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A dual photoredox-nickel strategy for remote functionalization *via* iminyl radicals: radical ring-opening-arylation, -vinylation and -alkylation cascades†

Elizabeth M. Dauncey, ‡[a] Shashikant U. Dighe, ‡[a] James J. Douglas [b] and Daniele Leonori *[a]

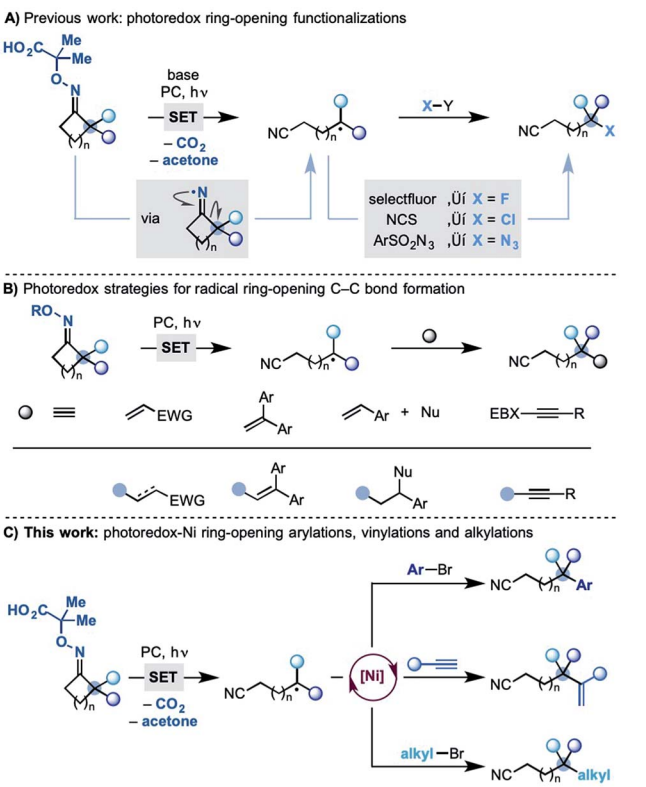
A divergent strategy for the remote arylation, vinylation and alkylation of nitriles is described. These processes proceed through the photoredox generation of a cyclic iminyl radical and its following ring-opening reaction. The distal nitrile radical is then engaged in nickel-based catalytic cycles to form C–C bonds with aryl bromides, alkynes and alkyl bromides.

The selective functionalization of unactivated sp^3 carbons streamlines access to molecules that can be difficult to prepare using classical disconnections.[1] Radical strategies are powerful platforms to achieve this goal owing to the ability of odd-electron species to undergo fast transpositions by σ-bond cleavage.[2] Processes based on 1,5-H-atom transfer (1,5-HAT) are frequently adopted as they allow selective functionalization at precise carbon sites in already assembled substrates.[3] Methodologies centred on radical ring-opening reactions[4] lead to skeletal rearrangements and as a result use different classes of starting materials. Most importantly they can functionalize sp^3 carbons that are elusive by HAT-based protocols.

Following the pioneering work of Forrester[5] and Zard,[6] we have recently developed a photo-induced methodology where readily prepared oximes undergo SET (single-electron transfer) oxidation and fragmentation *en route* to cyclic iminyl radicals (Scheme 1A).[7] With the correct juxtaposition of α-substituents and ring-size, efficient ring opening-functionalization cascades were developed accessing remotely fluorinated, chlorinated and azidated nitriles.

Other groups have also been active in the area and several photo-induced strategies have been subsequently developed enabling radical ring-opening followed by reaction with, most notably, Michael acceptors,[8] styrenes[8c,9] and alkynylbenziodoxolone reagents[10] (Scheme 1B).[11] These methodologies have provided significant synthetic capacity as they enabled distal C–C bond formations, albeit with structurally specific coupling partners.

Despite these advances, the possibility to use related radical transpositions as a tool for the general and modular construction of C–C bonds at remote sites is still an unmet goal.



