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## Introduction

For decades, carbon-centered radicals have found extensive use as valuable reactive intermediates in organic synthesis.<sup>1</sup> In particular, radical difunctionalizations of simple alkenes have emerged as powerful tools for preparing functionalized skeletons.<sup>2</sup> Various alkyl radical precursors have been successfully used for alkene functionalization, such as cyclic ethers,<sup>3</sup> amides,<sup>4</sup>  $\alpha$ -bromo esters,<sup>5</sup> diazo compounds,<sup>6</sup> alkoxyamines,<sup>7</sup> unactivated ketones<sup>8</sup> or aliphatic alcohols<sup>9</sup> – just to mention a few. In most of these alkene difunctionalizations, an additional reagent to trap the transient adduct C-radical has to be added, decreasing atom economy. In that regard, bifunctional reagents providing the C-radical and also the trapping moiety would be beneficial.<sup>10</sup> For example, this was realized for thermal alkoxyamine addition reactions<sup>7</sup> and also in atom as well as group transfer additions.<sup>2a,7,11,12</sup>

Recently, we developed a mild photomediated radical 1,2-difunctionalization of various electron-poor alkenes with  $\alpha$ -acetoxy nitrosoalkanes as bifunctional reagents (Scheme 1a).<sup>13</sup> In analogy to the Barton nitrite ester reaction<sup>14</sup> that involves the homolytic O-NO bond cleavage of a nitrite ester to generate an alkoxy radical and the persistent nitric oxide radical (NO), we used the visible light induced homolytic C-NO bond cleavage of acyloxy nitroso compounds to generate a transient C radical and the persistent NO radical. The electron-rich  $\alpha$ -oxy-C radical undergoes radical addition to an electrophilic alkene to give a transient adduct C-radical.<sup>13</sup> Persistent radical effect (PRE)<sup>15</sup>

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany. E-mail: studer@uni-muenster.de

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## Azodioxy compounds as precursors for C-radicals and their application in thermal styrene difunctionalization†

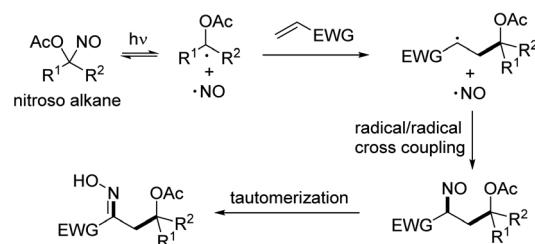
Stefanie Plöger, Christian Mück-Lichtenfeld, Constantin G. Daniliuc and Armido Studer \*

An atom-economic thermal  $\alpha,\beta$ -difunctionalization of various styrenes with readily prepared azodioxy compounds is reported. Mechanistic studies reveal that the starting azodioxy compounds can thermally be cleaved to the corresponding C-nitroso compounds, which under these thermal conditions further homolyze to generate reactive C-radicals along with the persistent NO radical. In the presence of a styrene, C-radical addition with subsequent nitrosylation followed by tautomerization is occurring, resulting in an overall styrene  $\beta$ -alkylation- $\alpha$ -oximation reaction.

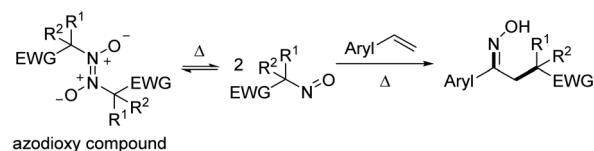
mediated highly selective cross-coupling of the NO radical with the adduct C-radical eventually provides the corresponding nitrosoalkane, which upon tautomerization leads to the final oxime product.

