A photocatalytic regioselective hydroaminoalkylation of aryl-substituted alkenes with simple amines

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ABSTRACT: A photocatalytic method for the α-selective hydroaminoalkylation of cinnamate esters has been developed. The reaction involves the regioselective addition of α-aminoalkyl radicals generated from aniline derivatives or aliphatic amines to the α-position of unsaturated esters. The scope of aromatic alkenes was extended to styrenes undergoing hydroaminoalkylation with anti-Markovnikov selectivity, which confirms the importance of the aromatic group at the β-position. Simple scale-up is demonstrated under continuous flow conditions, highlighting the practicality of the method.

The addition of carbon-centred radicals to alkenes, besides its importance in polymer chemistry,[1] is also a powerful method for the formation of C-C bonds in small molecule synthesis.[2] In particular, radical conjugate addition reactions, commonly known as Giese reaction,[3] have received much attention. α-Aminoalkyl radicals,[4] consistently with the nucleophilic character imparted on them by the influence of the N lone pair, engage readily in Giese-type reactions.[4a, 5] Exploiting this reactivity, photocatalytic hydroaminoalkylation reactions of electron-poor alkenes have been described throughout the last decade.[4b,c,6,7] A variety of common photocatalysts are readily quenched reductively by tertiary amines giving place, after deprotonation, to α-aminoalkyl radicals, which go on to react with Michael acceptors such as maleimides,[8] alkylidene malonates and malononitriles,[9] α,β-unsaturated carbonyl compounds,[10] amides[11] and esters,[12] as well as alkenylpyridine derivatives,[13] providing straightforward access to densely functionalised structures. In addition, photocatalytic Giese-type reactions[14] have been described with α-aminoalkyl radicals generated by different methods, such as oxidative desilylation[15] or decarboxylation,[16] among others.[17]

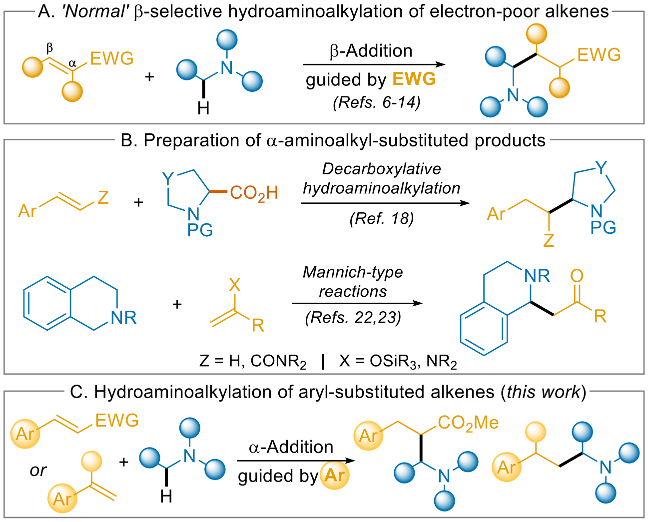
These transformations proceed generally with high regioselectivity for the β-position respect of the electron-withdrawing group (Figure 1a), consistent with an early transition state governed by the SOMO-LUMO orbital interaction. As a remarkable exception, Sparling observed α-selectivity in a photocatalytic decarboxylative radical addition to β-aryl α,β-unsaturated amides (Figure 1b).[18] The unusual selectivity in this case was attributed to a reversible radical addition, giving place under thermodynamic control to the more stable benzylic radical. However, this method was limited to decarboxylative generation of the α-aminoalkyl radical from α-amino acid substrates, which required a strongly oxidising catalyst for decarboxylation.[19]

Despite of these difficulties, a method for the direct aminoalkylation of α,β-unsaturated carboxylic acid derivatives would provide a practical, straightforward route for the preparation of β-amino acids, important pharmaceutical building blocks.[20] Moreover, this strategy may enable access to substitution patterns (β^2 and $\beta^{2,3}$) which are not easily accessible through more established routes.[21] Alternative photocatalytic methods for the preparation of β-amino carbonyl compounds from amines have been reported, based on Mannich-type reactions of photocatalytically generated iminium ions with silyl enol ethers[22] or with enamines generated *in situ* using enamine catalysis (Figure 1b).[23] However, these methods are limited to tetrahydroisoquinoline derivatives as the amine partner. A similar strategy for α-olefination of amines is similarly restricted to tetrahydroisoquinoline and tetrahydro-β-carbolines.[24]

