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# Oxindole synthesis *via* polar–radical crossover of ketene-derived amide enolates in a formal [3 + 2] cycloaddition†

Niklas Radhoff and Armido Studer \*

Herein we introduce a simple, efficient and transition-metal free method for the preparation of valuable and sterically hindered 3,3-disubstituted oxindoles *via* polar–radical crossover of ketene derived amide enolates. Various easily accessible *N*-alkyl and *N*-arylanilines are added to disubstituted ketenes and the resulting amide enolates undergo upon single electron transfer oxidation a homolytic aromatic substitution (HAS) to provide 3,3-disubstituted oxindoles in good to excellent yields. A variety of substituted anilines and a 3-amino pyridine engage in this oxidative formal [3 + 2] cycloaddition and cyclic ketenes provide spirooxindoles. Both substrates and reagents are readily available and tolerance to functional groups is broad.

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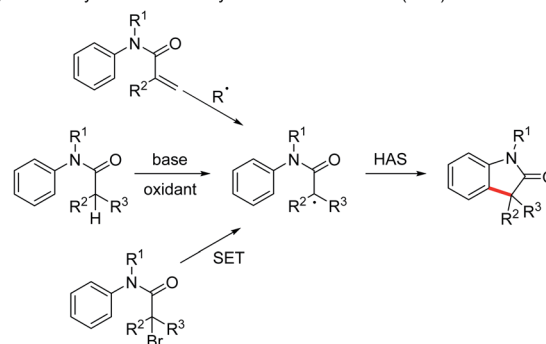
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Oxindoles, in particular the 3,3-disubstituted congeners, are highly valuable substructures in medicinal chemistry. The oxindole core can be found in various biologically active compounds, that are for example used in the treatment of cancer or as antibacterial agents.<sup>1</sup> In addition, the oxindole moiety also occurs in several complex natural products.<sup>2</sup> The first oxindole synthesis was reported by Baeyer and Knop in 1866.<sup>3</sup> That time, isatin was converted by sodium amalgam reduction to the corresponding oxindole. Since then, many methods for the preparation of 3,3-disubstituted oxindoles have been developed that proceed *via* functionalization of a pre-existing oxindole core.<sup>4</sup> In addition, methods for the construction of 3,3-disubstituted oxindoles starting from acyclic precursors have also been introduced.<sup>5,6</sup> Along these lines, transition metal-mediated reactions<sup>5,7</sup> or homolytic aromatic substitutions (HAS)<sup>8–14</sup> have found to be highly efficient for the construction of the oxindole core. Focusing on the latter approach, the intramolecular HAS proceeds *via*  $\alpha$ -carbonyl radicals derived from radical addition to *N*-arylacrylamides,<sup>8</sup> reduction of  $\alpha$ -haloarylamides<sup>9</sup> or oxidation of the corresponding enolates<sup>10–14</sup> (Scheme 1a).

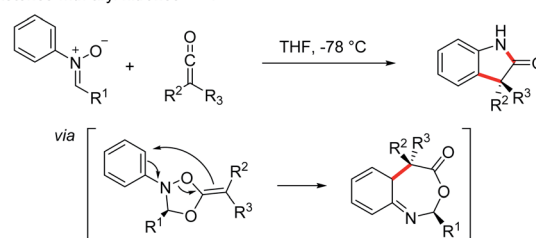
In 2017, the group of Taylor developed a transition metal-free enolate oxidation-HAS-approach towards oxindoles at low temperature using elemental iodine as the oxidant and malonic acid derived *N*-aryl amides as substrates which are readily deprotonated.<sup>14</sup>

The unique reactivity of ketenes<sup>15</sup> has been explored extensively,<sup>16</sup> especially in [2 + 2]-cycloadditions.<sup>17</sup> Moreover,

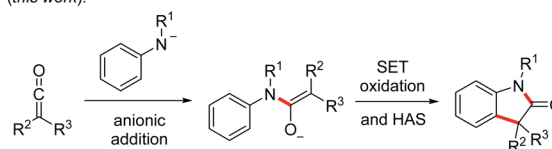
a) Oxindole synthesis *via* homolytic aromatic substitution (HAS)<sup>10–14</sup>:



b) Tandem [3+2]-cycloaddition-[3,3]-sigmatropic-rearrangement-cascade of ketenes with aryl nitrones<sup>18–22</sup>:



c) Oxindole synthesis *via* polar–radical crossover of ketene-derived amide enolates (this work):



Scheme 1 Selected strategies for the synthesis of oxindoles.