Notably, C-nitroso compounds were intensively studied due to their interesting reactivity and important bioactivity.<sup>16</sup> However, their synthetic utility in chemistry has so far mostly been limited to the role as C radical acceptors.<sup>17</sup> Nonetheless, we demonstrated in this initial study their promising potential as C-radical precursors.<sup>13</sup> However, it is well established that the majority of the C-nitroso compounds are not stable in solution and dimerize to the corresponding azodioxy compounds.<sup>18</sup> Unfortunately, in contrast to the monomeric blue nitroso

a) Photomediated radical coupling of  $\alpha$ -acetoxy nitroso alkanes with Michael-type acceptors involving nucleophilic C-radicals (ref. 13)



b) Azodioxy compounds as C-radical precursors for thermal  $\beta$ -alkyl- $\alpha$ -oximation of styrenes involving electrophilic C-radicals (this work)



Scheme 1 Use of C-nitroso compounds as bifunctional reagents for radical alkene 1,2-difunctionalization.



compounds, the dimers are generally transparent and show no photoactivity upon irradiation with visible light. We therefore decided to develop an alternative entry into C-nitroso radical chemistry that uses the azodioxy dimers as the C-radical precursors applying thermal conditions. Moreover, the reported photochemical approach allowed to generate exclusively nucleophilic  $\alpha$ -acetoxy alkyl radicals, while electrophilic C-radicals are not accessible using that strategy. The concept is presented in Scheme 1b.

The azodioxy dimer should be thermally reversibly cleaved to the corresponding monomeric nitroso compound which then engages in a thermal homolytic cleavage of the C-NO bond to generate the corresponding electron-deficient C-radical along with the NO radical. As in the photochemical process, C-radical addition to an alkene, subsequent trapping of the adduct radical with NO and tautomerization should eventually provide the corresponding 1,2-difunctionalized products. Herein, we report the realization of that strategy and show that azodioxy compounds react with styrenes to the targeted oximes. DFT calculations provide further insights into the process.

## Results and discussion

Initial experiments were conducted with the azodioxy compound **1a** and styrene **2a** in DMF. For details on the preparation of all azodioxy compounds used in this study, see ESI.† While no product formation could be observed at room temperature (Table 1, entry 1), we were delighted to see that at 100 °C for 3.5 h, 1,2-difunctionalization proceeded smoothly. We found that the targeted oxime further cyclizes to the dihydro-1,2-oxazine **3a** which was isolated in 53% yield as a 3 : 1-mixture of diastereoisomers (Table 1, entry 2). Of note, the temperature necessary for successful transformation is readily monitored by the

Table 1 Thermal reaction of **1a** with **2a** – optimization studies

| Entry <sup>a</sup> | Solvent | Temp. [°C] | Yield <sup>b</sup> [%] |
|--------------------|---------|------------|------------------------|
| 1                  | DMF     | r.t.       | n.d.                   |
| 2                  | DMF     | 100        | 53                     |
| 3                  | DMF     | 60         | 60                     |
| 4                  | DMSO    | 60         | 66                     |
| 5                  | Acetone | 60         | n.d.                   |
| 6                  | MeOH    | 60         | 32                     |
| 7 <sup>c</sup>     | DMSO    | 60         | 73                     |
| 8 <sup>c,d</sup>   | DMSO    | 60         | 44                     |

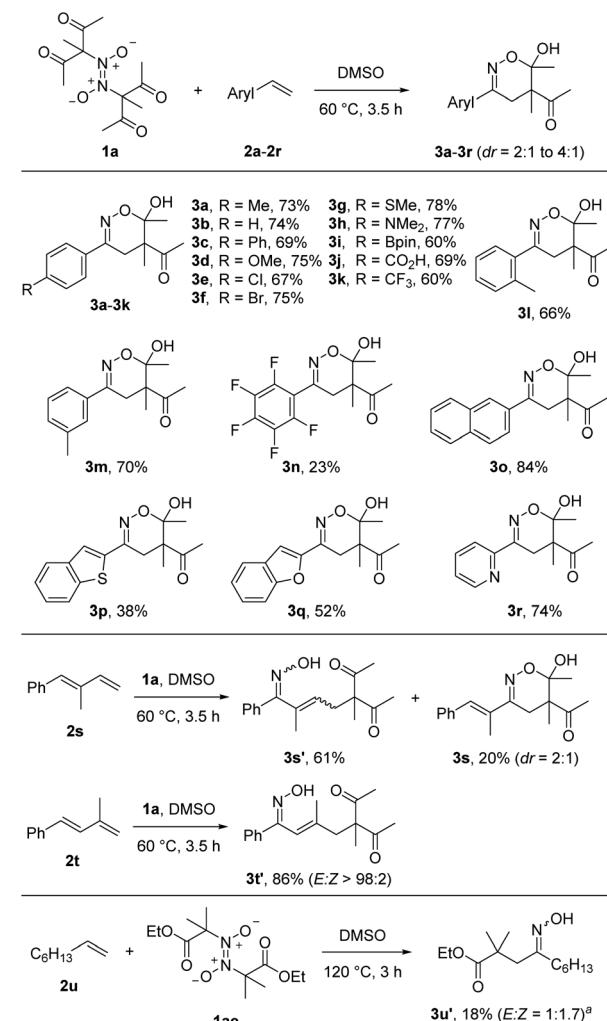
<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2b** (0.6 mmol), solvent (2 mL), Ar, **1a** was added in three portions every 30 min. <sup>b</sup> Yield of isolated product.