Scheme 1 Strategies for the photo-induced ring-opening functionalizations of cyclic iminyl radicals. (A) Previous work: photoredox ring-opening functionalizations. (B) Photoredox strategies for radical ring-opening C–C bond formation. (C) This work: photoredox-Ni ring-opening arylations, vinylations and alkylations.

[a]School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK. E-mail: daniele.leonori@manchester.ac.uk

[b]Early Chemical Development, Pharmaceutical Sciences, AstraZeneca, R&D, Macclesfield SK10 2NA, UK

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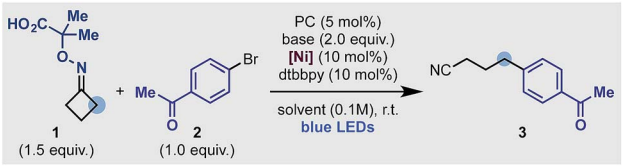
‡ These authors have contributed equally to this work.

We speculated that one way to partially address this fundamental challenge would be to incorporate the concept of metallaphotoredox catalysis[12] in these radical transpositions. In principle, this strategy would enable the use of readily available coupling partners, like aryl/alkyl bromides and alkynes, and access products currently elusive by other methodologies. In this paper, we demonstrate the successful development of a divergent dual photoredox–nickel process that gives access to remotely arylated, vinylated and alkylated nitriles by means of radical ring-opening–cross coupling cascades (Scheme 1C).

The proposed mechanism for this divergent strategy was centred on our previously developed reductive quenching photoredox cycle for iminyl radical generation.[13] As shown in Scheme 2, we would use a visible-light excited photocatalyst (***PC**) to promote the SET oxidation of oxime-carboxylate **A**. Following extrusion of CO_2 and acetone, the iminyl radical **B** should undergo facile ring-opening delivering the distal nitrile radical **C**. At this point, we hoped that a Ni(0) co-catalyst would simultaneously undergo oxidative addition on an aryl bromide coupling partner to give an aryl–Ni(II) species **D**.[14] Radical transmetalation between **C** and **D** ought to be possible thus delivering an aryl,alkyl–Ni(III) complex **E** from which reductive elimination is facile. This step would generate the remotely arylated nitrile **F** and a Ni(I) species. A final SET between the reduced photocatalyst ($\mathbf{PC}^{\bullet-}$) and the Ni(I)-complex (E_{red} Ni(II)/Ni(0) = −1.2 V *vs.* SCE, DMF)[15] would re-initiate both the Ni and the photoredox cycle. Related mechanistic frameworks should enable the use of alkynes and alkyl halides and therefore allow the remote installation of vinyl and alkyl groups respectively.

We started our investigation using the cyclobutanone-oxime **1** (one-step preparation on gram-scale)[16] and *p*-Br-acetophenone **2** as the coupling partner (Scheme 3). Pleasingly, using the Ir-photocatalyst **PC1**, $NiCl_2 \cdot$glyme, dtbbpy ligand and K_2CO_3 in DME under blue light irradiation, we obtained the desired product **3** in 15% yield (entry 1). Different photocatalysts were evaluated and while Fukuzumi's acridinium (**PC2**) was not suitable (entry 2), the organic dye 4CzIPN (**PC3**) and the Ir-complex **PC4** provided **3** in 24 and 41% yield respectively (entries 3 and 4). Using **PC4** we tested different inorganic and organic bases and identified tetramethyl guanidine (TMG) as optimum (entries 4–8). The final elements of reaction optimization involved the evaluation of a selection of Ni-catalysts (entries 9–11) as well as solvents from which EtOAc resulted ideal (entries 12–14). Control experiments confirmed the requirement for all reaction components (entries 15–18) and a quantum yield $\Phi = 0.19$ is in agreement with the observed requirement for continuous light irradiation.