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

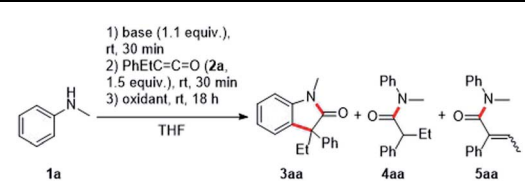
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Staudinger,<sup>18</sup> Lippman<sup>19</sup> and Taylor<sup>20</sup> showed that ketenes react with aryl nitrones in a tandem [3 + 2]-cycloaddition-[3,3]-sigmatropic-rearrangement cascade<sup>21</sup> followed by hydrolysis to provide oxindoles (Scheme 1b). The use of chiral nitrones leads to chirality transfer and enantiomerically enriched oxindoles can be obtained *via* this approach.<sup>21,22</sup> In contrast to the examples discussed in Scheme 1a, two  $\sigma$ -bonds are formed and the overall sequence can be regarded as a formal [3 + 2] cycloaddition. Despite good yields and high enantiomeric excess, nitrones have to be used as precursors and an aldehyde is formed as the byproduct diminishing reaction economy of these elegant cascades.

To address these drawbacks, we decided to use the nucleophilic addition<sup>23–26</sup> of deprotonated anilines to ketenes for the generation of the corresponding amide enolates that should then be oxidized in a single electron transfer process to  $\alpha$ -amide radicals which can undergo a homolytic aromatic substitution providing direct access to sterically challenging 3,3-disubstituted oxindoles in a straightforward one-pot sequence (Scheme 1c). This polar-radical crossover reaction shows high atom economy and as the reaction with the nitrones can also be regarded as a formal [3 + 2] cycloaddition.

We initiated the optimization study with *N*-methylaniline **1a** and ethyl phenyl ketene **2a**, which was prepared in an easy and scalable one-pot protocol starting from the corresponding carboxylic acid, as model substrates. Deprotonation of **1a** with *n*-BuLi in THF and subsequent addition to the ketene **2a** led to desired Li-enolate which was confirmed by protonation with water and isolation of the amide **4aa** (56%). Pleasingly, addition of ferrocenium hexafluorophosphate (FcPF<sub>6</sub>, 2.2 equiv.) at room temperature to the Li-enolate afforded the desired oxindole **3aa** in 29% yield (Table 1, entry 1). Switching to CuCl<sub>2</sub> (2.2 equiv.) as the oxidant increased the yield to 34% (Table 1, entry 2) and the use of iodine (2.2 equiv.) improved reaction efficiency (41%, Table 1, entry 3). A further increase in yield (44%) was achieved upon I<sub>2</sub>-oxidation of the corresponding Mg-enolate (Table 1, entry 4). Protonated enolate **4aa** (23% yield) and the  $\alpha,\beta$ -unsaturated amide **5aa** (27%) were observed as the major side products in this transformation. In contrast to the Li-enolate discussed earlier, the intermediate Mg-enolate is formed almost quantitatively, which was confirmed by protonation with water and isolation of compound **4aa** (91%). Lowering the reaction concentration to 0.02 M and 0.01 M increased the yield significantly to 78% and 90%, respectively (Table 1, entries 5 and 6). Decreasing the amount of oxidant to 1.2 equivalents led to a worse result (Table 1, entry 7). The use of a more electrophilic iodine source such as *N*-iodosuccinimide (NIS, 2.2 equiv.) also resulted in a lower yield of 39% (Table 1, entry 8). Notably, in this case, the  $\alpha,\beta$ -unsaturated amide **5aa** was formed as the major product in 60% yield. When the reaction temperature was lowered to  $-78$  °C prior to the addition of iodine (1.2 equiv.), the desired oxindole **3aa** was formed in 80% yield (Table 1, entry 9).<sup>14</sup> Light does not appear to play a crucial role in this transformation, as performing the reaction in the dark does not have a significant effect on the reaction outcome (Table 1, entry 10). Irradiation with a blue LED (467 nm) actually decreased the yield of targeted **3aa** to 74% (Table 1, entry 11). The reaction

