ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2015, **2**, 1352

Chemoselective and fast decarboxylative allylation by photoredox catalysis under mild conditions†

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Received 12th June 2015,
Accepted 1st August 2015

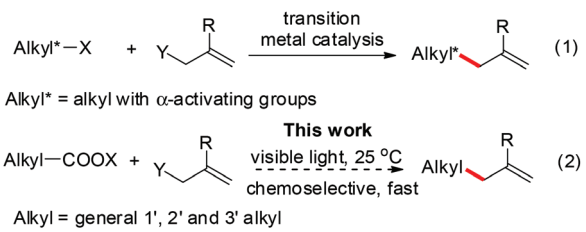
DOI: 10.1039/c5qo00187k

rsc.li/frontiers-organic

Here we report a visible-light-induced decarboxylative allylation to build C(sp^3)–allyl bonds. This allylation reaction works for primary, secondary, tertiary, benzyl, and alpha-heteroatom-substituted alkyl *N*-acyloxyphthalimides and is compatible with many sensitive functional groups. The reaction is complete in minutes at room temperature and can be run in both organic solvents and neutral aqueous solutions. A series of mechanistic experiments have been implemented and a functional-group-rich oligosaccharide modification is demonstrated with the decarboxylative allylation.

Introduction

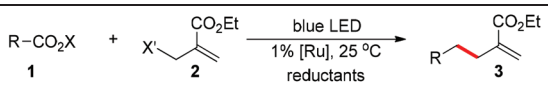
The allylation is a powerful synthetic method to build carbon–carbon bonds and the resulting alkene is a versatile synthetic building block. Transition-metal-catalyzed allylations are widely-used, while their applications for *C*(sp^3)-allylations are limited to α-activated alkyl groups to minimize β-hydrogen elimination (eqn (1)).[1] In contrast, the radical allylations are effective to build C(sp^3)–allyl bonds; however, the traditional use of heating or UV light compromises their functional group compatibility and chemoselectivity.[2] Recently, visible-light-catalysis has enabled radical initiations under mild photoredox conditions including neutral aqueous solutions.[3] Here we report a chemoselective and fast decarboxylative allylation for primary, secondary, tertiary, benzyl, and alpha-heteroatom-substituted alkyl *N*-acyloxyphthalimides by photoredox catalysis (eqn (2)).



Results and discussion

Using $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst under blue LED irradiation, we start our investigation with adamantyl *N*-acyloxyphthalimide **1** and find that the *C*(sp^3)-allylation product **3** is obtained with allyl bromides in 81% yield (entry 1 in Table 1).[4] With diisopropylethylamine and Hantzsch ester as reductants, the allyl sulfone is more effective with 86% yield and fewer side products (entry 2).[5] This reaction can be run with the addition of formic acids to neutralize the diisopropylethylamine, and the optimal 92% allylation yield is obtained within 30 minutes (90% isolated yield, entry 3). The photocatalyst is necessary to accelerate the reaction where the direct photo-induced reaction without the photocatalyst results in little conversion (entry 4).[6] Light irradiation and reductants are both critical for the reaction (entries 5 and 6).

Table 1 Optimization of the decarboxylative allylation



Entry	Conditions[a]	Time	Conversion[b]	Yield[b]
1	X′ = Br	30 min	>95%	81%
2	X′ = SO_2Ph	30 min	>95%	86%
3[c]	Entry 2, w/HCO_2H	30 min	>95%	92% (90%)
4	Entry 3, no [Ru]	2 h	<5%	<5%
5	Entry 3, no blue LED	2 h	<5%	0%
6	Entry 3, no reductants	2 h	<5%	0%

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), $Ru(bpy)_3(PF_6)_2$ (0.001 mmol), iPr_2NEt (0.20 mmol), and Hantzsch ester (HE, 0.15 mmol) in 1.0 mL CH_2Cl_2 under nitrogen with 468 nm LED irradiation. [b] Conversions and yields were determined by ^1H NMR analysis, isolated yields are in parentheses. [c] iPr_2NEt (0.10 mmol), HCOOH (0.10 mmol), and Hantzsch ester (HE, 0.15 mmol) were used as reductants. X = phthalimide. R = adamantyl.

