



Abrams, R., & Clayden, J. (2020). Photocatalytic Difunctionalization of Vinyl Ureas by Radical Addition Polar Truce–Smiles Rearrangement Cascades. *Angewandte Chemie - International Edition*, 59(28), 11600-11606. <https://doi.org/10.1002/anie.202003632>

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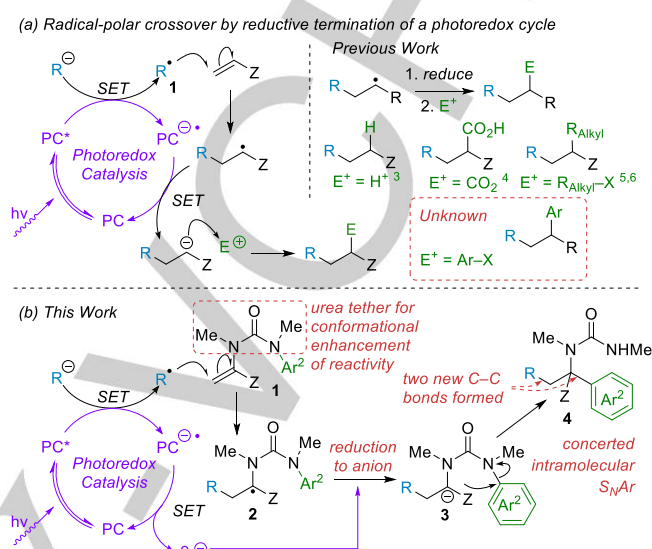
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Photocatalytic Difunctionalization of Vinyl Ureas by Radical Addition Polar Truce-Smiles Rearrangement Cascades

Roman Abrams and Jonathan Clayden*

Abstract: We report tandem alkyl-arylations and phosphoryl-arylations of vinyl ureas by way of a photocatalytic radical-polar crossover mechanism. Addition of photoredox-generated radicals to the alkene forms a new C–C or C–P bond and generates a product radical adjacent to the urea function. Reductive termination of the photocatalytic cycle generates an anion that undergoes a polar Truce-Smiles rearrangement, forming a C–C bond. The reaction is successful with a range of α -fluorinated alkyl sodium sulfinate salts and diarylphosphine oxides as radical precursors, and the conformationally accelerated Truce-Smiles rearrangement is not restricted by the electronic nature of the migrating aromatic ring. Formally the reaction constitutes an α,β -difunctionalisation of a carbon-carbon double bond, and proceeds under mild conditions with visible light and a readily available organic photocatalyst. The products are α,α -diaryl alkylureas typically functionalised with F or P substituents that may be readily converted into α,α -diaryl alkylamines.

Modern photoredox catalysis has provided a wide range of methods for synthesis using radical intermediates under mild conditions.¹ Of particular value for the functionalisation of alkenes are radical-polar crossover mechanisms,^{2,3} whereby the product of a radical addition is oxidised or reduced to a cation or anion in the redox reverse of the initial photocatalytic radical generation step. Radical-polar crossover mechanisms terminated by oxidation to a carbocation have been particularly successful in enabling the 1,2-disubstitution of alkenes.² Reductive termination to give a carbanion is rarer, and has typically been used for photoredox-catalysed mono-functionalisation of alkenes, whereby the product carbanion is simply protonated.³ Nonetheless, a few examples of reductive photoredox radical-polar crossover difunctionalisations have been recently reported (Scheme 1a). For example, Martin and co-workers have demonstrated that styrenes undergo alkyl-carboxylation where an intermediate benzylic carbanion formed is intercepted by carbon dioxide.⁴ Molander and co-workers⁵ and Aggarwal and co-workers^{6,7} have independently reported methods for the alkyl-cyclopropanation and cyclobutanation of alkenes by reductively terminated radical-polar crossover, in which the carbanion product of the photoredox cycle attacks a pendent alkyl halide. These methods allow the formation of two new C–C bonds to the alkene, but there are as yet no reports of the use of the intermediary carbanion in carbon-aryl bond formation by, for example, an S_NAr mechanism.



