Enantioselective Formal $\alpha$-Methylation and $\alpha$-Benzylation of Aldehydes by Means of Photo-organocatalysis

Giacomo Filippini, Mattia Silvi, and Paolo Melchiorre*

Abstract: Detailed herein is the photochemical organocatalytic enantioselective $\alpha$-alkylation of aldehydes with (phenylsulfonyl)alkyl iodides. The chemistry relies on the direct photoexcitation of enamines to trigger the formation of reactive carbon-centered radicals from iodosulfones, while the ground-state chiral enamines provide effective stereochemical control over the radical trapping process. The phenylsulfonyl moiety, acting as a redox auxiliary group, facilitates the generation of radicals. In addition, it can eventually be removed under mild reducing conditions to reveal methyl and benzyl groups.

The stereocontrolled $\alpha$-alkylation of carbonyl compounds using alkyl halides as electrophiles is a fundamental synthetic process to forge a new carbon–carbon bond while setting a stereogenic center.\[1\] While different chiral-auxiliary-based approaches are available,\[2\] developing effective asymmetric catalytic variants has proven difficult.\[3,4\] In addition to phase-transfer catalytic strategies,\[5\] the field of enantioselective organocatalyst catalysis\[6\] has recently provided some solutions for the direct $\alpha$-alkylation of unmodified aldehydes with organic halides. A few examples of $S_{\theta}2$-type alkylation have been reported,\[7\] while most methods have combined enamine catalysis with cationic ($S_{\theta}1$-type)\[8\] or radical reaction pathways.\[9\] Despite this progress, catalytic protocols for stereoselectively introducing either an alkyl or benzyl group at the $\alpha$-position of aldehydes remain rare (Figure 1a). While a single example of formal $\alpha$-methylation by an $S_{\theta}1$ pathway has been reported,\[10\] direct $\alpha$-benzylation methods generally require highly electron-poor benzyl bromides to facilitate the generation of radical intermediates upon single-electron transfer (SET) reduction.\[10,11\] A stereocontrolled $S_{\theta}2$ polar manifold for the alkylation of enamines with benzyl bromide was recently shown to be feasible,\[11\] but this chemistry could only be applied to $\alpha$-branched aldehydes to afford exclusively quaternized products. The paucity of methodologies for the catalytic enantioselective $\alpha$-methylation and $\alpha$-benzylation of aldehydes stands in sharp contrast to the prominence of these stereogenic units. Indeed, they are common motifs in medicinal agents, agrochemicals, and natural product isolates.\[12\] In particular, methylation is a fundamental process in medicinal chemistry, since introducing this small alkyl fragment can strongly modulate a molecule’s biological and physical properties.\[13\]

Herein, we report a simple photochemical organocatalytic method to install either a methyl or a benzyl moiety onto simple aldehydes with high stereoselectivity. The chemistry exploits the ability of chiral enamines (I) to directly reach an electronically excited state upon light absorption\[14\] and then generate carbon-centered radicals (II) by SET reduction of the (phenylsulfonyl)alkyl iodides 2 (Figure 1b). At the same time, the ground-state chiral enamines (I) provide effective stereochemical control over the enantioselective radical-trapping process. The resulting (phenylsulfonyl)alkylated...
intermediates 3 are then easily desulfonylated to reach the target products.

In implementing the α-alkylation of aldehydes with α-iodosulfones (2), we were inspired by our recent studies on the direct photoexcitation of enamines and their potential for generating radicals under mild reaction conditions. We demonstrated that I, upon light absorption, can reach an excited state (I*) to become a strong reductant, as implied by its reduction potential, which was estimated as about −2.0 V (vs. Ag/Ag⁺ in CH₂CN). Thus, I* could trigger the formation of radicals through SET reduction of easily reducible bromomalonates (E⁻ red diethyl bromomalonate = −1.69 V vs. Ag/Ag⁺ in CH₂CN). We surmised that a similar photochemical mechanism could generate (phenylsulfonyl)alkyl radicals (II) from 2. A critical design element was the phenylsulfonyl moiety, which would act as a redox auxiliary group to facilitate the reductive cleavage of the C–I bond by an SET mechanism (Figure 1b). In consonance with this scenario, we measured, by cyclic voltammetry, a reduction potential for the iodomethyl phenyl sulfone (2a: Y = H in Figure 1b) as low as −1.49 V (E⁻ red vs. Ag/Ag⁺ in CH₂CN). This experiment suggested 2a as a viable precursor of phenylsulfonyl methyl radicals.