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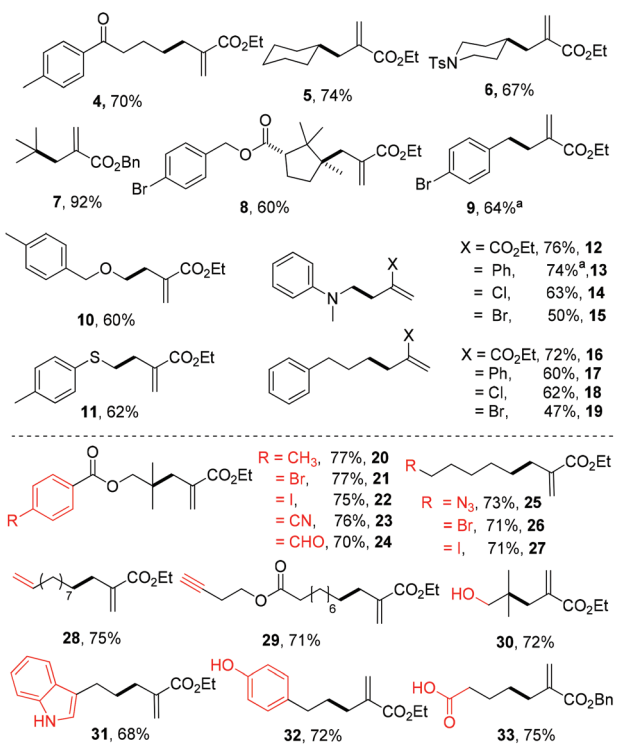
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5qo00187k

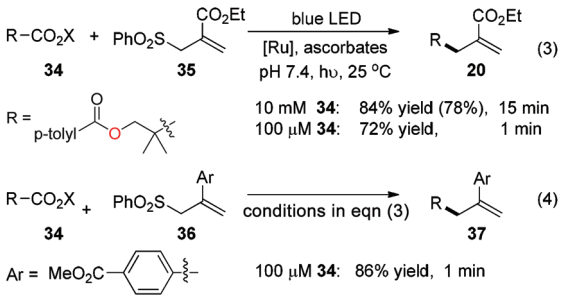
With the mild reaction conditions at room temperature, we next explore the substrate scope of the reaction. Primary, secondary and tertiary alkyl substituted *N*-acyloxyphthalimides all react well to give the allylation adducts (products **4–7** in Scheme 1). It is worth noting that bulky alpha-quaternary substituted alkyl substituted *N*-acyloxyphthalimides yield allylation adduct **8** smoothly (*trans* isomer only). The benzyl allylation product **9** is obtained in 64% yield, and the dimerization side products are not observed. The α-heteroatom substituted alkyl *N*-acyloxyphthalimides including substitutions with oxygen, nitrogen and sulfur are all tolerated in the reaction (products **10–15**). The allyl acceptors are not limited to electron-deficient alkenes with ester groups, and allyl acceptors with phenyl, chloride, or bromide substitution all reacted to give slightly decreased yields (products **12–19**).[7]

We further tested the functional group tolerance of the reaction. The transition-metal-sensitive aryl bromides and iodides have no interference with the reaction (products **20–22**). The reduction-sensitive aldehydes, nitriles, and alkyl azides are well tolerated (products **23–25**). Alkyl bromides and iodides as traditional alkyl radical precursors remain intact under the reaction conditions (products **26** and **27**). Both unactivated alkenes and alkynes are tolerated in the allylation reaction (products **28** and **29**). Further screenings indicate that typical reactive groups on biomolecules do not interfere with the reaction, including unprotected alcohols, indoles, phenols, and carboxylic acids (products **30–33**), which suggest their potential biomolecular applications.