<sup>c</sup> **1a** was added in six portions every 30 min. <sup>d</sup> Reaction was conducted open to air.

appearance of the typical blue color of the corresponding monomeric C-nitroso compound and a slightly better yield (60%) was obtained upon running the reaction at 60 °C (Table 1, entry 3). Solvent screening revealed that in DMSO the yield further increased to 66%, while worse results were achieved in acetone and MeOH (Table 1, entries 4–6).

The yield could be further increased (73%) by keeping the concentration of the azodioxy compound and accordingly also the nitrosoalkane concentration low upon adding **1a** in six portions every 30 min (Table 1, entry 7). Unfortunately, the use of syringe pump technique to keep the nitroso-compound concentration even lower was not feasible, since **1a** is insoluble in DMSO at room temperature. Exclusion of air is beneficial, as running the reaction under air atmosphere led to a decreased yield of 44% (Table 1, entry 8).

With the optimized reaction conditions in hand, we varied the radical acceptor keeping azodioxy **1a** as the bifunctional reagent (Scheme 2). We were pleased to see that along with styrene (**3b**) various *para*-substituted styrenes engaged in the 1,2-difunctionalization. Not only electron-donating



Scheme 2 Variation of the radical acceptor 2. <sup>a</sup> 40 equiv. of the alkene **2u** were used.



substituents (**3c**, **3d**, **3g**, **3h**) but also halogen atoms (**3e**, **3f**) and electron-withdrawing functional groups (**3k**) were tolerated as *para*-substituents providing the corresponding products in 60–78% yields. Notably, a free carboxylic acid functionality (**3j**) and the synthetically valuable Bpin-moiety (**3i**) were also tolerated. As expected, with the most electron-deficient 2,3,4,5,6-pentafluorostyrene the lowest yield was obtained (**3n**, 23%), indicating the relevance of polar effects considering the electrophilicity of the C-radical derived from **1a**. Steric effects at the aryl moiety are not of importance, as the *ortho*-tolyl derivative provided a good yield (**3l**, 66%). The *meta*-congener afforded a similar result (**3m**, 70%). Naphthalene and heteroarene based systems could also be used as radical acceptors and the desired products **3o**–**3r** were obtained in moderate to good yields (38–84%). Interestingly, conjugated dienes **2s** and **2t** also