Scheme 1. (a) Photoredox-catalysed alkene difunctionalisations by reductive termination radical-polar crossover. (b) This work: N to C aryl migration of urea-substituted anions generated by a reductive radical-polar crossover sequence.

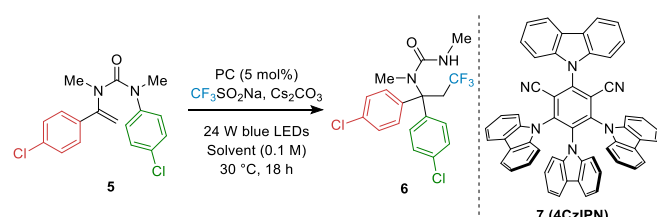
Arylation at sp^3 carbon centres typically involves transition metal-catalyzed coupling,⁸ but an appealing alternative, recently used for the stereoselective arylation of amino acid enolates,⁹ entails a conformationally induced Truce-Smiles rearrangement, which transfers an aryl ring to an anionic precursor. This transformation proceeds by a concerted S_NAr mechanism,¹⁰ but the use of a urea tether to impose a conformational preference on the intermediate¹¹ means that – unlike the classical Truce-Smiles rearrangement, which typically proceeds only with electron-deficient aromatic rings¹² – the electronic nature of the migrating aryl group is of little consequence to the reaction's outcome.^{9,13} The N to C aryl migration that results has been developed into a versatile transition metal-free route to a range of products including enantio-enriched α -quaternary amines,^{14a-c} hydantoins,^{14d,e} medium-ring heterocycles,^{14f,g} and α -quaternary amino acids.^{14h-j}

Anionic precursors for this C-arylation chemistry have been made by direct lithiation of benzylic¹⁵ or allylic ureas,¹⁶ by carbolithiation of a vinyl urea,¹⁷ or by deprotonation alpha to a carbonyl^{14e,h-k} or nitrile.^{14h,18} Generating the anion instead by photoredox catalysis offers the opportunity to conduct C-arylations under milder conditions, avoiding both strong base and transition metals, while also facilitating the preparation of previously inaccessible products. We envisaged that electrophilic radicals generated by a reductive quenching photoredox cycle would add to vinyl ureas **1** to form benzylic radicals **2**. Single-electron reduction would generate an anion α to the urea **3** that would undergo rearrangement to an α,α -diaryl alkylurea **4** (Scheme 1b). This approach represents a simple way to form two C–C bonds, one to each carbon of an alkene, and would provide

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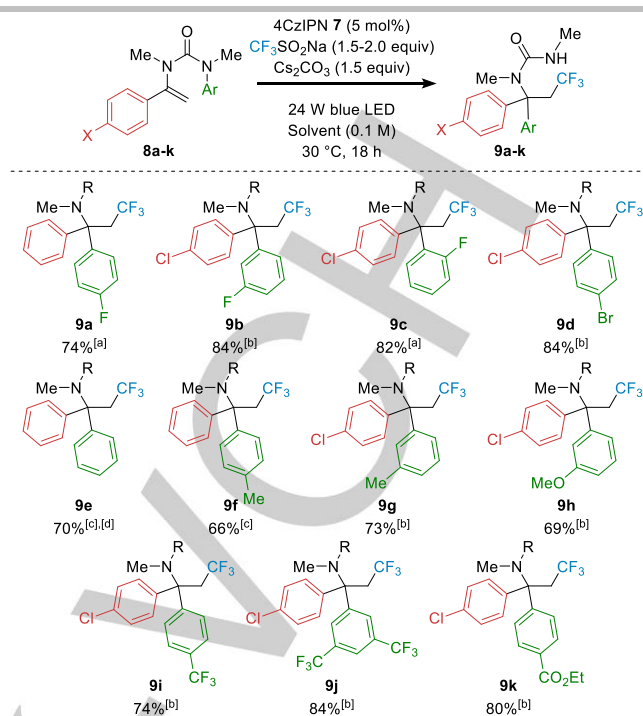
Table 1. Optimisation studies.^[a]