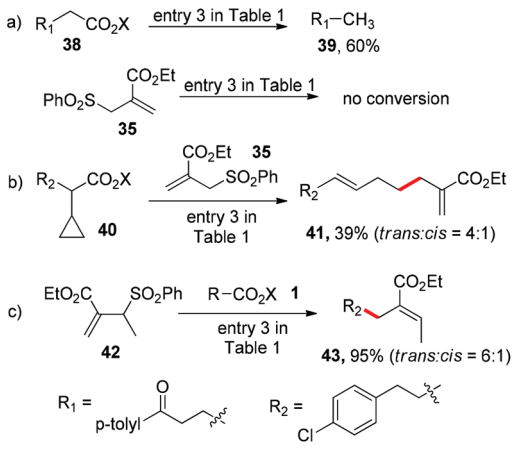


Scheme 1 Substrate scope and functional group compatibility of the decarboxylative allylation. Reaction conditions: entry 3 in Table 1. [a]3 equiv. of allyl sulfone was used.

With the excellent chemoselectivity and mild reaction conditions, we envision that this visible-light-induced decarboxylative allylation will be useful for biomolecular studies if neutral aqueous reaction conditions can be achieved.[8] The ascorbic acid is a mild water-soluble reductant suitable for biomolecular studies.[4g,9] We test the ascorbates in pH 7.4 PBS buffer (phosphate buffered saline) and observe the smooth allylation adduct **20** in 84% yield within 15 minutes (78% isolated yield, eqn (3)). Under aqueous conditions from pH 6 to 10 the allylations are all effective (ESI Table S1†). This allylation can be run very efficiently at as low as 100 μM of *N*-acyloxyphthalimide **34**, in which the allylation product **20** is obtained in 72% yield in less than 1 minute (eqn (3)). The aryl-substituted allyl sulfone **36** also reacts uneventfully to give the allyl product **37** in 86% yield in less than 1 minute at 100 μM concentrations, which is useful for time-sensitive applications where reaction kinetics as fast as minutes are required (eqn (4)).[10]



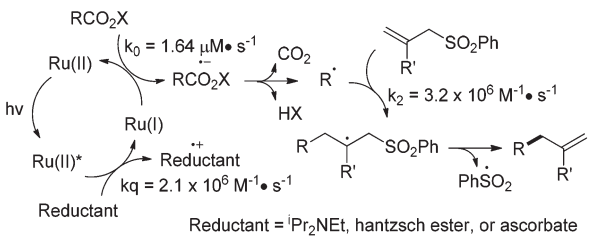
To gain mechanistic insights into this novel decarboxylative allylation, we carried out luminescence quenching experiments. A decrease in $[Ru(bpy)_3](PF_6)_2$ luminescence is observed in the presence of diisopropylethylamine, Hantzsch ester, or ascorbates, but not in the presence of *N*-acyloxyphthalimide or allyl sulfone (ESI Schemes S1–5†). This suggests the reductive quenching of the photoexcited $Ru(bpy)_3^{2+*}$ to the $Ru(bpy)_3^{+}$ intermediate.[11] We next tested if the alkyl radical or the allyl radical is generated under the photoredox conditions. The *N*-acyloxyphthalimide **38** is incubated under the reaction conditions without allyl sulfones and yields the decarboxylative hydrogenation product **39** in 60% yield (Scheme 2a). In contrast, the allyl sulfone **35** under the reaction conditions without *N*-acyloxyphthalimides results in no conversion,[12] which suggests the *N*-acyloxyphthalimide rather than the allyl sulfone as the single electron acceptor of the $Ru(bpy)_3^{+}$ intermediate. The radical clock *N*-acyloxyphthalimide **40** with allyl sulfone **35** afforded the alkene **41** in 39% yield (*trans* : *cis* = 4 : 1) after cyclopropyl ring opening, which further validates the alkyl radical intermediate (Scheme 2b). We also tested the methyl substituted allyl sulfone **42** with *N*-acyloxyphthalimide **1** and obtained trisubstituted alkene **43** in 95% yield (*trans* : *cis* = 6 : 1), whose regioselectivity suggests the alkyl radical addition to the alkene followed by sulfonyl radical elimination (Scheme 2c).



Scheme 2 Mechanistic investigations of the decarboxylative allylation.