Table 1 Optimization studies<sup>a</sup>


Entry	Base	Conc. (M)	Oxidant (equiv.)	Yield <b>3aa</b> (%) <sup>b</sup>
1	<i>n</i> -BuLi	0.1	FcPF <sub>6</sub> (2.2)	29 (18) <sup>c</sup>
2 <sup>d</sup>	<i>n</i> -BuLi	0.1	CuCl <sub>2</sub> (2.2)	34 <sup>c</sup>
3	<i>n</i> -BuLi	0.1	I <sub>2</sub> (2.2)	41 <sup>c</sup>
4	EtMgBr	0.1	I <sub>2</sub> (2.2)	44 <sup>c</sup>
5	EtMgBr	0.02	I <sub>2</sub> (2.2)	78
6	EtMgBr	0.01	I <sub>2</sub> (2.2)	90 (82) <sup>c</sup>
7	EtMgBr	0.01	I <sub>2</sub> (1.2)	25
8	EtMgBr	0.01	NIS <sup>e</sup> (2.2)	39
9	EtMgBr	0.01	I <sub>2</sub> (1.2) <sup>f</sup>	80
10	EtMgBr	0.01	I <sub>2</sub> (2.2) <sup>g</sup>	82
11	EtMgBr	0.01	I <sub>2</sub> (2.2) <sup>h</sup>	74
12	EtMgBr	0.01	I <sub>2</sub> (2.2) <sup>i</sup>	93

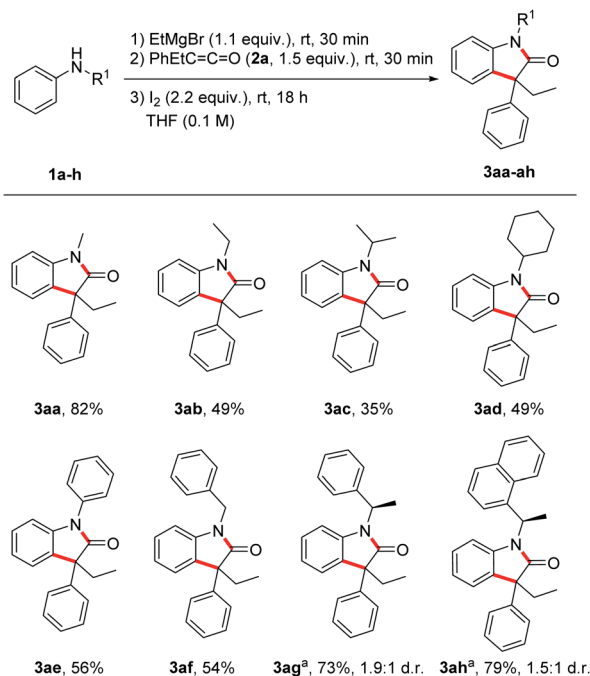
<sup>a</sup> Reactions (0.20 mmol) were conducted under argon atmosphere. <sup>b</sup> <sup>1</sup>H NMR yield using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> Step 1 and 2 were conducted at 0 °C. <sup>e</sup> *N*-Iodosuccinimide. <sup>f</sup> Iodine addition at  $-78$  °C, then slowly allowed to warm to room temperature.<sup>14</sup> <sup>g</sup> In the dark. <sup>h</sup> Irradiation with blue LED (40 W, 467 nm, rt, 8 h). <sup>i</sup> Refluxing THF for step 3, reaction completed within 2 h.

time of step 3 could be significantly reduced to two hours when the reaction was carried out in THF under reflux conditions, and the desired oxindole **3aa** was formed in 93% yield (Table 1, entry 12).