In contrast with the well-established Giese-type addition to electron-poor alkenes, efficient photocatalytic hydroaminoalkylation of less polarised alkenes has not been reported to date.[25] This is possibly a consequence of poor chemoselectivity in the absence of a good matching or the nucleophilic radical with an electrophilic alkene, giving place to polymerisation side-reactions.[26]

During our recent investigation on photocatalytic transfer hydrogenation of cinnamate derivatives we found a kinetic preference for attack at the α-position in a H atom transfer from Hantzsch ester radical cation to the alkene.[27] Here we report a photocatalytic method for the α-selective hydroaminoalkylation of cinnamate esters based on the regioselective addition of α-aminoalkyl radicals, where the reaction is controlled by the presence of an aromatic group at the β-position. Moreover, our method is valid for the direct hydroaminoalkylation of styrenes, which proceeds with high anti-Markovnikov selectivity (Figure 1c).

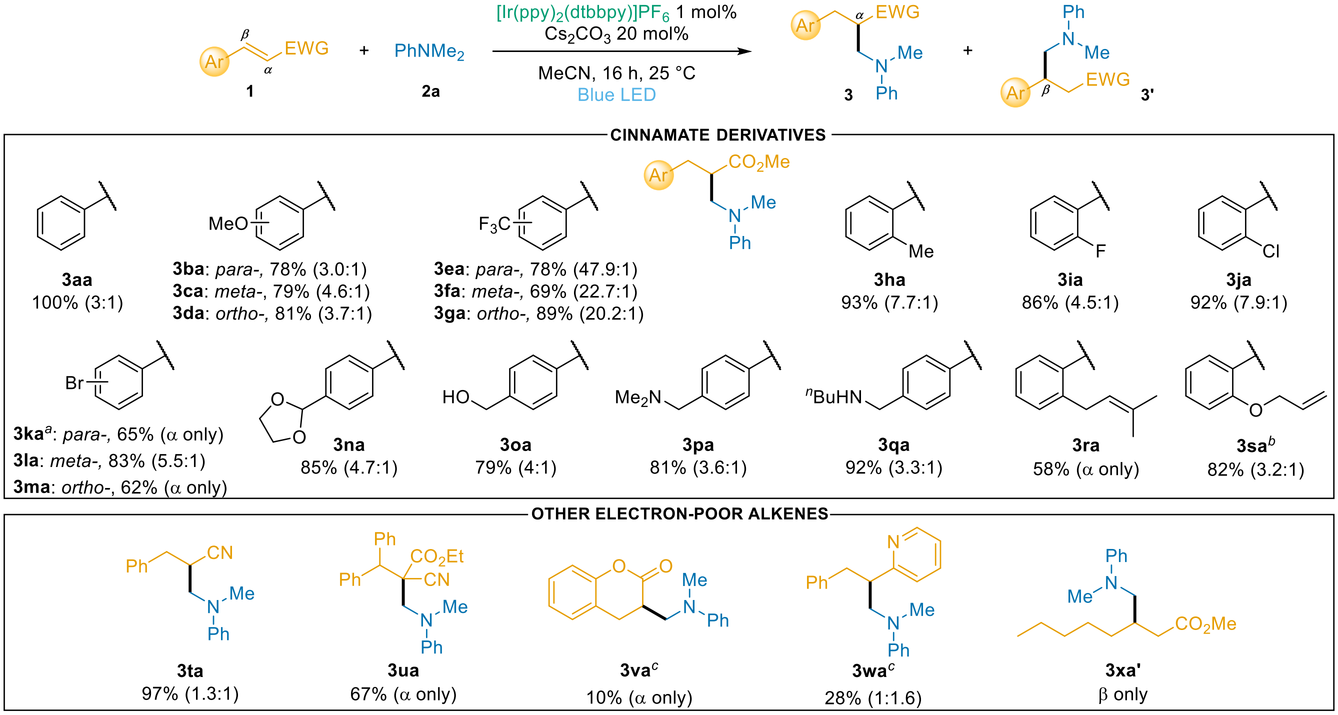
Figure 1. Summary of hydroaminoalkylation of electron-poor alkenes and related transformations.



