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A visible light-mediated, decarboxylative, desulfonylative Smiles rearrangement for general arylethylamine syntheses†

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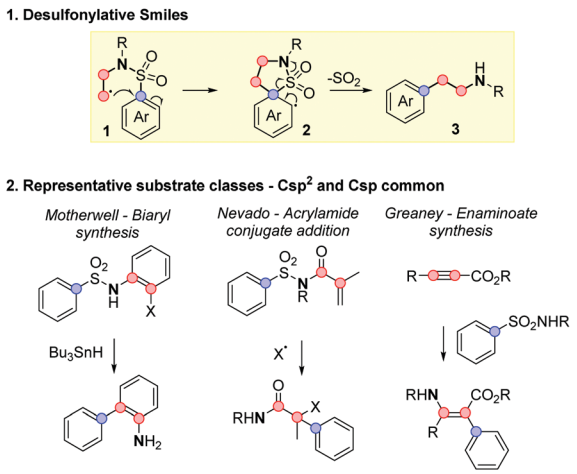
A decarboxylative, desulfonylative Smiles rearrangement is presented that employs activated-ester/energy transfer catalysis to decarboxylate β-amino acid derived starting materials at room-temperature under visible light irradiation. The radical Smiles rearrangement gives a range of biologically active arylethylamine products highly relevant to the pharmaceutical industry, chemical biology and materials science. The reaction is then applied to the synthesis of a chiral unnatural amino acid, 2-thienylalanine, used in the treatment of phenylketonuria. We also show how the reaction can proceed under metal-free and catalyst-free conditions.

The desulfonylative Smiles rearrangement is a powerful arylation method that exploits easy to make sulfonamides, to forge more challenging C_{aryl}–Csp^3 bonds *via ipso*-substitution (Scheme 1.1).[1] The reaction often features mild and operationally simple conditions, creating versatile pathways to functionalized amino heteroarenes **3** with no requirement for stoichiometric arylmetals. The best exemplified arylations in this regime proceed through a 5-membered transition state with where one or both of the two carbon centres illustrated in red are sp^2 hybridised.[2–5] Representative examples are shown in Scheme 1.2: seminal work in this area from Motherwell established the reaction for Csp^2 radicals in biaryl synthesis,[2b] the Nevado group have developed an acrylamide system triggered by a wide range of radical conjugate additions,[3i,j,k] and our own laboratory have used sulfonamide addition to sp-carbons for carbanion aryl transfer.[3b,c]

Smiles reaction on Csp^3-tethered substrates, by contrast, is far more limited in the literature, and represents a highly appealing target for method development. The product arylethylamines **3** are amongst the most privileged scaffolds in chemistry and biology, found in endogenous signalling molecules such as melatonin, adrenaline, serotonin and dopamine, and have been widely exploited in medicines for central nervous system (CNS) disorders (*e.g.* antidepressants agomelatine and venlafaxine, Parkinson's treatment baclofen, and stimulants such as amphetamine and Ritalin).[6]

A small number of aryl transfer routes to arylethylamines are known, including some of the earliest reports from Speckamp on the α-halomethylpiperidinyl system.[2,7] Zard established the reaction for xanthates **4**, using thermal cleavage with a peroxide initiator to give the substituted arylethylamines **5** (Scheme 2.1).[8] Recent work by Stephenson used the visible light SET oxidation of *p*-methoxystyrenes to trigger sulfonamide addition, followed by Smiles rearrangement to give 1,1-diarylethylamines **8**.[3a] Our laboratory has effected radical Smiles rearrangement using visible light-mediated addition of bromodifluoroacetate to alkenes **9**, giving the *gem*-difluoro substituted arylethylamines **11**.[9] In most cases, the reaction design generates secondary radicals for desulfonylative Smiles



Scheme 1 Desulfonylative Smiles rearrangements to access arylethylamine structures.