With the optimized reaction conditions in hand, we investigated the scope by first varying the R<sup>1</sup>-substituent at the N-atom using the ketene **2a** as the reaction partner (Scheme 2). In general, increasing the steric bulk at the nitrogen leads to diminished yields of the targeted oxindoles. The lower yields go along with the formation of a larger amount of the corresponding  $\alpha,\beta$ -unsaturated amide side product **5**. Thus, as compared to the parent *N*-methyl derivative, all other *N*-alkyl derivatives were formed in lower yields (49%, **3ab**; 35%, **3ac**; 49%, **3ad**). The *N*-benzyl protected oxindole **3af** and the *N*-phenyl oxindole **3ae** were isolated in 54% and 56% yield, respectively. Next, a diastereoselective oxindole synthesis was attempted using chiral anilines **1g** and **1h**. Surprisingly, despite the bulkiness of these nucleophiles containing styryl-type *N*-substituents, good yields were obtained for the oxindoles **3ag** and **3ah** (73–79%). Unfortunately, diastereocontrol was low in both cases (1.9 : 1 d.r. and 1.5 : 1 d.r.). Of note, addition of Mg-**1g** and Mg-**1h** to ketene **2a** was rather slow under the standard reaction condition and a significant amount of unreacted aniline was recovered. That problem could be solved by prolonging the reaction time of both step 1 (deprotonation) and also step 2 (Mg-enolate formation).

Next, the substrate scope was investigated by using different anilines in combination with the ketene **2a** (Scheme 3). *N*-

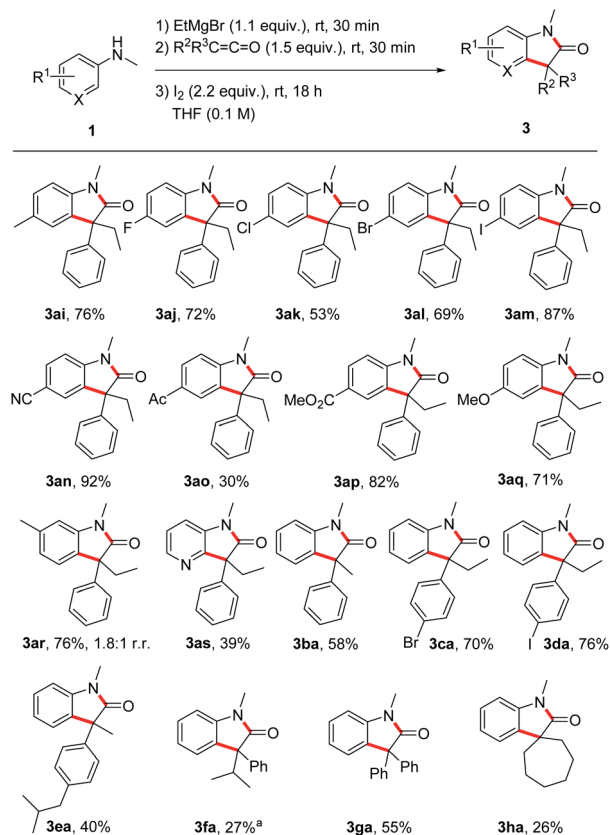




**Scheme 2** Substrate scope – variation of substituents at the nitrogen. Reactions (0.20 mmol) were conducted under argon atmosphere. <sup>a</sup> For step 1 and 2 reaction time was 1 h.

Methyl-*p*-toluidine **1i** and *N*-methyl-*p*-haloanilines **1j–m** could be successfully transformed to the corresponding oxindoles **3al–am** in moderate to good yields (53–87%). Electron-withdrawing and also electron-donating substituents are tolerated and oxindoles derived from *p*-cyano- (**3an**, 92%), *p*-acetyl- (**3ao**, 30%), *p*-methoxycarbonyl- (**3ap**, 82%) and *p*-methoxy- (**3aq**, 71%) anilines were isolated in moderate to excellent yields documenting a high functional group tolerance of this reaction. The meta-methyl aniline afforded oxindole **3ar** in 76% yield as a 1.8 : 1 mixture of the two regioisomers (only the major isomer drawn). For the pyridyl derivative **3as**, a lower yield was obtained (39%), but reaction occurred with complete regiocontrol. Of note, *ortho*-methyl *N*-methylaniline provided the corresponding oxindole only in trace amounts (not shown).