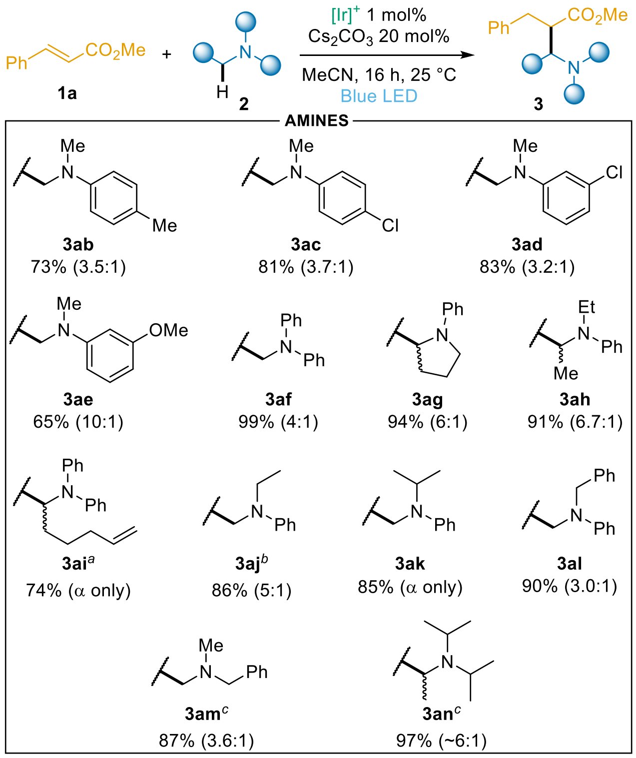
Irradiation with blue light of a MeCN solution of cinnamate ester **1a** and dimethylaniline **2a** (1.5 equiv) in the presence of photocatalyst [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%) and Cs$_2$CO$_3$ (20 mol%) resulted in quantitative formation of β-amino ester **3aa** and its γ-isomer in 3:1 ratio (Scheme 1), resulting in a preference for α-addition of the aminoalkyl radical. The use of the organic, soluble base DBU provided results comparable to Cs$_2$CO$_3$, as did the use of increased loadings of base. Other modifications to the reaction conditions resulted generally in decreased yields.[28]

To determine the scope of the reaction we first applied it to a range of cinnamate derivatives (Scheme 1). The presence of electron-donating MeO substituent on either position of the aryl ring was well tolerated, resulting in products **3ba-da** with yields ranging from 78 to 81% and regioselectivities between 3:1 and 4.6:1. Similarly, electron-withdrawing group CF$_3$ provided products **3ea-ga** in 69 to 81% yield and significantly increased 20:1 to 48:1 regioselectivity, always favouring the product of α-addition. In both cases the position of substitution had no apparent effect on the reaction, suggesting that steric hindrance was not very relevant. Consistently, *ortho*-Me substituted product **3ha** was also readily formed (93% yield, 7.7:1). Halogens were tolerated as well and led to increased regioselectivities compared to **3aa** (between 62 and 92% yield and 4.5:1 to quantitative regioselectivity for products **3ia** through **3ma**). These halogen substituents provide useful handles for further functionalisation of the products through metal-catalysed cross-couplings or photocatalytic transformations. Acetal-protected aldehyde **3na** could be obtained in 85% yield and 4.7:1 selectivity, offering further diversity of functionalities. Similarly, the reaction was compatible with the presence of benzylic alcohol, tertiary and even secondary amine (respectively: **3oa**, 79%, 4:1; **3pa**, 81%, 3.6:1; **3qa,** 92%, 3.3:1). Finally, the reaction worked in the presence of a dimethylallyl or an allyloxy substituents, leading to formation of products **3ra** (58%, α only) and **3sa** (82%, 3.2:1, starting from the *Z*-alkene) with no detectable reaction on the allyl groups. This suggests that the radical formed after addition rapidly reacts further to provide compound **3**.[29]

