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Alkene Carboarylation via Catalyst-Free, Visible Light-Mediated Smiles Rearrangement.

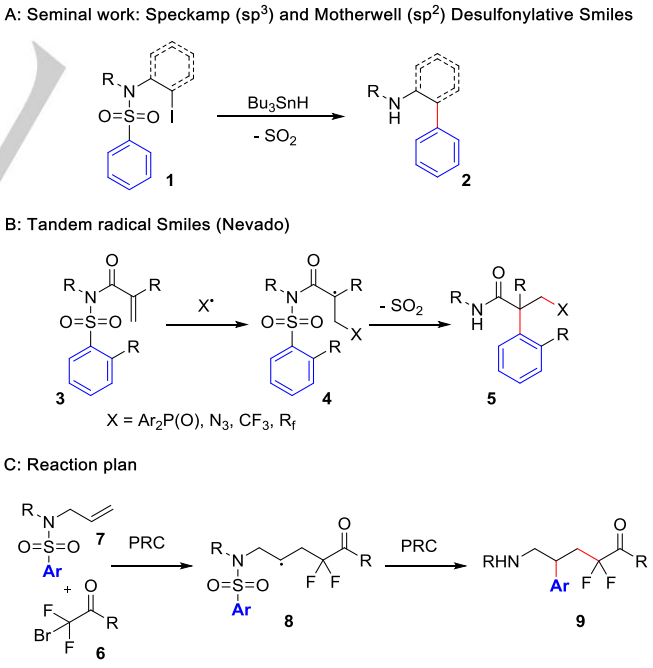
David M. Whalley, Hung A. Duong,* and Michael F. Greaney*

Abstract: A light-mediated Truce-Smiles arylative rearrangement is described that proceeds in the absence of any photocatalyst. The protocol creates two C-C bonds from simple starting materials, with the installation of an aryl ring and a difluoroacetate moiety across unactivated alkenes. The reaction proceeds via a radical mechanism, utilizing a light mediated reduction of ethyl bromodifluoroacetate by *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to set up intermolecular addition to an unactivated alkene, followed by Truce-Smiles rearrangement.

The Truce-Smiles rearrangement is a powerful transformation in arene chemistry, involving the migration of aryl rings via *ipso*-substitution.[1] By cleaving easily formed C-X bonds, and creating arene C-C bonds, it can convert readily available, simple starting materials to higher-value functionalized arene products. The desulfonylative Truce-Smiles, in particular, has seen extensive application in recent years, exploiting tractable sulfonamide and sulfonates as starting materials and extrusion of SO_2 to irreversibly drive the reaction. Both polar and radical-variants are well established, with the radical reaction featuring particularly strong substrate scope around the migrating aryl moiety. Seminal work by Speckamp and Motherwell[2] in this area (Scheme 1A) established the reaction for purely intramolecular sp^2 and sp^3 carbon-centered radical systems, and the reaction has since been widely exploited. [3] A powerful recent development is to embed the Truce-Smiles in a cascade process, where the key radical intermediate is generated from a precursor bond-forming event *e.g.* Scheme 1B from Nevado and co-workers, [4] where the Michael acceptor **3** can undergo a variety of intermolecular radical additions, setting up the radical Smiles to construct sophisticated heterocyclic scaffolds.

Our recent work on tandem Smiles chemistry in the polar regime[5] encouraged us to examine a radical variant, with the explicit aim of developing a photoredox process using visible light. Photoredox catalysis enables radical generation under mild reaction conditions, [6] using operationally simple, user-friendly reaction set-ups. Novel photoredox Smiles processes have recently been reported in the literature, with Brachet, Belmont and co-workers describing a phthalazine synthesis from alkynylsulfonohydrazone rearrangement,[7] and Stephenson and co-workers developing desulfonylative and C-N cleaving Smiles rearrangements [8] using ruthenium and iridium catalysis, respectively. Recently, the Stephenson group have described a intermolecular aminoarylation reaction that uses desulfonylative Smiles chemistry catalyzed by an iridium complex and visible light.[8d]

