré, D. W. C. MacMillan, *Chem* **2021**, 7, 1. (b) X. Zhao, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2020**, *142*, 19480. (c) H. Sakai, W. Liu, C. Le, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2020,** *142*, 11691. (d) D. J. P. Kornfilt, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2017**, *141*, 6853. (e) L. Wang, J. M. Lear, S. M. Rafferty, S. C. Fosu, D. A. Nagib, *Science* **2018**, 362, 225. (f) P. Nuhant, M. S. Oderinde, J. Genovino, A. Juneau, Y. Gagné, C. Allais, G. M. Chinigo, C. Choi, N. W. Sach, L. Bernier, Y. M. Fobian, M. W. Bundesmann, B. Khunte, M. Frenette, O. O. Fadeyi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15309.
14 (a) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021. (b) L. Caiger, C. Sinton, T. Constantin, J. J. Douglas, N. S. Sheikh, F. Julia, D. Leonori, *Chem. Sci.* **2021**, *12*, 10448. (c) B. Gorski, A. -L. Barthelemy, J. J. Douglas, F. Julia, D. Leonori, *Nat. Catal.* **2021**, *4*, 623. (d) H. Zhao, A. J. MacMillan, T. Constantin, R. Mykura, F. Julia, D. Leonori,

*J. Am. Chem. Soc.* **2021**, *143*, 14806. (e) F. Yue, J. Dong, Y. Liu, Q. Wang, *Org. Lett.* **2021**, *23*, 7306. (f) Y. Songlin, Y. Weijie, Z. Jianye, F. Hongmei, L. Zhifeng, Z. Zhenming, W. Tao, *J. Org. Chem*. **2021**, DOI: 10.1021/acs.joc.1c02659.

15 T. -Y. Shang, L. -H. Lu, Z. Cao, Y. Liu, W. -M. He, B. Yu, *Chem. Commun*. **2019**, *55*, 5408.

16 The bass-balance accounts for the unreacted staring material, reduced product and dimerized product.