Entry ^[a]	PC	NaSO ₂ CF ₃ (equiv.)	Cs ₂ CO ₃ (equiv.)	yield (%) ^[b]
1 ^[c]	4CzIPN	3	0	0 ^[d]
2 ^[c]	4CzIPN	3	1.5	66
3 ^[e]	4CzIPN	3	1.5	94
4 ^[f]	4CzIPN	3	1.5	94
5 ^[e]	4CzIPN	3	1	40
6 ^[e]	4CzIPN	1.5	1.5	89 (87)
7 ^[f]	3DPAFIPN	1.5	1.5	Trace
8 ^[f]	[Ir(dF(CF ₃)ppy) ₂ (dtbpy)]PF ₆	1.5	1.5	70
9 ^[f]	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	1.5	1.5	Trace
10 ^[e]	-	1.5	1.5	0
11 ^{[e], [g]}	4CzIPN	1.5	1.5	0

[a] Reactions performed on a 0.1 mmol scale: light source 24 W blue LED strips (see ESI); reaction time 16 h. [b] Yield determined by ¹⁹F NMR using CF₃C₆H₅ as internal standard. Isolated yield in parentheses (0.2 mmol scale reaction). [c] DMF used as solvent. [d] Oxidative cyclisation products formed: see ESI. [e] MeCN used as solvent. [f] Acetone used as solvent. [g] Reaction carried out in the dark. PC – photocatalyst.

the first example of a radical-polar crossover mechanism in which the carbanion product of the photoredox cycle is used in C-aryl bond formation.

The trifluoromethyl group is a desirable function in medicinal chemistry,¹⁹ and ·CF₃ is a versatile electrophilic radical, readily generated by oxidation of sodium trifluoromethylsulfinate, NaSO₂CF₃, known as the Langlois reagent.²⁰ 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyano-benzene **7** (4CzIPN) was selected as an easily accessible photocatalyst that would render the conversion of **5** to **6** a transition-metal free process.²¹ However, initial attempts to transform **5** to **6** using 4CzIPN **7** yielded only products arising either from cleavage of the vinyl urea or from trifluoromethylation and oxidative cyclisation (Table 1, entry 1, see SI for structures). Oxidative products presumably arise from the sulfur dioxide by-product which can accept an electron (SO₂ oxidation potential: -0.8 V vs SCE)²² from the radical anion of 4CzIPN (**7** oxidation potential: -1.2 V vs SCE).²¹ Carbonate salts may be used to sequester sulfur dioxide by adsorption or direct reaction,²³ and, gratifyingly, Cs₂CO₃ was found to inhibit the formation of these unwanted products of net oxidation, giving **6** in 66% yield (entry 2). Replacing DMF with acetonitrile or acetone improved the yield of **6** to 94% (entries 3 and 4). Reducing the amount of Cs₂CO₃ to 1 equivalent lowered the yield of **6** (Table 1, entry 5), but reducing the stoichiometry of **7** from 3.0 to 1.5 was tolerated and gave **6** in an isolated yield of 87% (entry 6). Other less oxidising photocatalysts were investigated but gave lower