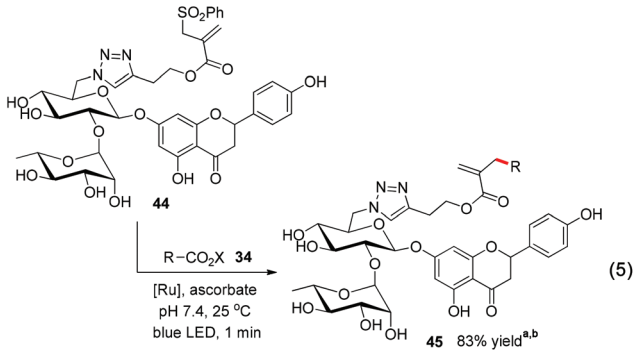
Based on the above mechanistic investigations, we propose that $Ru(bpy)_3^{2+}$ is photoexcited to $Ru(bpy)_3^{2+*}$ and reduced by diisopropylethylamine, Hantzsch ester, or ascorbates to $Ru(bpy)_3^{+}$ (Scheme 3).[11] The resulting $Ru(bpy)_3^{+}$ reduces *N*-acyloxyphthalimide *via* single electron transfer and generates the alkyl radical after decarboxylation and phthalimide elimination.[4] The alkyl radical undergoes addition to the allyl sulfone and yields the allylation adduct after desulfonation.

As the alkyl allylation reaction under aqueous conditions is exceptionally fast, we envision that the quantitative study of kinetic parameters is useful. The allylation reaction includes three elementary reaction processes: the single-electron-transfer between the photoexcited $Ru(bpy)_3^{2+*}$ and the ascorbate (k_q), the reductive decarboxylation to generate the alkyl radical (k_0), and the carbon–carbon bond-forming allylation (k_2) (Scheme 3). The electron transfer rate (k_q) from the ascorbate to the photoexcited $Ru(bpy)_3^{2+*}$ in pH 7.4 Tris buffer is obtained by measuring the fluorescence lifetime quenching at increasing ascorbate concentrations, and is determined by Stern–Volmer analysis to be 2.1×10^6 M^{-1} s^{-1} (ESI Scheme S9†).[13] The zero-order rate constant k_0 of the alkyl radical formation is measured by the consumption of *N*-acyloxyphthalimide **34** to be 1.64 μM s^{-1} (ESI Scheme S12†). The second-order carbon–carbon bond-forming rate constant of radical allylation k_2 is measured by the competition experiments with thiophenol-induced hydrogenation (k_H is 1.3×10^8 M^{-1} s^{-1}), and is determined to be 3.2×10^6 M^{-1} s^{-1} (ESI Scheme S15†).[14] The light-induced carbon–carbon bond-forming reactions have been widely used for light-modulated biomolecule manipulations,[3d,10c,d] which has the advantage of high temporal and spatial precision.[15] The use of visible light instead of UV light for this allylation imposes better biomolecular compatibilities and applications.[16]



Scheme 3 Mechanistic proposal of the decarboxylative allylation.

Finally, we tested if this chemoselective and fast decarboxylative allylation can be used for protecting-group-free modification of functional-group-rich complex molecules. We treated the oligosaccharide naringin conjugate **44** under the allylation conditions and gratifyingly obtained the allylation adduct **45** in 83% yield within 1 minute, with no detectable occurrence of a side reaction (eqn (5)).



(5)

[a]Reaction conditions: **44** (500 μM), **45** (100 μM), $Ru(bpy)_3Cl_2$ (10 μM), and ascorbates (1 mM) in 1:1 CH_3CN/aqueous buffer (20 mM pH 7.4 Tris) with blue LED irradiation for 1 min. [b]Conversions and yields were determined by HPLC analysis.

Conclusions

In conclusion, we have developed a visible-light-induced chemoselective and fast decarboxylative allylation for primary, secondary, tertiary, benzyl, and alpha-heteroatom-substituted $C(sp^3)$-allylations. This reaction is complete in minutes at room temperature and demonstrates excellent chemoselectivity in both organic solvents and neutral aqueous solutions. Further biomolecular application of this decarboxylative allylation is under investigation in our laboratory.

Acknowledgements

Financial support was provided by National Basic Research Program of China 2014CB910304, National Natural Science Foundation of China 21272260, 21472230, "Thousand Talents Program" Young Investigator Award, and start up fund from State Key Laboratory of Bioorganic and Natural Products Chemistry, and Chinese Academy of Sciences.

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