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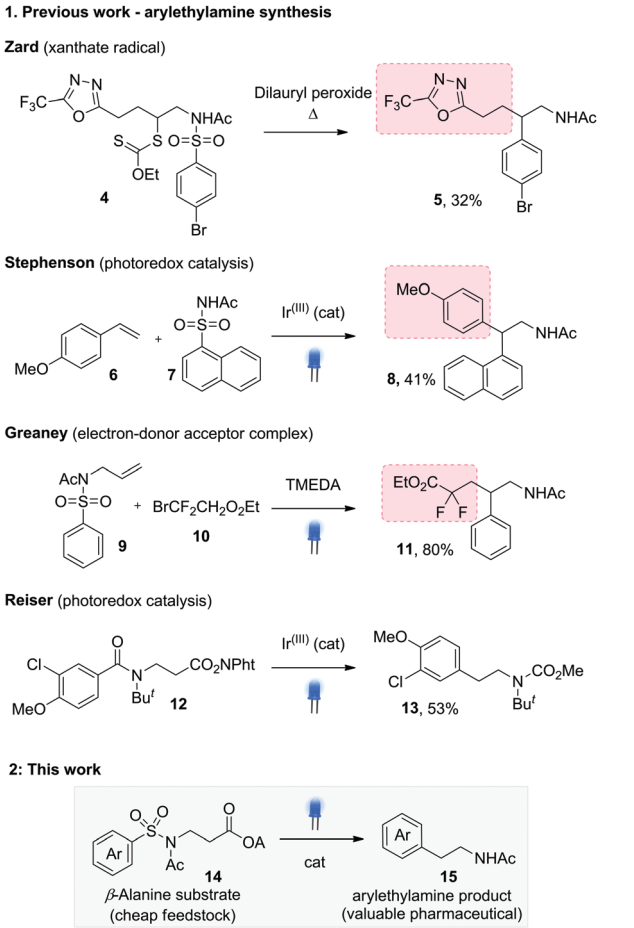
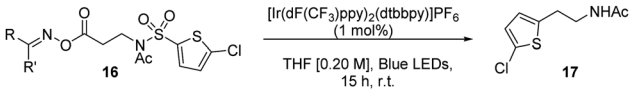


Scheme 2 Extrusion Smiles rearrangements to access arylethylamine structures.

rearrangement, producing branched products. A notable exception from Reiser and co-workers used decarbonylative Smiles rearrangement from the *tert*-butylated benzoylamides **12** to access the parent phenylethylamines **13**.[5c] The more demanding amide decarbonylation step necessitated an intramolecular single electron transfer mechanism, requiring electron rich migrating aryl groups for efficient reaction.

We were interested in establishing a general approach to unsubstituted and substituted arylethylamines under mild, catalytic conditions. Our reaction design is shown in Scheme 2.2 and represents the first example of a desulfonylative, decarboxylative Truce–Smiles rearrangement. The extrusion of CO_2 provides expedient access to the key Csp^3 radical species (**1** in Scheme 1.1) and uses readily available amino acid starting materials **14**, exploiting their low cost, high availability and in certain cases, enantiopurity. On the other hand, the extrusion of SO_2 to irreversibly drive the Truce–Smiles rearrangement has proven to be an efficient means to incorporate a plethora of aryl species including electron rich and poor arene rings as well heterocycles. We hypothesised that the synergy of these two strategies would provide arylethylamine examples largely inaccessible by other reports in the field of Smiles chemistry.

Table 1 Oxime ester optimization[a]



Entry	R	R′	Conversion[b]
1	Ph	Ph	41
2	Ph	H	50
3	H	p-ClC_6H_4	45
4	p-FC_6H_4	p-FC_6H_4	63

[a] 0.05 mmol scale. [b] Yields determined using a 1,3,5-trimethoxybenzene NMR standard.

We began by preparing a series of β-alanine oxime esters **16** (three steps, no purification of intermediates required, see ESI†). Recent work from Glorius has used these moieties in the room-temperature decarboxylation of aliphatic carboxylic acids *via* visible light-mediated energy transfer catalysis.[10] This approach is attractive as it removes the need for stoichiometric reductants, commonly necessary for redox-active phthalimide based strategies.[11] We used thiophenes as the migrating arenes in our initial optimization studies, owing to their prevalence in pharmaceuticals[12] and their success in literature aryl transfer reactions (Table 1).[3a,g,5d] Using $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ as catalyst, we were delighted to observe successful reaction for various oxime esters, with the *p*-fluoro derivative giving the best conversion.

A screen of catalysts, solvents, and concentrations established the iridium photosensitizer (1 mol%) in a tetrahydrofuran (THF) solvent 0.08 M under blue LED irradiation, successfully delivered the arylethylamine product in 56% yield (**17a**). Notably, we also found that we could lower the catalytic loading to 0.25 mol% with only a small reduction in reaction efficiency (see ESI†).