Encouraged by these works, along with our own experience in developing photoredox catalysis reactions, [9] we planned the sequence set out in Scheme 1C. We envisaged a reaction whereby a photocatalyst could undergo oxidative quenching by ethyl bromodifluoroacetate **6** (E^{red} = −0.57 V vs SCE)[10] to yield an electrophilic radical species that could undergo addition to an unactivated alkene such as **7** bearing a sulfonamide residue. The bromodifluoroacetate moiety provides a stable radical that has been widely exploited in photoredox catalysis, [11] and introduces a valuable *gem*-difluoro group into the reaction products. The resulting secondary alkyl radical **8** is then in a 1,5-relationship to the *ipso* position on the aryl ring, allowing Truce-Smiles rearrangement to take place. With the use of a tertiary amine, the catalytic cycle could be completed via SET reduction of the oxidized catalyst as well as providing a hydrogen atom source to reduce the resulting N-centered radical in the product molecule. Important precedent from Zard and coworkers[12] has demonstrated successful 1,5-aryl migration from a closely related radical intermediate to **8**, generated from a xanthate precursor, suggesting that the Smiles process would be viable if the right PRC-conditions could be found to mediate the overall transformation.[13]



Scheme 1. Truce-Smiles rearrangement methodologies and reaction plan. PRC = photoredox catalyst.

Our studies began with *N*-allyl-*N*-(arylsulfonyl)acetamide **7a** as the alkene acceptor, ethyl bromodifluoroacetate **6** and the

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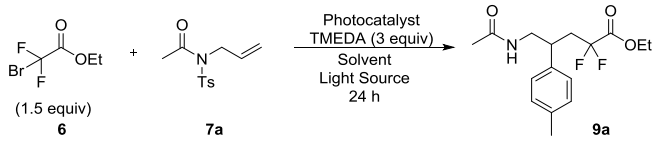
archetypal iridium catalyst *fac*-Ir(ppy)$_3$ with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as stoichiometric reductant. We were pleased to isolate product **9a** in an encouraging 42% yield at room temperature under these conditions, using DCM as solvent. Efforts then turned towards developing the protocol to encompass more sustainable, cost effective photocatalysts such as eosin Y and a copper complex pioneered by Collins and coworkers.[14] Both systems returned moderate yields of product with dichloromethane as a solvent at room temperature, however, switching to a higher boiling point solvent and increasing the reaction temperature aided the reaction (entry 6). In the course of conducting control experiments, we were surprised to find that the reaction could proceed without any photoredox catalyst, heating to 80 °C in DMSO (Table 1, entry 7). This introduced the exciting possibility of developing a visible light photochemical Smiles process with no requirement for any photoredox catalyst. Further control experiments established that the catalyst-free reaction proceeded slowly at room temperature, and that there was no reactivity in the dark (Table 1, entries 8 and 9).