Entry	PC	[Ni]	Base	Solvent	Yield (%)
1	**PC1**	$NiCl_2$•glyme	K_2CO_3	DME	15
2	**PC2**	$NiCl_2$•glyme	K_2CO_3	DME	–
3	**PC3**	$NiCl_2$•glyme	K_2CO_3	DME	24
4	**PC4**	$NiCl_2$•glyme	K_2CO_3	DME	41
5	**PC4**	$NiCl_2$•glyme	Cs_2CO_3	DME	35
6	**PC4**	$NiCl_2$•glyme	K_2HPO_4	DME	–
7	**PC4**	$NiCl_2$•glyme	DBU	DME	38
8	**PC4**	$NiCl_2$•glyme	TMG	DME	55
9	**PC4**	$NiBr_2$•glyme	TMG	DME	39
10	**PC4**	$Ni(acac)_2$	TMG	DME	–
11	**PC4**	$Ni(OAc)_2$•$4H_2O$	TMG	DME	12
12	**PC4**	$NiCl_2$•glyme	TMG	acetone	41
13	**PC4**	$NiCl_2$•glyme	TMG	DMF	23
14	**PC4**	$NiCl_2$•glyme	TMG	EtOAc	61
15	–	$NiCl_2$•glyme	TMG	EtOAc	–
16	**PC4**	–	TMG	EtOAc	–
17	**PC4**	$NiCl_2$•glyme	–	EtOAc	–
18[a]	**PC4**	$NiCl_2$•glyme	TMG	EtOAc	–

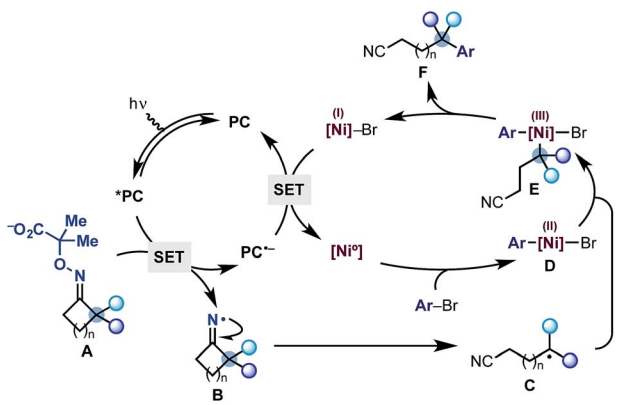
[a] The reaction was run in the dark

PC1: $(Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ **PC3**: 4CzIPN
PC2: MesAcr(ClO_4) **PC4**: $[Ir(dtbbpy)(ppy)_2]PF_6$

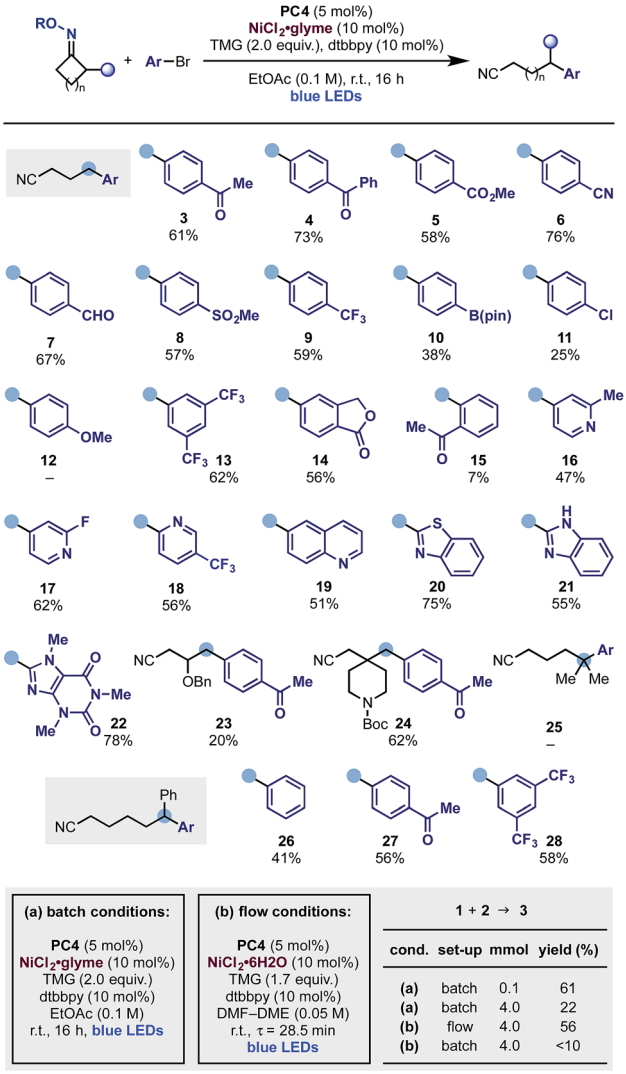
Scheme 3 Development of dual photoredox–Ni ring-opening-arylation process.