The ketene component was also varied using *N*-methylaniline **1a** as the reaction partner. The transformation of methyl phenyl ketene **2b** provided the oxindole **3ba** in 58% yield. *p*-Bromophenyl ethyl ketene **2c** and *p*-iodophenyl ethyl ketene **2d** afforded the oxindoles **3ca** and **3da** in good yields (70% and 76%). For the ibuprofene-derived ketene **2e** a lower yield was obtained (**3ea**, 40%) and the bulkier phenyl isopropyl congener **3fa** was isolated in 27% yield as an inseparable mixture with the protonated enolate **4fa** (56% combined yield). In the latter case, increasing the reaction time did neither lead to a higher yield of **3fa** nor to a suppression of the formation of **4fa**. The lower yield is likely caused by steric effects. Surprisingly, diphenyl ketene **2g** delivered the targeted oxindole **3ga** in acceptable 55% yield despite the steric demand of the two phenyl groups and the high stability of the corresponding  $\alpha$ -amide radical. Spirocyclic oxindoles are of great interest due to their high pharmaceutical

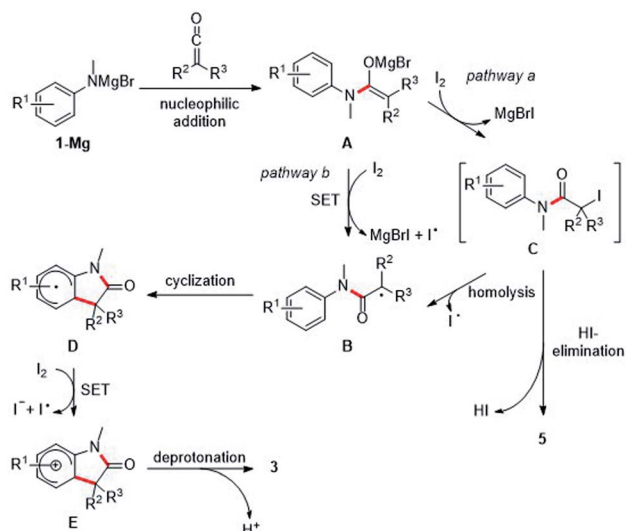


**Scheme 3** Substrate Scope – variation of anilines and ketenes. Reactions (0.20 mmol) were conducted under argon atmosphere. <sup>a</sup> Isolated as an inseparable mixture (1 : 1.4) with the protonated enolate **4fa** (56% combined yield).

potential.<sup>27</sup> We were pleased to find that our method also works for the preparation of such spiro compounds as documented by the successful synthesis of **3ha** (26%).

Mechanistically, we propose initial formation of the enolate **A** by nucleophilic attack of the deprotonated aniline to the ketene **2**, which is then oxidized by elemental iodine to the  $\alpha$ -amide radical **B** (pathway b). The radical nature of the transformation is supported by the fact that electronic effects on the arene show no influence on the efficiency of the cyclization, as would be shown by a conceivable polar aromatic substitution. Radical **B** readily cyclizes onto the aniline ring to generate the cyclohexadienyl radical **D** which is oxidatively rearomatized *via* cationic intermediate **E** to finally give the oxindole **3** (Scheme 4).<sup>10–14</sup> Alternatively, enolate **A** can be iodinated with  $I_2$  to give the unstable iodide **C** which then undergoes C–I bond homolysis to generate the radical **B** (pathway a). Indeed, Taylor and coworkers<sup>14</sup> observed under similar reaction conditions the decay of  $\alpha$ -iodinated compounds of type **C** *via* C–I homolysis<sup>14,28</sup> to give radicals of type **B**. Usually, we observed  $\alpha,\beta$ -unsaturated amides analogous to **5aa** as by-products. However, the corresponding protonated enolates were detected only in tiny amounts in most of these cases. This strongly suggests that those amides are not formed *via* disproportionation of radical **B**. HI-elimination seems more likely, pointing towards the