We explored the scope of the reaction for thiophenylethylamines, initially. Compound **16b**, containing the 3-chlorothiophene substituent, gave a substantially higher yield, possibly due to prevention of side-reactions through *ortho* addition to the thiophene. It was possible to carry out this reaction under metal free conditions using an organic thioxanthone photosensitizer (10 mol%), albeit at reduced efficiency. Both the brominated and un-substituted thiophene rings reacted in moderate yield (**17c** and **17d**), along with the Boc-protected substrate **17e**, establishing an orthogonal nitrogen-protecting group pathway.[14]

Substitution on the ethyl backbone was easily tolerated, with the α and β-methyl substrates rearranging in excellent yield (**17f** and **17g**). Pleasingly, we were able to show for **17g** that reaction occurred without racemization, with both *R* and *S* starting materials delivering the enantiopure heterocyclic amphetamine-type structures, biosteres of other biologically active amines.[13]

Moving away from thiophene, the transformation could facilitate the migration of phenyl rings, creating a collection of biologically active phenylethylamines **17h–17o**. Fluorinated aryl rings have gained much attention within the medicinal chemistry community and we were keen to demonstrate the applicability to

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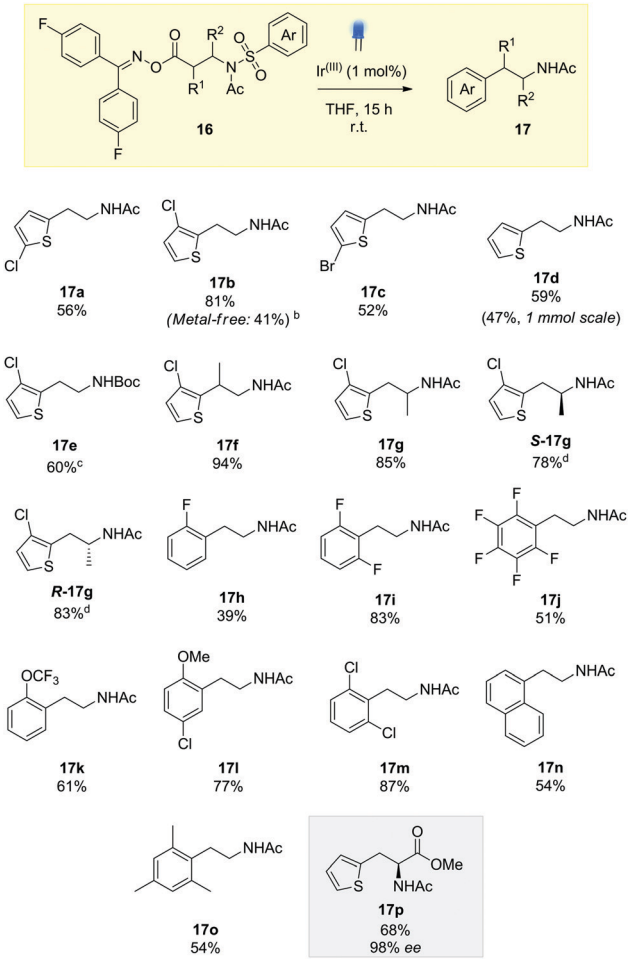
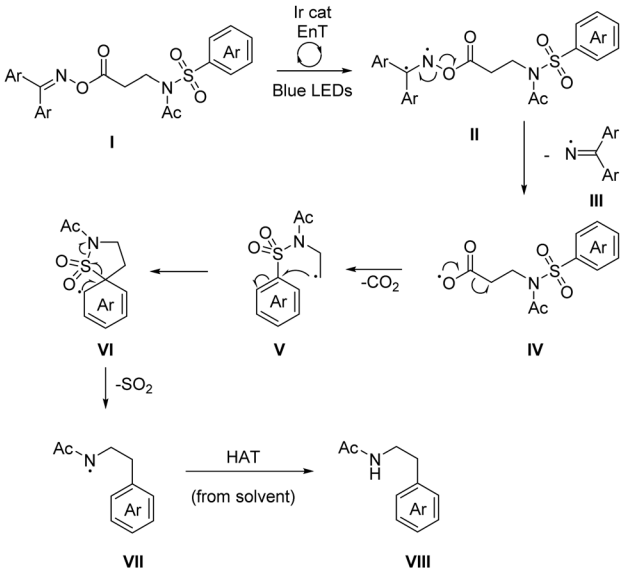
our system. Hydrolysis products of **17h–17j** have all been used in the literature as components for pharmaceutically relevant compounds as well as active components in organic semiconductors.[14] Whilst the unsubstituted phenyl ring proved to be an ineffective migrating group, 2-fluorophenylethylamine **17h** could be incorporated with moderate yield by increasing the electrophilicity of the *ipso* position. This is further demonstrated in example **17i** where both the 2 and 6 positions are blocked, preventing deleterious alkyl radical addition products. 2-Trifluoromethoxyphenyl **17k** also acted as a good substrate for desulfonylative Smiles chemistry.[15] Additional examples with 2-substitution included **17l**, showing that we could incorporate anisyl rings in our chemistry, as well as *meta* substitution for further functionalisation of the arene system (**17m**). 1-Naphthylethylamine, a known tryptamine analogue, could be synthesized (**17n**), potentially opening up new synthetic routes to the antidepressant agomelatine.[16] In accordance with other reports on radical *ipso* substitution, the reaction was tolerant of steric hindrance demonstrated with compound **17o**, containing a mesityl ring.[17]