With these optimised reaction conditions, we evaluated the scope of the aromatic partner in conjunction with the cyclobutanone oxime **1** (Scheme 4). Pleasingly the process exhibited broad scope and tolerated a wide variety of common functionalities such as ketone (**3** and **4**), ester (**5**), nitrile (**6**), aldehyde (**7**), sulfone (**8**), trifluoromethyl (**9**) as well as groups that can be used as a handle for further functionalization like pinacol boronic ester (**10**) and aryl chloride (**11**) albeit in lower yields.[17] Electron rich aryl bromides are a limitation of the protocol (**12**), possibly due to a more difficult oxidative addition process from the Ni(0) catalyst. Moreover, while *meta*-substituted aryl bromides were successfully engaged in this protocol (**13** and **14**), the presence of an *ortho*-substituent was detrimental to the reactivity and, for example, **15** was obtained in low yield. We then evaluated the use of hetero-aromatic coupling partners as these systems are frequently encountered in medicinal chemistry programs. Pleasingly the reaction enabled ring-opening-arylation with differentially functionalized pyridines at either C-2 (**16** and **17**) and C-3 (**18**), as well as quinoline (**19**), electron rich benzothiazole (**20**) and benzoimidazole (**21**) and Br–caffeine, which gave **22** in good yield.

Other cyclobutanone oximes were tested and we used a substrate containing an OBn ether at C-3 (**23**) as well as



Scheme 2 Proposed dual photoredox-Ni catalytic cycle for the radical ring-opening-arylation cascades.



Scheme 4 Scope of the dual photoredox–Ni ring-opening-arylation process.

a spirocyclic *N*-Boc-piperidine (**24**). This gave access to a C-4 benzylated piperidine, which is a common pharmacophoric unit in many NMDA antagonist drugs like ifenprodil.

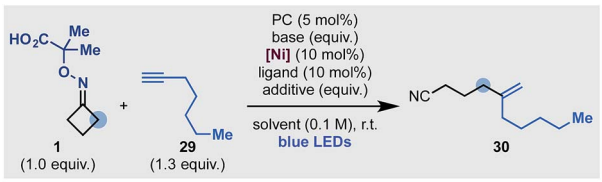
As the ring-opening of cyclic iminyl radicals is thermodynamically feasible on larger rings with the correct juxtaposition of α-substituents,[7] we evaluated the use of *gem*-dimethyl cyclopentanone and 2-Ph-cyclohexanone oxime starting materials. While the arylation cascade leading to **25** could not be implemented, we successfully extended it to the deconstruction of the six-membered ring and access the ε-di-arylated nitriles **26–28** in good to moderate yields. We propose the failure in obtaining **25** to be due to the known difficulty of tertiary C-radical to undergo transmetalation processes.

Flow chemistry has emerged as an effective solution to the scale up of visible light-mediated processes.[18] Dual photoredox–nickel catalysis can be challenging to conduct in flow, due to the typically heterogenous mixtures and long reaction times. We initiated the attempted scale-up of the ring-opening-arylation cascade by developing homogenous reaction conditions amenable to continuous flow (Scheme 4B). This allowed the preparation of **3** on a useful preparative scale (4 mmol over 4 h) with yield comparable to the small-scale (0.1 mmol) batch reaction (56% in flow *vs.* 61% batch). The developed flow process compared favourably to the original batch conditions employed at large-scale. Using these without further optimization gave reduced yield with increasing scale after 18 h (0.1 mmol scale 59%, 2 mmol 45%, 4 mmol 22%). The use of the developed homogenous conditions in batch gave a comparable 52% yield (0.1 mmol scale), however at increased scale resulted in <10% yield, indicating the benefit of the flow process.[19]