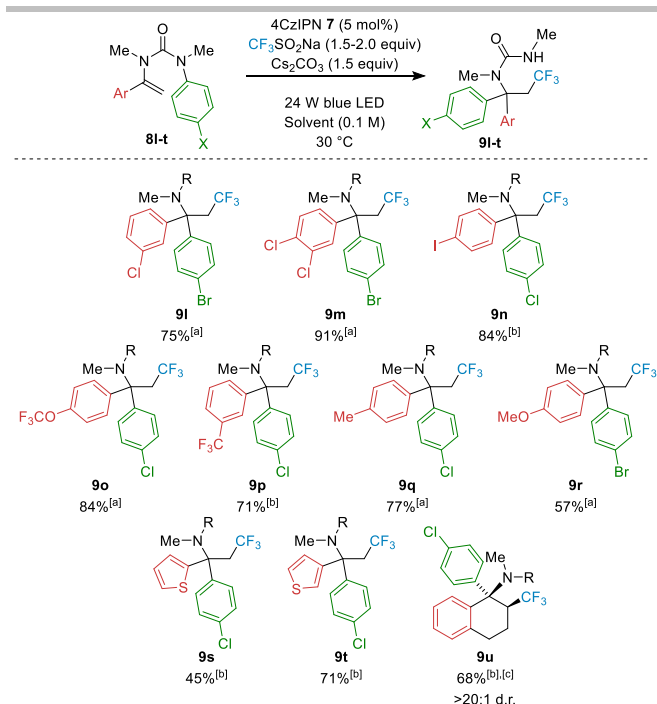
Scheme 2. Scope of migrating aryl groups for the trifluoromethyl-arylation reaction. Reactions were carried out on a 0.20 mmol scale. The heat generated by the LEDs resulted in reaction temperatures of ca. 30 °C. Yields of product isolated by chromatography. R = -C(O)NHMe. [a] Acetone used as solvent. [b] MeCN used as solvent. [c] DMF used as solvent. [d] 3 equiv. of NaSO₂CF₃ used.

yields of **6** formation (Entries 7-9). Control experiments were carried out to confirm that both the light source and the photocatalyst are required for formation of **6** from **5** (entries 10 and 11).

These optimised conditions were applied to the trifluoromethyl-arylation of a range of vinylic ureas. Firstly, we explored the scope of aromatic rings that would undergo migratory coupling (Scheme 2). Fluorinated and brominated aromatics performed well under trifluoromethyl-arylation conditions to give their respective α,α -diaryl alkylureas **9a-9d**. Notably, and consistent with related base-promoted rearrangements, arylation with relatively electron-rich phenyl (**9e**) and *para*-tolyl rings (**9f**) were successful when DMF was used as solvent. (Use of acetone or acetonitrile inhibited the rearrangement step, giving significant amounts of hydrotrifluoromethylated product). Likewise, *meta*-tolyl (**9g**) and *meta*-methoxy phenyl (**9h**) were both tolerated, giving the corresponding α,α -diarylalkylureas in good yield, as was the migration of electron-deficient aromatic rings (**9i-k**).

With the broad scope of the migrating rings established, we examined different aromatic rings α to the site of arylation that could facilitate the rearrangement of vinyl ureas (Scheme 3). Both chlorinated and iodinated aromatics were tolerated as functionality α to the site of arylation (**9l-n**). Trifluoromethyl-arylation was successful with vinyl ureas bearing both electron-deficient trifluoromethylated and trifluoromethoxylated aromatic rings (**9o** and **9p**), and electron-rich *p*-tolyl (**9q**) and *p*-methoxy phenyl (**9r**) groups. Even the thiophene-substituted substrates (**9s** and **9t**) participated successfully. Furthermore, a cyclic vinyl urea – the dihydronaphthalene **8u** – also underwent trifluoromethyl-

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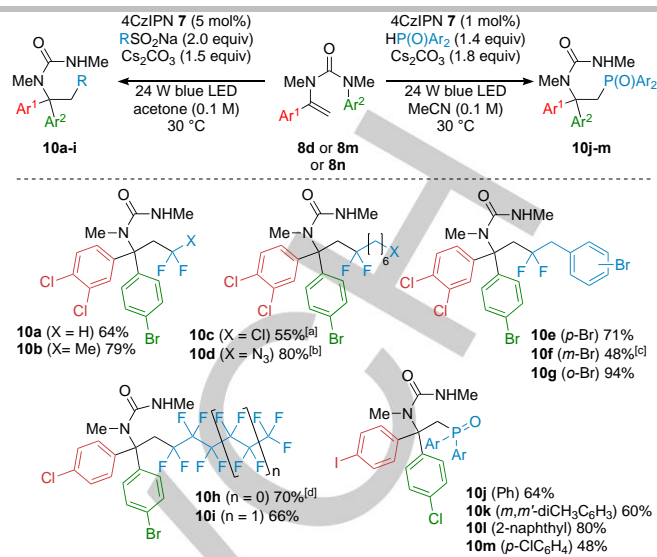


arylation in good yield and with excellent *anti*-diastereoselectivity (**9u**).