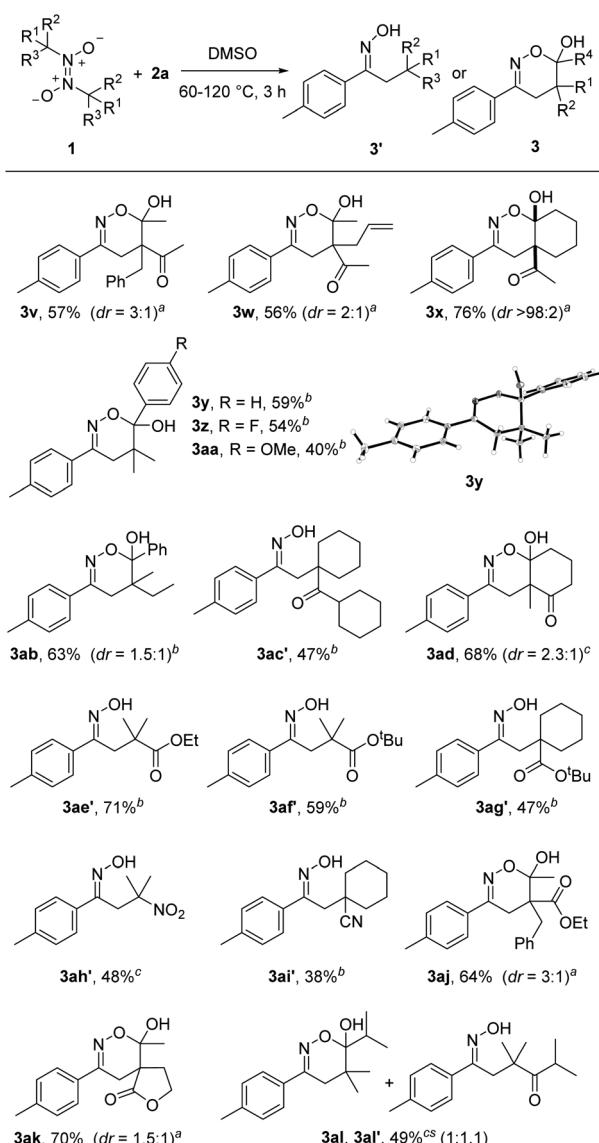
serve as coupling partners. In the case of **2s**, a 3 : 1 mixture of the two regioisomers resulting from the 1,4-difunctionalization (**3s'**, 3 isomers, see ESI†) and the 1,2-difunctionalization (**3s**) were formed in 81% overall yield. In contrast, the diene **2t** with a methyl group at the 2-position provided exclusively the 1,4-difunctionalization product **3t'** in 86% yield with complete *E*-selectivity. For non-activated aliphatic alkenes, the C-radical addition is slow so that direct trapping with NO competes. Indeed, reaction of **1a** with 1-octene (**2u**) under the optimized condition did not work. However, C-radical precursor **1ae** with **2u** provided the desired compound, albeit in low yield (**3u'**, 18%). In this case, **1ae** was added *via* syringe pump to keep the NO concentration low.

Switching back to styrene **2a** as radical acceptor, we next tested various azodioxy compounds **1** as radical precursors. The methyl group in **1a** could be replaced by a benzyl (**3v**) and allyl (**3w**) substituent and the targeted products were isolated in 56% and 57% yield with moderate diastereoselectivities (*dr* = 3 : 1). Along with the acetylacetone derivatives other 1,3-diketones engaged in the 1,2-difunctionalization. As an example, **3x** was obtained in 67% yield with complete diastereoselectivity.

The doubly activating 1,3-diketo moiety in the C-radical is not required and azodioxy compounds leading to  $\alpha$ -monoketo-C-radicals also worked, as documented by the successful preparation of the dihydro-1,2-oxazines **3y**–**3aa** (40–59%). In this series, the lowest yield was noted for the azodioxy compound leading to the more electron-rich *para*-MeO-phenyl-keto C-radical. The structure of **3y** was confirmed by single-crystal X-ray diffraction analysis (see Scheme 3).<sup>19</sup> Similar results were noted for other “mono ketones” (see **3ab**, **3ac'** and **3al**, **3al'**). Interestingly, the keto functionality in **3ac'** is obviously sterically too shielded and cyclization to the corresponding dihydro-1,2-oxazine did not occur, while for **3al** a mixture of the cyclized/non-cyclized forms was isolated. The azodioxy compound derived from 2-methylcyclohexane-1,3-dione participated in the reaction to give the annulated oxazine **3ad** in 68% yield.