Having developed an oxidative cascade for ring-opening-arylation, we tested the feasibility of using terminal alkynes as coupling partners to construct *gem*-disubstituted olefins.[20] The optimization of this process was performed using oxime **1** and 1-heptyne **29** (Scheme 5). In this case, conditions used for the arylation cascade failed to provide the desired product (entry 1) but, by switching the base to K_2CO_3 and the solvent to DMF, **30** was obtained in an encouraging 10% yield (entry 2 and 3). The efficiency of the process was improved to 33% by lowering the amount of base (entry 4) and adding 20 equiv. of H_2O as an additive (entry 5). Other nickel–ligand combinations were tested but they provided **30** in generally lower yield, if any (entries 6–8). Evaluation of other photocatalysts and solvents identified **PC3** (entry 9) and CH_3CN (entry 10) as optimum. Finally, with the use of the preformed $NiCl_2 \cdot$dttbpy catalyst and Cs_2CO_3 as the inorganic base, **30** was obtained in 73% yield (entries 11 and 12). Also in this case, control experiments confirmed the requirement for all reaction components as well as continuous blue-light irradiation (entries 13–16).

The scope of terminal alkynes that can be engaged in this reactivity pattern is illustrated in Scheme 6. Pleasingly, coupling partners containing linear (**30** and **31**) as well as cyclic (**32**) alkyl groups could be used including a substrate containing a cyclopropyl unit (**33**) albeit in lower yield.[17] The methodology tolerated several important functionalities like nitrile (**34**), *N*-Boc-protected amine (**35**), alkyl chloride (**36**) and a phthalamide unit (**37**). Expansion of this chemistry to *N*-Boc-azetidone and a spirocyclic *N*-Boc-piperidine based oximes gave access to allylic (**38** and **39**) as well as a C-4 disubstituted piperidine (**40**), which are useful building blocks for further derivatization. Current limitations are the use of aryl-substituted alkynes (*e.g.* **41**) and also its expansion to higher ring-size iminyl precursors (**42** and **43**).

This radical ring-opening-vinylation strategy could also be performed in intra-molecular settings as demonstrated by the successful conversion of **44** into **45**. Control experiments in the absence of the Ni-catalyst or H_2O demonstrated that a radical ring-opening followed by 5-*exo-dig* and final H-abstraction was not operating,[19] thus leaving the proposed dual photoredox–Ni-process as the likely pathway for the formation of **45**. This reaction product is an interesting building block that, using literature methods, was converted into the bicyclic ketone **46** in good yield and as the single *syn*-diastereomer.



Entry	PC	[Ni]	L	Base	additive	Solvent	Yield (%)
1	PC4	$NiCl_2$•glyme	dtbbpy	TMG (2.0)	–	EtOAc	–
2	PC4	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (2.0)	–	EtOAc	–
3	PC4	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (2.0)	–	DMF	10
4	PC4	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (0.5)	–	DMF	21
5	PC4	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (0.5)	H_2O (20)	DMF	33
6	PC4	$NiCl_2$•glyme	DOBpy	K_2CO_3 (0.5)	H_2O (20)	DMF	17
7	PC4	$Ni(acac)_2$	dtbbpy	K_2CO_3 (0.5)	H_2O (20)	DMF	–
8	PC4	$Ni(OAc)_2$•$4H_2O$	dtbbpy	K_2CO_3 (0.5)	H_2O (20)	DMF	11
9	PC3	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (0.5)	H_2O (20)	DMF	41
10	PC3	$NiCl_2$•glyme	dtbbpy	K_2CO_3 (0.5)	H_2O (20)	CH_3CN	49
11	PC3	$NiCl_2$•dtbbpy	–	K_2CO_3 (0.5)	H_2O (20)	CH_3CN	61
12	PC3	$NiCl_2$•dtbbpy	–	Cs_2CO_3 (0.5)	H_2O (20)	CH_3CN	73
13	–	$NiCl_2$•dtbbpy	–	Cs_2CO_3 (0.5)	H_2O (20)	CH_3CN	–
14	PC3	–	–	Cs_2CO_3 (0.5)	H_2O (20)	CH_3CN	–
15	PC3	$NiCl_2$•dtbbpy	–	–	H_2O (20)	CH_3CN	–
16[a]	PC3	$NiCl_2$•dtbbpy	–	Cs_2CO_3 (0.5)	H_2O (20)	CH_3CN	–