Other sodium sulfinate radical precursors were also used without any alteration to our optimised conditions (Scheme 4). Specifically, product ureas incorporating difluoromethyl (**10a**), 1,1-difluoroethyl (**10b**) and 1,1-difluoroalkyl chains bearing chloro (**10c**) or azide (**10d**) were formed in good yields, as were those containing (2,2-difluoroethyl)benzene groups (**10e-10g**). Perfluorinated sodium alkylsulfonates were also successful precursors, giving products **10h** and **10i** in good yield. Sodium alkylsulfonates that were not α -fluorinated (e.g. sodium butanesulfinate) failed to react with the vinyl urea, presumably because the resulting radical is too electron-rich to add to the nucleophilic alkene.

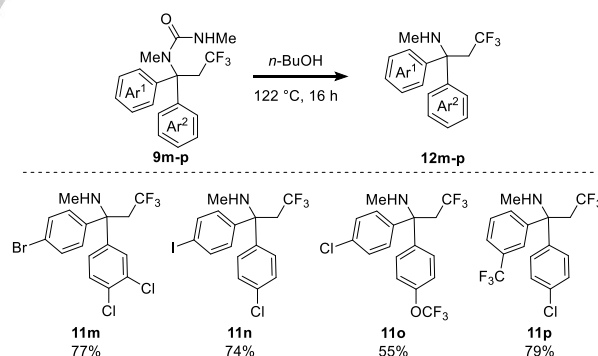
Organophosphorus compounds have a range of applications,²⁴ and may be prepared by the addition of phosphinoyl radicals to olefins.²⁵ Nonetheless, examples of non-annulative aryphosphonylations of alkenes still remain sparse.²⁶ We found that diarylphosphine oxides functioned effectively as radical precursors or the aryphosphonylation of vinyl urea **8n** without any appreciable alteration to conditions, yielding 1,1-diaryl-2-phosphoryl ureas (**10j-m**) (Scheme 4).

The functional group tolerance of these reactions towards halo substituents is greater than that of related reactions involving organolithiums.¹⁷ The reactivity of these radicals also nicely complements that of the organolithium component of related carbolithiation reactions, which conversely work best with more nucleophilic organometallics.¹⁷



Scheme 4. Scope of sodium sulfinate and diarylphosphine oxides radical precursors. The heat generated by the LEDs resulted in reaction temperatures of ca. 30 °C. Yields of product isolated by chromatography. [a] contains 15% of X=SEt, originating from the commercial sodium sulfinate radical precursor. [b] 1.9 equiv. of sodium sulfinate radical precursor used. [c] DMF used as solvent. [d] MeCN used as solvent.

Diarylalkylamines are a class of compounds that are of medicinal interest²⁷ that also find use as starting materials in the synthesis of nitrogen heterocycles.²⁸ Straightforward conversion of trifluoromethylated α,α -diarylalkylurea products (**9m-p**) into trifluoromethyl-containing α,α -diarylalkylamines (**11m-p**) was realised by solvolysis in *n*-butanol (Scheme 5).^{14a,29} Our radical addition Truce-Smiles arylation method thus formally delivers the β -trifluoromethylated α -arylation of an amino group, a reaction not possible using existing radical-initiated Smiles rearrangements.³⁰