Pleasingly, along with the  $\alpha$ -keto C-radicals, other electrophilic radicals could be generated using this novel strategy. Thus,  $\alpha$ -ester radicals are accessible and the reaction with **2a** provided the *N*-hydroximinoesters **3ae'** (71%), **3af'** (59%) and **3ag'** (47%). For the esters, cyclization did not occur and oximes were isolated as products. The scope could be further expanded by the successful implementation of  $\alpha$ -nitroalkyl and  $\alpha$ -cyanoalkyl radicals. As examples,  $\beta$ -nitrooxime **3ah'** (48%) and nitrileoxime **3ai'** (38%) were prepared, albeit in slightly lower yields. Moreover,  $\beta$ -ketoester  $\alpha$ -C-radicals (**3aj**, 64%) and  $\beta$ -ketolactone radicals (**3ak**, 70%) could be thermally generated from the corresponding azodioxy compounds, further broaden the versatility of the herein presented method.

To testify the practicality of the method, the dihydro-1,2-oxazine **3c** and the oxime **3ae'** were prepared on a 7 mmol scale without compromising the yield (Scheme 4a). We also investigated the follow-up chemistry using **3c** and **3ae'** as model substrates to document the synthetic value of our products (Scheme 4b). The oxime functionality of **3ae'** could be reduced to a primary amine with zinc in acetic acid. Subsequent *N*-acetylation gave the *N*-protected  $\gamma$ -amino acid ester **4** in 58%



**Scheme 3** Variation of the azodioxy compound. <sup>a</sup>The reaction was conducted at 60 °C. <sup>b</sup>The reaction was conducted at 120 °C. <sup>c</sup>The reaction was conducted at 80 °C.



overall yield. Since N-heterocycles are important structures for pharmaceuticals,<sup>20</sup> the 5,6-dihydro-1,2-oxazine **3c** was reduced with NaCNBH<sub>3</sub> to obtain the *N*-hydroxy pyrroline **5** in 49% yield as a mixture of diastereoisomers (see ESI†). This reaction proceeds *via* oxime reduction to the corresponding hydroxylamine, that cyclizes to give the intermediate nitrone which eventually gets reduced to the hydroxyl amine. The remaining keto functionality gets also reduced. Hydrolysis of the oxime functionality in **3c** afforded the triketone **6** in 68% yield.

We observed a clean migration of one acetyl group to the oxime group upon heating of the hemiacetal **3c** in DMF to 150 °C for 90 min. The *O*-acetyl oxime **7a** was isolated in 74%

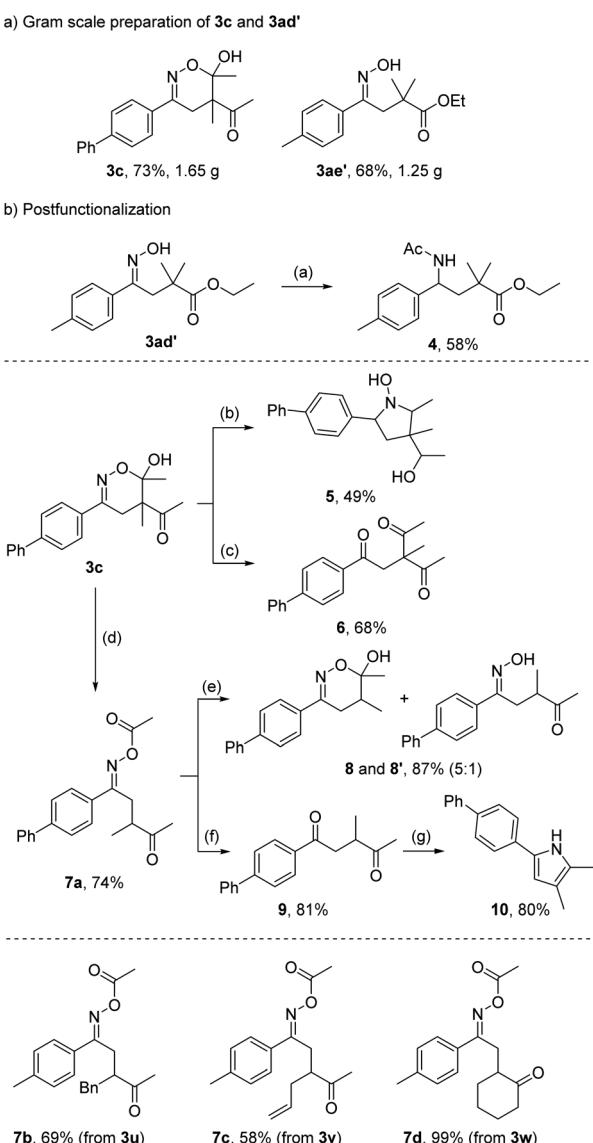
yield. In analogy, oxime esters **7b**–**7d** were obtained in good to excellent yields from the corresponding dihydro-1,2-oxazines. Importantly, the acetyl migration leading to compounds **7a**–**7d** represents a valuable transformation since it formally allows to add secondary C-radicals onto radical acceptors *via* the C-nitroso approach. The direct implementation of secondary alkyl-nitroso compounds is impossible, because immediate tautomerization to the corresponding oximes would take place and the oximes do not show any activity as C-radical precursors. The equilibrium lies entirely – or at least almost exclusively – on the side of the oxime.<sup>18b,21</sup> Accordingly, the installation of the acetyl group not only activates the nitroso compound but also prevents as a temporal protecting group its unwanted tautomerization.