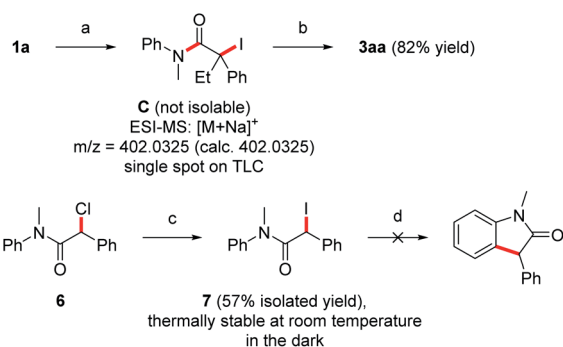




Scheme 4 Suggested mechanism.

presence of the iodinated species **C** and thus the contribution of pathway **b** to product formation. In addition, dimerization of radical **B** was also not observed.

To further support pathway **b**, isolation of the iodinated intermediate **C** was attempted at low temperature. Upon addition of iodine (1.2 equiv.) to the preformed Mg-enolate **A** derived from aniline **1a** and ketene **2a** at  $-78\text{ }^{\circ}\text{C}$ ,<sup>14</sup> TLC analysis showed a clean conversion to a single new compound, which was analyzed by rapid ESI-MS analysis and provided evidence for the formation of the iodinated intermediate **C** (Scheme 5). However, isolation of this highly unstable compound was not possible due to rapid HI-elimination to the amide **5aa**. Note that oxindole formation worked well upon  $\text{I}_2$ -addition at  $-78\text{ }^{\circ}\text{C}$  and subsequent warming to room temperature (see Table 1, entry 9). In contrast to the unstable tertiary iodide **C**, the secondary iodide **7** proved to be stable at room temperature as well as in refluxing THF in the absence of light. Due to the stronger C–I bond of **7** as compared to its tertiary congeners, thermal



Scheme 5 Mechanistic experiments. (a) (1) EtMgBr (1.1 equiv.), rt, 30 min, (2) **2a** (1.5 equiv.),  $-78\text{ }^{\circ}\text{C}$ , 30 min, (3)  $\text{I}_2$  (1.2 equiv.),  $-78\text{ }^{\circ}\text{C}$ , 15 min in THF (0.01 M). (b) Warm to room temperature in THF (0.01 M), 18 h. (c) NaI (1.2 equiv.) in acetone (0.77 M), rt, 18 h. (d) Irradiation with blue LED (40 W, 467 nm) in THF (0.01 M), rt, 8 h.

activation of this iodide is not possible. Upon irradiation of **7** with a blue LED (467 nm), the compound decomposed to release iodine without producing the expected oxindole product (Scheme 5). This is consistent with the observation from our optimization studies that irradiation with blue light does not contribute to the yield of oxindole **3aa** (Table 1, entry 11). Furthermore, the use of more electrophilic NIS instead of iodine should favor the formation of intermediates of type **C** over direct SET. In this case, the elimination product **5aa** was obtained as the main product (60% yield) and the oxindole **3aa** was formed in only 39% yield (Table 1, entry 8). In light of these results, we suggest that both the direct SET of Mg-enolate **A** to iodine (pathway **a**) and the C–I bond homolysis of intermediate **C** (pathway **b**) might operate in these transformations.

## Conclusions

In conclusion, we demonstrated a simple, efficient and transition metal-free procedure for the preparation of sterically challenging valuable 3,3-disubstituted oxindoles *via* a polar-radical crossover of ketene-derived aniline enolates followed by homolytic aromatic substitution at room temperature starting from mostly commercially available anilines and ketenes, which are easily prepared in one-pot reactions from a plethora of commercially available compounds. 26 different (hetero) aromatic 3,3-oxindoles as well as spirooxindoles could be prepared following this method. Functional group tolerance is broad and the herein reported cascades nicely document the potential of polar-radical cross-over chemistry by benefiting from both ionic as well as from radical bond forming reactions.

## Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

## Author contributions

N. R. conducted all experiments and characterized the novel compounds. N. R. and A. S. designed the experiments and wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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