To test the feasibility of our design plan, we focused on the reaction between butanal (1a) and 2a (Table 1). The experi-

ments were conducted at 5 °C in toluene and under irradiation by a single black-light-emitting diode (black LED, λ_max = 365 nm). When adding the chiral secondary amine catalyst A (20 mol %), the desired (phenylsulfonyl)methylated aldehyde 3a was formed in good enantioselectivity but with moderate chemical yield (entry 1). Despite extensive experimentation, we could not increase the yield of the photochemical alkylation, which reached a standoff at about 40% of conversion and could not evolve further. A useful insight into tackling this reactivity issue came from the optical absorption spectra of the reaction components, and confirmed our expectation that I, generated upon condensation of the catalyst A with 1a, could absorb up to the visible region (blue line in Figure 2a; absorption band up to λ = 415 nm). In addition, we noticed that 2a could also absorb light up to λ = 390 nm (red line). This observation prompted us to investigate the photochemical stability of 2a under the reaction conditions by irradiating a toluene solution of 2a at λ = 365 nm over 16 hours. The colorless solution developed a yellow color over time (Figures 2b and ii). Although we recovered 95% of 2a, the color change suggested the possibility of a photoinduced homolytic cleavage of the C–I bond within 2a, a minor pathway which could generate small amounts of intensely colored molecular iodine (2I⁻→I₂). Diiodine, even in traces, is a well-known inhibitor of radical-chain reactions, as it can trap carbon-centered radicals at very high rates (rate constants of about 10⁸ M⁻¹·s⁻¹). In addition, the intense light absorption of molecular iodine may also interfere with other photochemical steps by an inner filter effect. A positive standard iodine detection test confirmed the generation of I₂ from 2a under the reaction conditions, adding a starch solution, sodium iodide, and water to the photoalyzed yellow solution of 2a, depicted in Figure 2bii, produced the characteristic dark-blue color (Figure 2biii). Finally, the solution switched back to achromatic (Figure 2biv) when adding solid sodium thiosulfate.
(Na₂S₂O₃, E°ₚ ≈ 0.28 vs. Ag/Ag⁺ in H₂O),[18] which can easily reduce I₂ to iodide (Figure 2d). To evaluate if the presence of iodine could be detrimental for the photo-organocatalytic process, we performed the model reaction by adding I₂ (10 mol%), and it resulted in a profoundly reduced reactivity (Table 1, entry 2).

On the basis of these results, we sought to implement reaction conditions which could remove any trace of diiodine. Adding solid Na₂S₂O₃ (10 mol%) to the reaction mixture increased the yield of 3a (50%; Table 1, entry 3). Further optimizations revealed that using a toluene/hexanes/water solvent mixture (1:1:2 ratio) and adding 50 mol% of Na₂S₂O₃ led to the formation of 3a in high yield with good enantioselectivity (76% yield of the isolated 3a, 80% ee; entry 4).