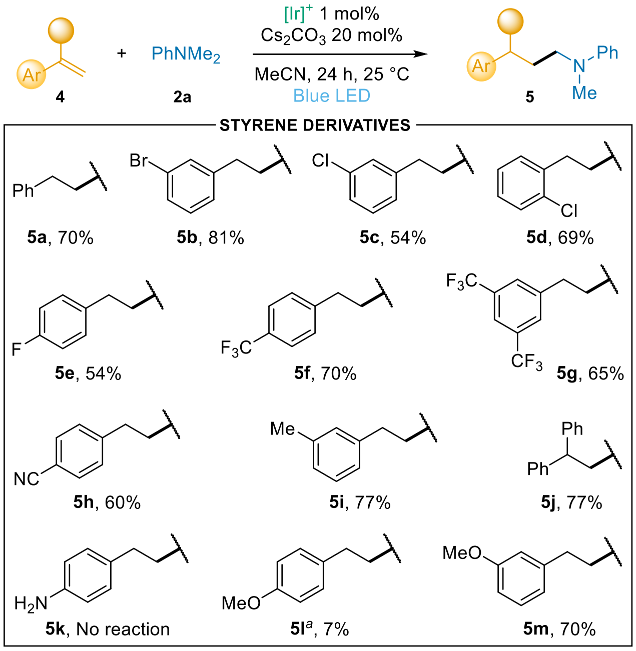
Cinnamonitrile was also a valid substrate for the reaction, although the corresponding product **3ta** was obtained with a very poor regioselectivity against its β-addition analogue (1.6:1). Product **3ua**, conversely, was obtained with complete regioselectivity in 67% yield from the corresponding tetrasubstituted



Scheme 1. Hydroaminomethylation of electron-poor alkenes (**1**) with *N*,*N*-dimethylaniline (**2a**). Reactions carried out with **1** (0.2 mmol), **2a** (1.5 equiv), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%) and Cs$_2$CO$_3$ (20 mol%) in MeCN (2 mL), under blue light irradiation for 16 h while controlling the temperature at 25 °C. Yields are of isolated product unless otherwise noted. Numbers in brackets are α to β ratio determined by ^{1}H NMR. [a] The ethyl ester was used in this case instead of methyl. [b] Starting material was the *Z*-alkene. [c] Yield determined by ^{1}H NMR using an internal standard.



Scheme 2. Hydroaminomethylation of methyl cinnamate (**1a**) with amines (**2**). Reaction conditions as in Scheme 1. $[Ir]^+ = [Ir(ppy)_2(dtbbpy)]PF_6$. [a] 0.2 mmol of **2** and 3 equiv. of **1a** were used. [b] Product was obtained as a 7:1 mixture of regioisomers. [c] Characterised as mixture of α/β.



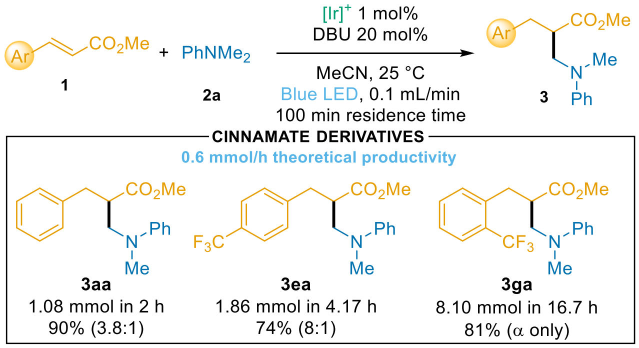
Scheme 3. Hydroaminomethylation of styrene derivatives (**4**) with *N*,*N*-dimethylaniline (**2a**). Reactions carried out with **4** (0.2 mmol), **2a** (2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%) and Cs_2CO_3 (20 mol%) in MeCN (8 mL), under blue light irradiation for 24 h while controlling the temperature at 25 °C. Yields are of isolated product. $[Ir]^+ = [Ir(ppy)_2(dtbbpy)]PF_6$. [a] Yield determined by ^1H NMR using an internal standard.

alkene. A cyclic α,β-unsaturated ester, coumarin, was transformed to **3va** regioselectively but in very low yield (12%), and 2-styrylpyridine gave **3wa** in low yield and selectivity, with a slight preference for the β-addition product (28%, 1:1.6). Finally, an α,β-unsaturated ester bearing only an aliphatic substituent reacted to give exclusively the β-addition product **3xa’**.