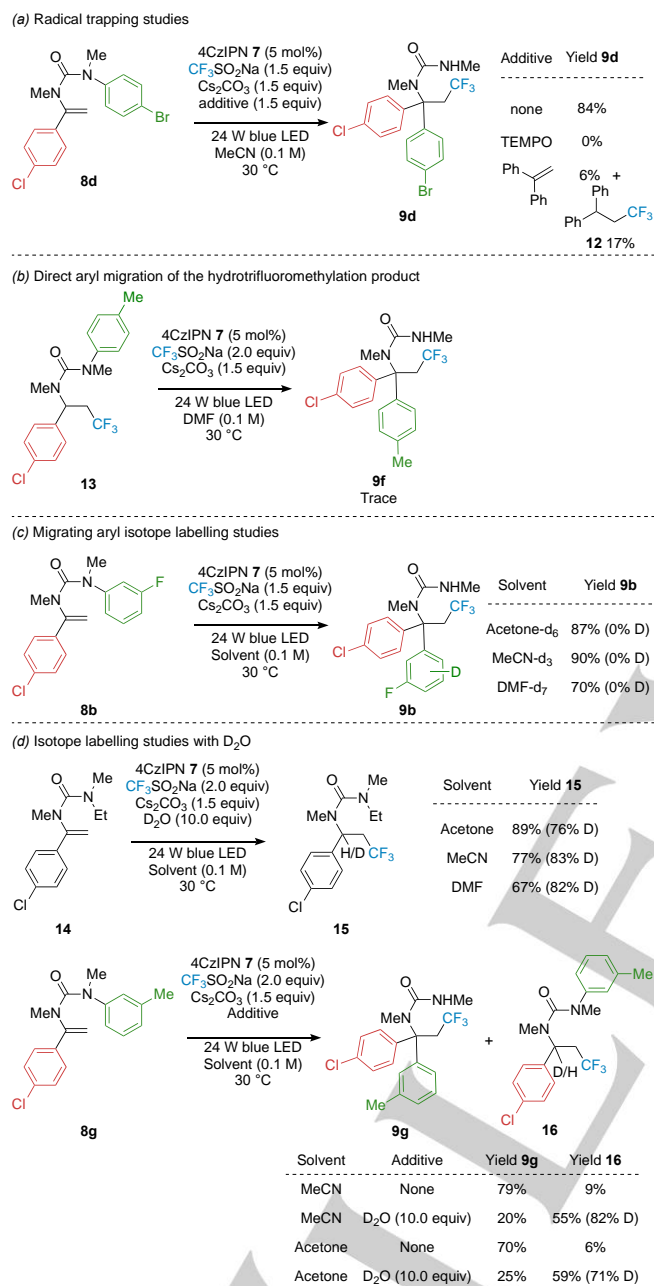


Scheme 5. Solvolysis of trifluoromethyl-arylation products. Yields of product isolated by chromatography.

Experiments were carried out to probe the mechanism of the tandem alkylation-arylation reaction. None of the product urea **9d** was formed when the reaction of **8d** was carried out in the presence of TEMPO, however no TEMPO adducts could be detected.³¹ Radical trap 1,1-diphenylethylene,^{2f,4,32} also attenuated formation of **9d**, and gave the trifluoromethyl adduct **12**, confirming that trifluoromethyl radical is generated under the reaction conditions in a redox-neutral manifold (Scheme 6a). This was further validated by Stern-Volmer luminescence studies, which showed that the excited state of **7** is quenched by

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NaSO_2CF_3 ($E_{p/2} = 1.05$ V vs SCE) to a greater degree than vinyl urea (**8b**: $E_{p/2} = 1.33$ V vs SCE). Measurement of a quantum yield (Φ) of 0.18 for the reaction of **8b** with NaSO_2CF_3 , suggests that alternative radical chain mechanisms are not operative (See ESI for details).



Scheme 6. Preliminary mechanistic studies. (a) Radical probe experiments. (b) Negligible contribution from a sequential hydrotrifluoromethylation/C-H arylation pathway. (c) Absence of deuterium incorporation into migrating aryl ring from solvent. (d) Inhibition of rearrangement step and deuteration by D_2O .