Control experiments were conducted to obtain more mechanistic clues. Carefully excluding light completely suppressed the process (Table 1, entry 5). Reactivity was also inhibited under an aerobic atmosphere and in the presence of TEMPO (1 equiv; entry 6). Performing the reaction using a 300 W Xenon lamp equipped with a band-pass filter at λ = 400 nm (entry 7) did not alter the overall reactivity of the model reaction. Since 1 is the only photoabsorbing compound at λ = 400 nm, the experiment indicates that the direct photoexcitation of the enamine triggers the radical generation from 2a. On the basis of these observations, we propose the mechanism depicted in Figure 3. The photoexcited enamine Ia* induces the reductive cleavage of the C–I bond in 2a by SET, which affords the electrophilic radical IIa. The ground-state chiral enamine Ia then traps IIa in a stereocontrolled fashion. Considering the redox properties of the resulting α-amino radical III (E°/IV estimated to be ca. −0.95 V vs. Ag/Ag⁺ in CH₃CN),[19] which make it incapable of reducing 2a by SET (E°ₚ of 2a = −1.49 V vs. Ag/Ag⁺ in CH₃CN), and according to the tendency of α-aminoalkyl radicals toward halogen abstraction,[19] we propose that III abstracts an iodine atom from 2a, thereby regenerating IIa. The resulting adduct IV is not stable and evolves to an iodine/iminium ion pair (V), which eventually hydrolyzes to release 3a and A. Overall, the chemistry can be considered an example of an enantioselective catalytic atom-transfer radical addition (ATRA).[20] In consonance with the classical ATRA mechanism, the present reaction proceeds through a self-propagating radical chain initiated by the photochemical activity of the enamines, which feeds in radicals from outside the chain. This scenario is congruent with the quantum yield (Φ) of 3.9 measured for the model reaction (λ = 400 nm in CH₃CN, using potassium ferrioxalate as the actinometer). In addition, it well explains the striking effect of diiodine, which is a powerful inhibitor of iodine atom transfer chains.[17]

Using the optimized reaction conditions described in entry 4 of Table 1, we then demonstrated that our (phenylsulfonyl)methylation reaction (Figure 4a) is quite general in scope with respect to the aldehyde component. It could satisfactorily tolerate aldehydes bearing either long alkyl fragments or of significant steric bulk, a terminal olefin, and heteroatom moieties (Figure 4b). These experiments afforded chiral aldehyde products which were isolated as the corresponding alcohols 4a–j after in situ NaBH₄ reduction in moderate to high yield and enantiomeric excess. We could also install substituents other than phenyl at the sulfone
moiety, since α-iodosulfones containing either a tosyl or a mesyl group actively participated in the enantioselective alkylation, leading to the products 4k and 4l, respectively (Figure 4c).

The main goal of our studies was to provide an efficient method for stereoselectively installing a methyl group, and we used the synthetic versatility of the phenylsulfonyl moiety for this purpose. Desulfonylation of 4c and 4h was easily achieved under reducing conditions (Mg in MeOH) to unveil the methyl group and afford the desired adducts 5c and 5h, respectively, without eroding the enantiomeric purity (Figure 4d). To infer the (S) absolute configuration of 2-methyloctan-1-ol (5e), we compared it with the optical rotation value reported in literature.[10]

We then evaluated the possibility of applying our strategy to the α-aryl-substituted iodosulfones 2 (Figure 5a), to develop a formal α-benzylation of aldehydes. A new cycle of optimization revealed that using a para-fluoro phenyl substituent at the sulfone moiety along with a different solvent mixture (CH₂Cl₂/H₂O 1:1) was essential for reactivity, thus leading to the corresponding derivatives 6a–e in moderately yield but with high enantiocontrol (Figure 5b). The low diastereoselectivity generally observed did not affect the overall process, since this stereochemical information is erased upon desulfonylation. Indeed, 6a (mixture of two diastereoisomers) was transformed into the corresponding enantioenriched benzylated derivative 7a in good yield and high enantioselectivity using samarium iodide as a reducing agent (Figure 5c). As detailed in Sections D1 and D2 of the Supporting Information, the majority of products 4 and 6 have been successfully desulfonylated under reducing conditions using either magnesium- or samarium-based methods.

In summary, we have reported a photochemical strategy for the enantioselective catalytic formal α-methylation and α-benzylation of aldehydes. This two-step method uses mild reactions conditions and easily available substrates and catalysts to provide compounds which are difficult to synthesize with other catalytic approaches. The chemistry exploits the phenylsulfonyl moiety within the radical precursor 2, which facilitates the generation of open-shell species acting as a redox auxiliary group, while unveiling the methyl and benzyl groups upon easy desulfonylation of the alkylation products. Key for reaction development was also the ability of chiral enamines to generate radicals upon light excitation and then trap them in a sterecontrolled fashion.

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Conflict of interest

The authors declare no conflict of interest.

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