Then, we explored the reactivity of different amines (Scheme 2). The reaction proceeds well with substituted dimethylaniline derivatives (**3ab** to **3ae**) as well as with methyldiphenylamine (**3af**). *N*-phenylpyrrolidine and *N*,*N*-diethylaniline provided products **3ag** and **3ah** in excellent yields and regioselectivities (respectively: 94%, 6:1 and 91%, 6.7:1), although with no diastereoselectivity. Similar to above mentioned observations for products **3qa** and **3ra**, an alkene-substituted diphenylamine derivative resulted in formation of product **3ai** (74%, exclusive α) with no cyclisation of the pendant terminal alkene. Non-symmetrically substituted anilines tended to react at the position leading to the least stable radical. Thus, *N*-ethyl-*N*-methylaniline gave **3aj** (86%, 5:1 α:β ratio) as the major product, while *N*-methyl-*N*-isopropylaniline and *N*-methyl-*N*-benzylaniline gave **3ak** (85%, α only) and **3al** (90%, 3:1 α:β ratio), with no reaction observed at the isopropyl and benzyl substituents, respectively. Remarkably, the reaction was not limited to aniline derivatives: products **3am** and **3an** were readily obtained from their parent amines in good yields and selectivities (respectively: 87%, 3.6:1; 97%,~6:1).

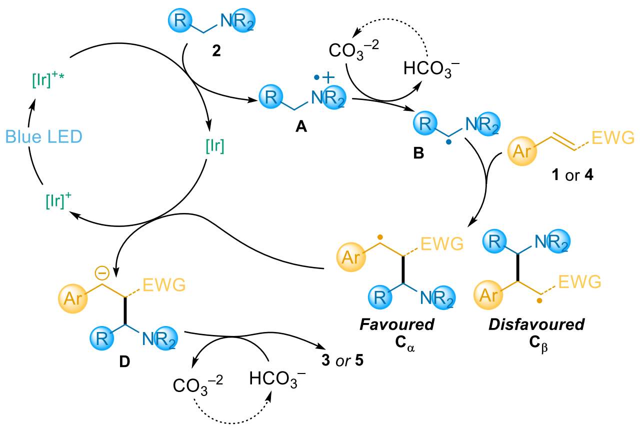
Finally, we explored the reactivity under our conditions of styrene derivatives, not bearing the electron-withdrawing group on the alkene (Scheme 3). Both styrene and a range of derivatives reacted smoothly with *N*,*N*-dimethylaniline to give the corresponding hydroaminomethylation products **5a-i** in good yields (54 to 81%) and with complete anti-Markovnikov regioselectivity.[30] Similarly, 1,1-diphenylethene provided product **5j** in 77% yield. It is worth noting that, while these examples show that an electron-withdrawing group directly bound to the alkene was not necessary, high electron density was still detrimental to the reaction: Thus, *p*-aminostyrene did not react and *p*-methoxystyrene provided only low yields of the product (**5k**, **5l**). A *m*-methoxy substituent, having an overall electron-withdrawing effect (Hammet $\sigma_m = +0.115$ *vs.* $\sigma_p = -0.268$), provided **5m** in 70% yield.

The simple conditions employed allowed for the straightforward translation into a readily scalable continuous flow method. Thus, a MeCN solution of alkene, amine and catalyst containing 20 mol% of DBU was pumped through a coil of PTFE tube which was illuminated with blue LEDs. The collected solution, after workup and purification, afforded the corresponding β-amino ester product. This method was applied, with excellent



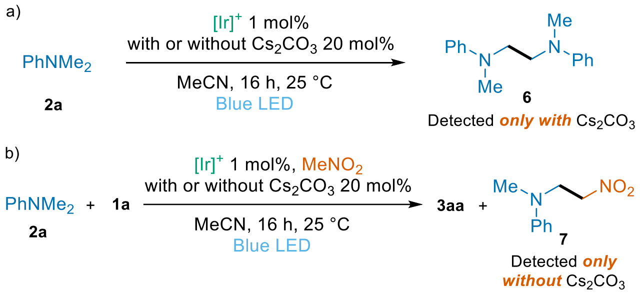
Scheme 4. Continuous-flow production of β-amino esters.

Figure 2. Plausible mechanism for the hydroaminoalkylation.



results, to the preparation of compounds **3aa**, **3ae** and **3ag** (Scheme 4).