Table 1. Optimization of the Truce-Smiles Rearrangement via radical addition

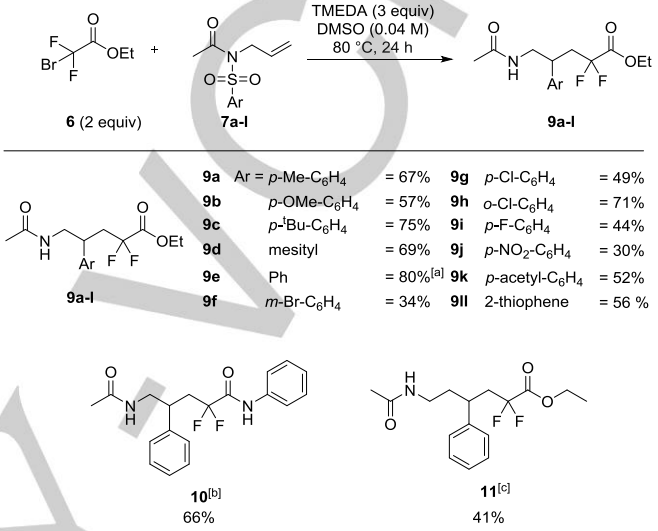


Entry	Catalyst[c]	Light Source	Reaction Temperature	Solvent	Yield
1[a]	A	Blue LEDs	r.t.	DCM[d]	42%[g]
2	B	Blue LEDs	r.t.	DCM[d]	40%[g]
3	C	Green LEDs	r.t.	DCM[e]	46%[g]
4	C	Green LEDs	r.t.	DCM[e]	49%[g]
5	B	Blue LEDs	r.t.	DMSO[e]	39%[h]
6	B	Blue LEDs	80 ºC	DMSO[e]	59%[g]
7[b]	-	Blue LEDs	80 ºC	DMSO[f]	**67%**[g]
8[b]	-	Blue LEDs	r.t.	DMSO[f]	26%[h]
9[b]	-	-	80 ºC	DMSO[f]	0%[h]

Ts = toluenesulfonyl. r.t. = room temperature. Reactions conducted on a 0.1 mmol scale. [a] 15 h reaction time. [b] 2 equiv of **6**. [c] A = *fac*-Ir(ppy)$_3$ (1 mol%), B = Cu(BINAP)(dq)BF$_4$ 3 mol% (BINAP = (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) dq = 2,2'-biquinoline) C = Eosin Y 3 mol%. [d] 0.10 M concentration. [e] 0.033 M concentration. [f] 0.040 M concentration. [g] isolated yield. [h] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard.

With this catalyst free protocol in hand, we turned to examining the scope of this reaction. Our previous reports of polar Truce-Smiles rearrangements required electron poor aryl and heteroaryl systems to stabilize the anionic Meisenheimer intermediate. Here, however, we expected the radical system to be free of this restriction and able to incorporate a larger variety of aryl substituents. This proved to be the case, with a variety of electron rich (**7a** – **7d**), neutral (**7e**), and poor (**7f** – **7l**) aryl systems undergoing a smooth tandem reaction to yield the products **9**. The ethyl bromodifluoroacetate used in the transformation provides a safe and cost effective method for installing geminal difluoro groups on to an organic scaffold, and we could switch the ester group to a phenylamide without a problem (**10**).

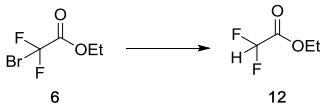
We were pleased to observe successful reaction for a homoallyl sulfonamide substrate, producing the hexyl product **11** in moderate yield. The 1,5-Smiles process here proceeds through a six-membered transition state, offering a counterpoint to the 1,4-reaction which dominates radical Smiles chemistry in the literature.[15]



Scheme 2. Reactions conducted on 0.1 mmol scale. [a] 59% for 1 mmol scale. [b] Using 2-bromo-2,2-difluoro-*N*-phenylacetamide in place of **6**. [c] *N*-(but-3-en-1-yl)-*N*-(phenylsulfonyl)acetamide used in place of **7e**

Ethyl difluorobromoacetate **6** has been widely employed in intermolecular difluoroalkylation reactions using ruthenium and iridium photoredox catalysis (usually in the presence of an inorganic base).[11] Likewise, its facility as a fluoroalkyl radical precursor in $S_{RN}1$ processes is well-known,[16] but with the usual requirement for metal salts to promote the initial electron transfer event. However, a number of visible light photochemical metal-free systems have recently being reported[17] for **6** and related haloalkanes that use tertiary amine donors as reductants. To elucidate how the ethyl bromodifluoroacetate starting material could be reduced in our process we studied its interaction with TMEDA by ^{19}F NMR (Table 2). First, a mixture of **6** and TMEDA in DMSO-d$_6$ at ambient temperature in the dark was observed to yield no reduced product. Second, heating the two compounds to 80 ºC also gave no reduced product, supporting the results in table 1 that the reaction is not initiated thermally. However, when the two components were irradiated by blue LEDs for 15 hours, 97% conversion to ethyl difluoroacetate is observed. Furthermore, when a solution of **6** was irradiated in the absence of TMEDA, no reduced product was observed. UV/Vis spectroscopy revealed that upon mixing these two components, the UV/Vis absorbance is increased, particularly in the near UV region, accompanied by a bathochromic shift (Figure 1). It is therefore likely that TMEDA and **6** form an electron-donor complex in solution, whereby an electron transfer event can be triggered by the near-UV/shorter wavelengths of blue visible light typically used in photoredox experiments.[18] Finally, when the reaction (conditions as Table 1, entry 7) was subjected to three

equivalents of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl, the reaction failed to yield **10a**, supporting the postulated radical character of the mechanism.