Although we assume that the N to C aryl migration occurs by an anionic intramolecular $\text{S}_{\text{N}}\text{Ar}$ (Truce-Smiles) mechanism, its electronic versatility is also characteristic of reactions mediated by radicals.^{30,33} Experiments were carried out to establish the nature of the reaction intermediates and to distinguish between these two mechanistic possibilities. We ruled out the participation of a neutral hydrotrifluoromethylation intermediate **13** by

resubjecting **13** to the conditions of the reaction: only trace amounts of **9f** were formed (Scheme 6b).

Several experiments were conducted to distinguish a radical from an anionic intermediate α to N. Reaction of **8b** in deuterated solvents (Scheme 6c) led to no deuterium incorporation into the migrating aryl ring of **8b**. This result implies that a 1,5-aryl translocation by 5-*exo-trig* radical cyclisation, followed by hydrogen atom abstraction by the cyclohexadienyl radical and elimination of the nitrogen leaving group does not occur.

Experiments with vinyl urea **14**, which can undergo radical addition but not rearrangement, showed that under the conditions of the reaction it is possible to form an anion α to N: in the presence of D_2O , significant amounts of deuterated product **15** were formed (Scheme 6d). Direct indication of the intermediacy of an anion was gained by performing the trifluoromethyl-arylation of **8g** in the presence of deuterium oxide as an anion trap. In both MeCN and acetone, the major product became the (mainly deuterated) product **16**, showing that a proton source can interrupt the migration. A similar switch in selectivity from **9f** to **13** was also noted in the trifluoromethyl-arylation of **8f** with solvents of lower $\text{p}K_{\text{a}}$ (See ESI for details).

In summary, a transition-metal free difunctionalisation (alkyl-arylation and phosphoryl-arylation) of vinyl ureas is made possible using a readily available organic photocatalyst. The tandem reaction sequence entails the first example of polar Truce-Smiles arylations initiated by photoredox catalysis and first example of a radical addition leading to Truce-Smiles arylation α to nitrogen. The transformation is tolerant of a range of functional groups and aromatic rings, and provides an operationally simple method for preparing fluorinated and phosphorylated α,α -diarylalkylureas, which may be converted into functionalised α,α -diarylalkylamines.

Acknowledgements

We thank Ellie Stammers and Dr Alastair Lennox for assistance with cyclic voltammetry experiments. The work was supported by the EPSRC Centre for Doctoral Training in Catalysis.

Keywords: photochemistry • rearrangement • $\text{S}_{\text{N}}\text{Ar}$ • urea • trifluoromethylation

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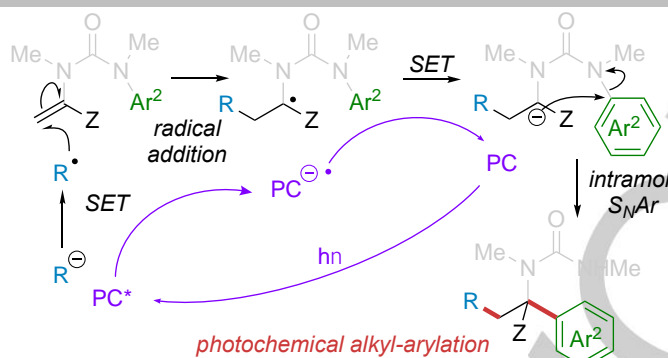
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COMMUNICATION

Cascade formation of two C–C bonds at an electron-rich alkene is made possible by sequential capture of a radical (by intermolecular addition) and an anion (by intramolecular aromatic substitution), each formed in the photoredox cycle from the same organic photocatalyst.



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Jonathan Clayden*

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**Photocatalytic
Difunctionalization of
Vinyl Ureas by Radical
Addition Polar Truce-
Smiles Rearrangement
Cascades**