[a] The reaction was run in the dark

Scheme 5 Development of dual photoredox–Ni ring-opening-vinylation process.

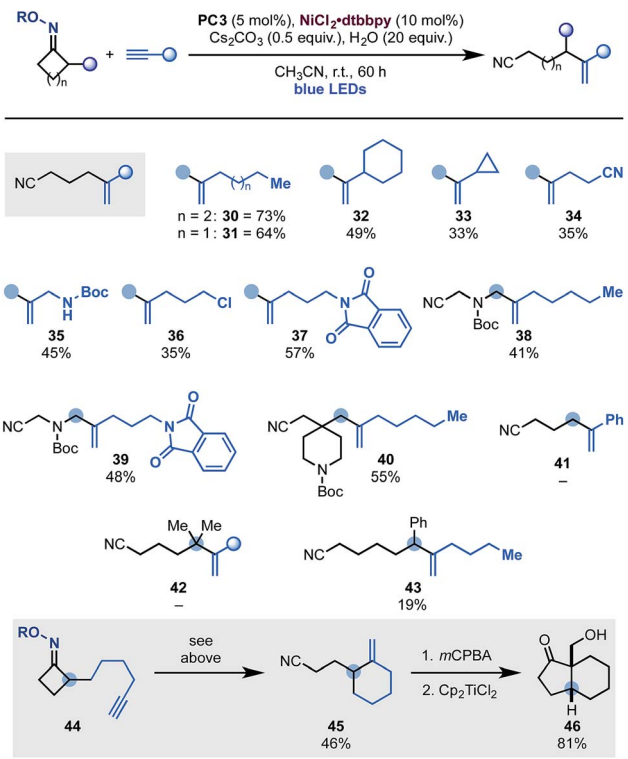
As this dual photoredox-Ni approach has enabled the construction of sp^3–sp^2 C–C bonds with both aromatic and vinyl substituents we questioned if alkyl halides could also be used and therefore achieve the very challenging assembly of sp^3–sp^3 C–C bonds.[21] Indeed, remote alkylations *via* radical transposition are still very difficult to perform, with the exception of strategies involving the use of Michael acceptors as SOMOphiles.

We started the optimization of this process using the oxime **1** and the simple alkyl bromide **47** (Scheme 7). Reaction conditions similar to the one developed for the ring-opening-arylation cascade did not provide the desired product (entry 1). However, evaluation of photoredox catalysts (entries 2–4), solvents (entry 5) and bases (entries 5–7) showed that the process could be achieved and **48** obtained in 25% yield using **PC1** and Cs_2CO_3 in CH_3CN (entry 9). Pleasingly, we have been able to increase the yield to 66% by adopting the preformed nickel catalyst $NiCl_2$·dtbbpy (entry 10) and by increasing the equivalents of base (entry 10). Also in this case, all reaction components as well as continuous blue-light irradiation were required (entries 11–14).

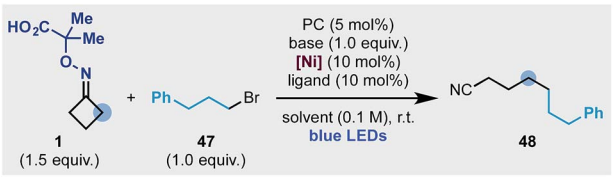
With this set of conditions in hand, we evaluated the scope of the process (Scheme 8). Pleasingly, using cyclobutanone oxime **1** we succeeded in engaging several primary alkyl bromides with different substitution patterns. This included ester (**49**), nitrile (**50**), alkyl chloride (**51**), *N*-phthalimide (**52**) and an acetal (**53**). At the moment this reactivity is limited to primary alkyl electrophiles as secondary ones (*e.g.* **54**) did not react.