6 12

Conditions	Conversion to **12**
TMEDA, DMSO-d6, rt, dark, 15 h	0
TMEDA, DMSO-d6, 80 °C, **dark**, 15 h	0
TMEDA, DMSO-d6, rt, **Blue LEDs**, 15 h	97%

Table 2. Reduction of ethyl bromodifluoroacetate. Reaction conditions: 0.5 mL of DMSO-d_6, 0.15 mmol of **6**, 0.30 mmol of TMEDA.

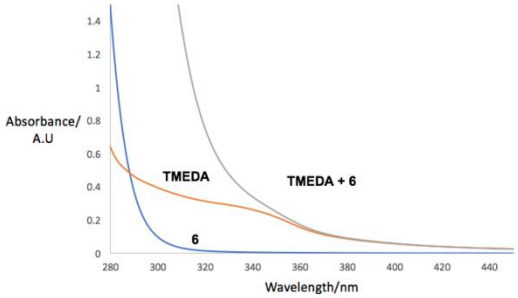


Figure 1. UV/Vis study. 0.3 M concentration solutions in DMSO

Based on these results, we propose the pathway in Scheme 3 for the reaction, beginning with TMEDA photoreduction of bromodifluoroacetate **6** to the radical **13**. Intermolecular addition gives the alkyl radical **8**, which can undergo Truce-Smiles aryl shift with extrusion of SO_2. The resultant amidyl radical **14** can then undergo hydrogen atom transfer, likely from the TMEDA which is present in excess, to yield the C-arylated product **9**.

In conclusion, we have developed a novel Truce Smiles protocol that uses blue light and simple TMEDA as an electron donor to promote a Truce Smiles cascade process. The reaction exploits the ready availability of sulfonamide aryl groups, transforming them to valuable C-arylated products, and is free from the transition metal catalysts, and/or organic dyes, and ancillary reagents that typically characterize photoredox processes. Future studies will examine the application of this light-mediated electron-transfer event in alternative C-C bond forming transformations.

Acknowledgements

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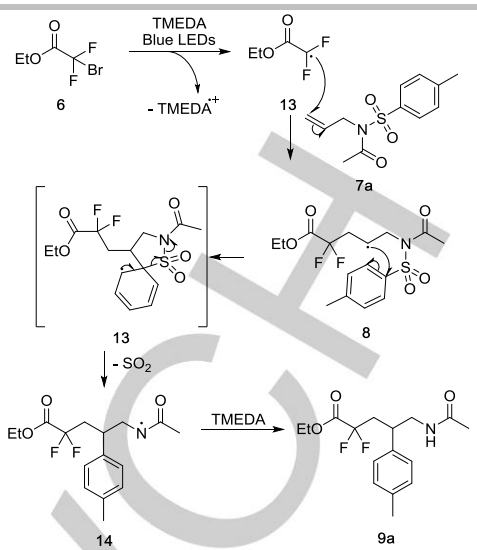
Keywords: rearrangement • photochemistry • radical reactions



Scheme 3. Proposed mechanism for the Truce Smiles via radical addition

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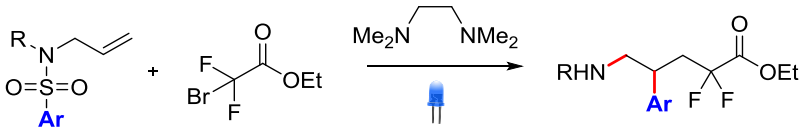

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