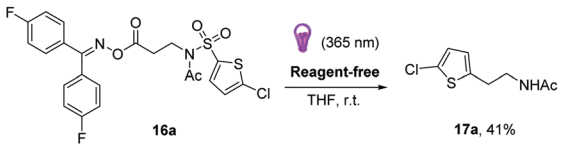
Scheme 3 Scope of the decarboxylative, desulfonylative Truce–Smiles rearrangement.[a,a] 0.20 mmol scale, Ir(III) = $Ir(dF(CF3)ppy)_2(dtbbpy)PF_6$, 2.5 mL THF. [b] 10 mol% thioxanthone catalyst, blue LED irradiation. [c] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [d] No evidence of racemization, isolated as single enantiomers.



Scheme 4 Proposed mechanism of the decarboxylative, desulfonylative radical Truce–Smiles rearrangement. Ar = 4-F-phenyl.

Finally, we were keen to demonstrate the methodology in the synthesis of a phenylalanine pharmaceutical. β-2-Thienylalanine has been used to treat infants with phenylketonuria, a genetic disorder resulting in the accumulation of phenylalanine in the blood, leading to brain damage if left untreated.[18] Using the oxime ester derived from cheap and readily available L-methyl aspartate, photocatalytic Smiles rearrangement gave the protected β-2-thienylalanine **17p** in 68% yield and 98% ee. Our approach compliments existing routes to this class of molecule, which use asymmetric Rh hydrogenation[19] or enzymatic catalysis with phenylalanine ammonia lyase.[20]

The mechanism for the Smiles arylation likely begins with an energy transfer (EnT) event between the excited iridium catalyst and the activated imine **I** giving **II**, a diradical species (Scheme 4). Homolytic N–O bond cleavage can then take place, releasing iminyl radical **III** which can be quenched *via* hydrogen atom abstraction (HAT),[21] from the solvent's relatively weak C–H bond (α-CH: BDE = 385 kJ mol^{-1}).[22] **IV** can spontaneously decarboxylate to give a primary alkyl radical **V**.[23] This can then undergo a radical desulfonylative-Smiles rearrangement *via ipso* substitution, forming a spirocyclic intermediate **VI**, releasing SO_2 to irreversibly drive the process to completion. One further HAT event between amidyl radical **VII** and the solvent gives the product, **VIII**. Owing to the inability of similarly reducing photocatalyst (see ESI†) to yield any product, the absence of a suitable stoichiometric reductant, and the irreversible reduction



Scheme 5 Reagent-free desulfonylative, decarboxylative Truce–Smiles rearrangement.

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potential of −2.0 V (*vs.* SCE)[10] we can rule out a photoredox mechanism as a viable pathway for N–O bond cleavage. Furthermore the reaction can proceed with reasonable efficiency using the organic photosensitizer thioxanthone (**17b**, Scheme 3). In the dark no conversion is observed but under blue LED irradiation (catalyst free), a 20% NMR yield of the product is observed.

In view of this last observation, we were intrigued to see if the reaction could be carried out catalyst-free by direct excitation of the oxime moiety using UVA radiation at room temperature (Scheme 5). This would allow for a reagent-free approach to sp^3–sp^2 C–C bond formation, at room temperature. We were pleased to find that we obtained a 41% NMR yield of the final product (*cf.* example **17a**, Scheme 3), indicating the viability of this approach.[24]

In conclusion, we have developed a new decarboxylative, desulfonylative Truce–Smiles rearrangement enabled by visible light energy transfer catalysis. The reaction uses starting materials derived from commercially available β-amino acids, giving extensive control over the aryl species, ethyl chain substitution and amino protection for the synthesis of new arylethylamines. The reaction can be carried out metal-free and catalyst-free and applied to the synthesis of chiral unnatural amino acids.

Conflicts of interest

There are no conflicts to declare.

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