In analogy to the ring-opening-arylation cascades we have not been able to engage the *gem*-dimethyl-cyclopentanone oxime (**55**) but we successfully used the 2-Ph-cyclohexanone starting material, which gave access to ε-alkylated nitriles **56** and **57** in good yield.

To showcase the potential of the methodology, we have used commercially available L-Br-serine **58** as the coupling partner. This functionalized building block provided access to the unnatural amino acid **59** that was converted into the 1-carbon elongated L-lysine analogue **60**.[22]



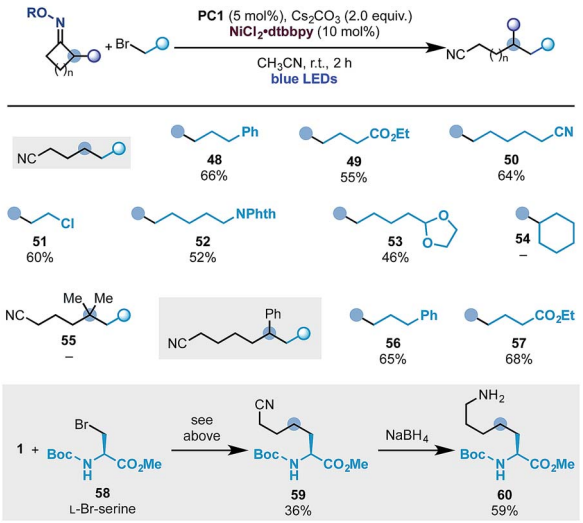
Scheme 6 Scope of the dual photoredox–Ni ring-opening-vinylation process.



Entry	PC	[Ni]	L	Base	Solvent	Yield (%)
1	PC4	$NiCl_2$•glyme	dtbpy	K_2CO_3	EtOAc	–
2	PC1	$NiCl_2$•glyme	dtbpy	K_2CO_3	EtOAc	5
3	PC2	$NiCl_2$•glyme	dtbpy	K_2CO_3	EtOAc	–
4	PC3	$NiCl_2$•glyme	dtbpy	K_2CO_3	EtOAc	–
5	PC1	$NiCl_2$•glyme	dtbpy	K_2CO_3	CH_3CN	10
6	PC1	$NiCl_2$•glyme	dtbpy	KOAc	CH_3CN	8
7	PC1	$NiCl_2$•glyme	dtbpy	TMG	CH_3CN	25
8	PC1	$NiCl_2$•dtbpy	–	Cs_2CO_3	CH_3CN	31
9	PC1	$NiCl_2$•dtbpy	–	Cs_2CO_3	CH_3CN	45
10[a]	PC1	$NiCl_2$•dtbpy	–	Cs_2CO_3	CH_3CN	66
11	–	$NiCl_2$•dtbpy	–	Cs_2CO_3	CH_3CN	–
12	PC1	–	–	Cs_2CO_3	CH_3CN	–
13	PC1	$NiCl_2$•dtbpy	–	–	CH_3CN	–
14[b]	PC1	$NiCl_2$•dtbpy	–	Cs_2CO_3	CH_3CN	–

[a] 2.0 equiv. of Cs_2CO_3; [b] The reaction was run in the dark

Scheme 7 Development of dual photoredox–Ni ring-opening-alkylation process.



Scheme 8 Scope of the dual photoredox–Ni ring-opening-alkylation process.

Conclusions

In conclusion, we have reported the first example of a photoredox strategy where the ring-opening of iminyl radicals has been merged with Ni-catalysis. This divergent platform has enabled the development of distal arylation, vinylation and, for the first time, alkylation of nitrile-containing molecules. Current interest in our laboratory is towards rendering these processes asymmetric.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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