Cleavage of the acetyl group in **7a** led to a mixture of 5,6-dihydro-1,2-oxazine **8** and the corresponding uncyclized oxime **8'** in high combined yield (87%). Acetyl removal and subsequent hydrolysis of the oxime functionality afforded the 1,4-diketone **9** (81%) which could be further converted in a Paal–Knorr reaction with ammonium acetate to pyrrole **10** (80%).

To show that azodioxy compounds of type **1** serve as thermal C-radical precursors, a probe experiment was conducted. Reaction of **1a** with vinyl cyclopropane **2v** provided the ring-opened  $\beta,\gamma$ -unsaturated oxime **11** in 49% yield, supporting the presence of radical intermediates (Scheme 5). We also tested whether the azodioxy **1a** can be photochemically activated. However, irradiation of **1a** in the presence of **2a** at room temperature with white LEDs did not lead to any 1,2-difunctionalization product **3a**. Moreover, at 60 °C white LEDs did not show a measurable effect on the rate and yield of the transformation.

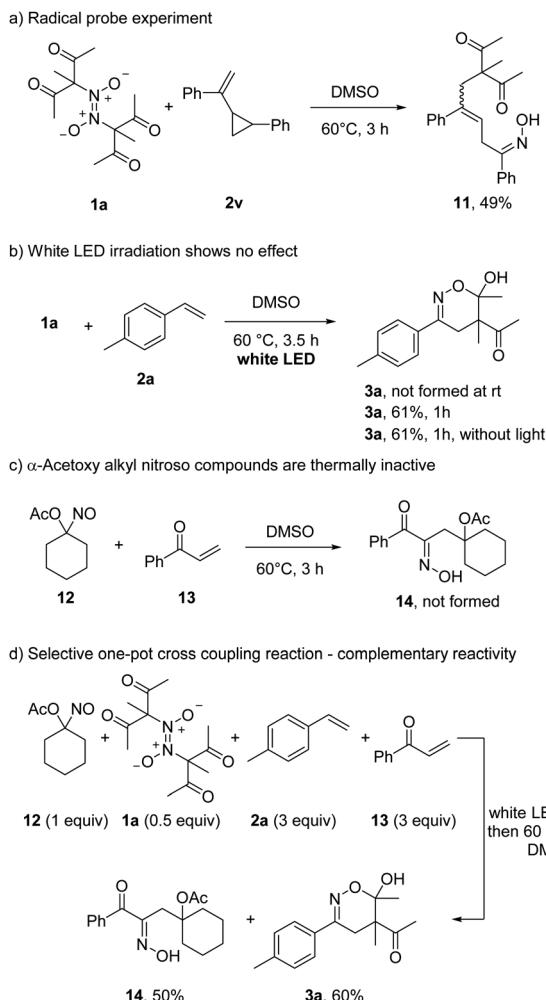
Comparing the herein presented reaction with the visible light induced radical coupling of  $\alpha$ -acyloxy alkyl nitroso compounds,<sup>13</sup> the homolytic C–NO cleavage of electron-deficient C-nitroso compounds occurs thermally. Surprisingly, the acetoxy C-nitroso compound **12** did not react thermally with phenyl vinyl ketone (**13**). Even at 120 °C, the targeted oxime **14** was not formed (not shown). Thus, while electrophilic C-radicals are accessible upon thermal treatment of *in situ* generated C-nitroso compounds, the  $\alpha$ -acetoxy alkyl nitroso congeners (stable in the monomeric form) leading to nucleophilic C-radicals do not engage in thermal C–NO bond homolysis. This surprising observation allowed us to run a self-sorting process where 4 different reaction components are mixed and pairwise selectively addressed depending on the reaction conditions chosen. Hence, a mixture of **12**, **1a**, **2a** and **13** in DMF at room temperature was first irradiated for 2 h with white LEDs. Then, the mixture was heated to 60 °C without irradiation for additional 2 h resulting in the selective formation of **3a** (60%) and **14** (50%). The other potential coupling products (**1a** with **13** and **12** with **2a**) were not identified.