A plausible mechanism for the reaction (Figure 2) would involve reductive quenching of the excited catalyst (E° Ir/*Ir$^+$ = 0.66 V) by amine **2** (E° **2**$^+$/**2** = 0.71 V) followed by deprotonation to form and aminoalkyl radical **B**,[31,32] which would then add across the alkene substrate (**1** or **4**) double bond. Reduction of the resulting benzylic radical $\mathbf{C}_\alpha$ followed by protonation would lead to product **3** or **5**. To probe this mechanism, we irradiated *N*,*N*-dimethylaniline **2a** under our standard reaction conditions in the absence of alkene, upon which we detected the formation of ethylenediamine **6** (Scheme 5a). The same reaction in the presence of nitromethane did not result in any observable formation of the nitromethane adduct **7** (Scheme 5b), which would be expected if oxidation of the amine to iminium occurred in any significant amount.[33] Conversely, analogous experiments in the absence of Cs_2CO_3 resulted, respectively, in no observable formation of **6** and detection of **7** with nitromethane.

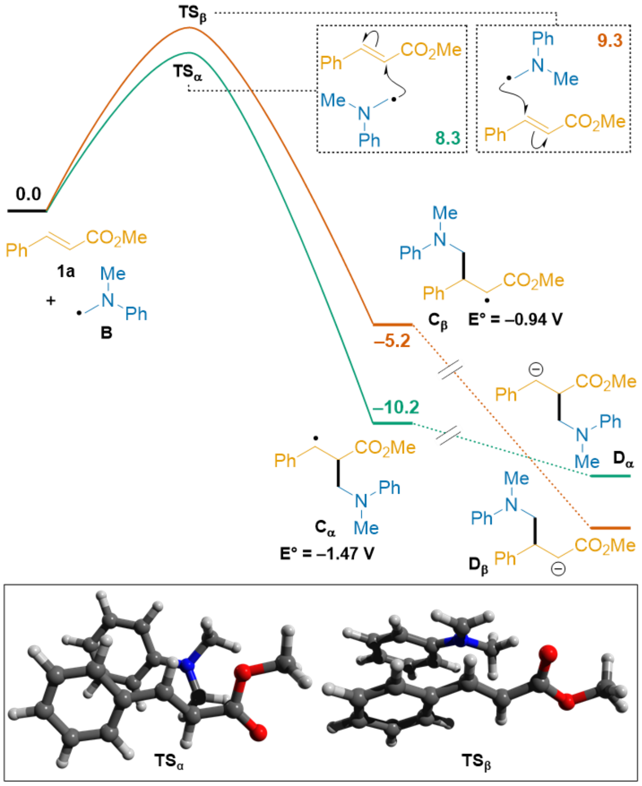


Scheme 5. Experiments for detection of aminoalkyl radical or iminium.

DFT calculations (PBE0-GD3/6-31+G(d,p), SMD model for MeCN, Figure 3) were also consistent with our mechanistic hypothesis: Transition states for the radical addition at positions α and β were both energetically accessible, with addition at α favoured by 1.0 kcal/mol, a small but significant difference consistent with the observed regioselectivity. Furthermore, the radical addition step was exergonic by −10.2 and −5.2 kcal/mol, respectively, for the α and β additions, and the calculated reduction potentials of the resulting benzylic or enol radical (−1.47 and −0.94 V) indicate an easy reduction to the corresponding anions by the reduced form of the catalyst (E^0 = −1.51 V vs. SCE).[32a] These observations, combined with the absence of cyclisation products in the reactions leading to compounds **3ra**, **3sa** and **3ai**, provide support for a kinetic control of regioselectivity rather than a reversible radical addition under thermodynamic control.

In conclusion, the methodology presented allows the hydroaminoalkylation of a wide variety of moderately electron-poor alkenes, including styrene derivatives, with aniline derivatives as well as aliphatic amines. Besides, the method is readily scalable under continuous flow conditions. Computational data suggest that the reaction is driven by the presence of the aromatic substituent, which controls reactivity and regioselectivity. An accurate balance between the aromatic substituent and the electron-withdrawing group are necessary for selectivity, with stronger EWGs leading to Giese-type addition, which will be of importance for the development of related regioselective methodologies further expanding the scope of these transformations.

Figure 3. DFT-calculated energy profile for the radical addition [PBE0-GD3/6-31+G(d,p), energies reported are Gibbs free energy in solution (SMD model for MeCN)].



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The manuscript was written through contributions of all authors.

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