DFT calculations show that dimer **1a** is formed exothermically from 1,1-diacyl-nitrosomethane ( $\Delta G = -7.8$  kcal mol<sup>-1</sup>) while the formation of the dimer of **12** is slightly endothermic ( $\Delta G = +0.2$  kcal mol<sup>-1</sup>). The C–nitroso bond dissociation energy of **12** (40.1 kcal mol<sup>-1</sup>) is significantly higher than the bond energy of the nitroso monomer of **1a** (22.2 kcal mol<sup>-1</sup>), proving



**Scheme 4** Gram scale preparation of **3c** and **3ad'** and follow-up chemistry. Reaction conditions: (a) Zn (5.0 equiv.), AcOH (10 equiv.), Ac<sub>2</sub>O, 68 °C, 18 h; (b) NaCNBH<sub>3</sub> (3.2 equiv.), AcOH, 18 h; (c) CH<sub>2</sub>O, HCl (3 mol L<sup>-1</sup>), EtOH, reflux, 3 h; (d) DMF, 150 °C, 1.5 h; (e) Co<sub>2</sub>(CO)<sub>8</sub> (1.0 equiv.), NEt<sub>3</sub> (1.0 equiv.), Et<sub>2</sub>O, 15 min; (f) Co<sub>2</sub>(CO)<sub>8</sub> (1.0 equiv.), NEt<sub>3</sub> (1.0 equiv.), Et<sub>2</sub>O, 15 min, then CH<sub>2</sub>O, HCl (3 mol L<sup>-1</sup>), EtOH, reflux, 3 h; (g) NH<sub>4</sub>OAc (7.6 equiv.), EtOH, reflux, 4 h.





Scheme 5 Mechanistic experiments and complementary reactivity.

the higher thermal stability of the former. Two model nitroso compounds with 1-acetoxy and 1-methoxycarbonyl substituents show the same trends (see ESI for details<sup>†</sup>).

## Conclusions

In summary, we have shown that azodioxy compounds are general precursors for electrophilic C-radicals that engage in thermal styrene 1,2-difunctionalization reactions. The method shows a broad functional group tolerance and the reactions leading to interesting products are experimentally easy to conduct (just mixing and heating). Different tertiary C-radicals can be thermally generated *via* this strategy. We have noted that C-nitroso compounds leading to electrophilic C-radicals exist at room temperature mainly in the dimeric azodioxy form, whereas the previously studied  $\alpha$ -acetoxy alkyl nitroso compounds mainly exist in their monomeric form, as supported by DFT calculations. Further, the monomeric  $\alpha$ -acetoxy alkyl nitroso systems are photoactive and white LED irradiation leads to clean C-radical generation. However, these monomeric nitroso compounds are thermally not active. The complementary photo/thermal reactivity of  $\alpha$ -acetoxy alkyl nitroso

compounds with respect to the azodioxy systems allows for highly chemoselective cross coupling chemistry.

## Data availability

The data that support the findings of this study are available in the ESI.<sup>†</sup>

## Author contributions

S. P. conducted all experiments and characterized the novel compounds. C. M.-L. conducted the DFT calculations. C. G. D. conducted the single-crystal X-ray diffraction analysis. S. P. and A. S. designed the experiments and wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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