Abstract: α-C–H arylation of N-alkylamides using 2-iodoaryl sulfonyl radical translocating arylating (RTA) groups is reported. The method allows the construction of α-quaternary carbon centers in amides. Various mono- and disubstituted RTA-groups are applied to the arylation of primary, secondary, and tertiary α-C(sp³)–H-bonds. These radical transformations proceed in good to excellent yields and the cascades comprise a 1,6-hydrogen atom transfer, followed by a 1,4-aryl migration with subsequent SO₂ extrusion.

The functionalization of C–H bonds has attracted great attention in synthesis during the last 30 years. In this context, the principle of directed functionalization is a highly valuable strategy and many protocols for C(sp²)–H functionalization using transition metals (TM) as mediators or catalysts have been developed. However, TM-catalyzed processes for remote arylation of C(sp³)–H bonds are relatively scarce. Complementary to TM-mediated processes, remote radical C–H functionalization via selective hydrogen atom transfer (HAT) processes has been established. HAT can be achieved to reactive N-centered radicals, as documented early by the pioneering studies of Hofmann. Löfler and Freytag. Moreover, reactive C radicals can also be applied for HAT-mediated remote C(sp³)–H functionalization. In the late 1980s, the group of Curran introduced the elegant concept of protecting radical translocating groups by installing aryl radical precursors as protecting groups for alcohols and amines. The formation of a transient aryl radical then triggers a selective 1,5-HAT to generate the corresponding translocated C radical that can be trapped, eventually leading to a remote C–H functionalization. In recent years, radical aryl migration reactions induced by 1,7-HAT processes have emerged as a powerful tool for the regioselective arylation of C(sp³)–H bonds. Along these lines, our group developed a method for remote radical C(sp³)–H arylation of alcohols using 2-iodoaryl sulfonyl chlorides as radical translocating arylating groups (RTA, Scheme 1 a). Generation of an aryl radical in the corresponding sulfonates followed by selective 1,7-HAT, 1,5-aryl migration, and desulfonylation provided γ-arylated alcohols in moderate to good yields.

All-carbon α-quaternary amides are valuable compounds in pharmacological chemistry since they can express biological activity, for example, as anti-nausea (Netupitant) and spasmytic agents. Recently, three different strategies were introduced for the α-arylation of amides proceeding via an aryl migration reaction either using radical or ionic chemistry. Importantly, these methods allow for the construction of quaternary C centers. The Nevado group used acrylamides as radical acceptors, where an initial conjugate radical addition is followed by a 1,4-aryl migration reaction to

**Scheme 1.** C-arylation using radical and ionic chemistry. a) Remote C–H arylation of unactivated C(sp³)–H bonds using RTA groups. b) Radical α-arylation of prefunctionalized α-positions (Nevado, Zhang, Wang). c) Anionic α-C–H arylation via aryl migration (Clayden). d) Radical C–H arylation towards α-quaternary amides (this work).
Table 1: Reaction optimization.

| Entry | Initiator/PC | Additive | Light       | Yield Source | Yield [a] |
|-------|--------------|----------|-------------|--------------|-----------|
| 1[a,c] | AIBN (30)    | Bu 3SnH (1.3) | None        | n.i.         |           |
| 2     | Ir(ppy) (1)  | Cs 2CO 3 (3.0) | blue LEDs   | 73%          |           |
| 3     | Ir(ppy) (1)  | Cs 2CO 3 (2.0) | blue LEDs   | 67           |           |
| 4     | Ir(ppy) (1)  | Cs 2CO 3 (1.2) | blue LEDs   | 30           |           |
| 5     | Ir(ppy) (1)  | Cs 2CO 3 (0.5) | blue LEDs   | 19           |           |
| 6     | Ir(ppy) (1)  | /          | blue LEDs   | n.i.         |           |
| 7     | None          | Cs 2CO 3 (1.2) | blue LEDs   | n.i.         |           |
| 8[b]  | Ir(ppy) (1)  | Cs 2CO 3 (3.0) | blue LEDs   | 37%          |           |
| 9     | Ir(ppy) (1)  | Cs 2CO 3 (3.0) | CFL         | 37%          |           |
| 10    | Ir(ppy) (1)  | Na 2CO 3 (3.0) | blue LEDs   | 22%          |           |
| 11    | Ir(ppy) (1)  | K 2CO 3 (3.0) | blue LEDs   | 10           |           |
| 12    | None          | /          | 254 nm      | 94 (82%)     |           |

Reactions were conducted under an argon atmosphere on a 0.1 mmol scale. Blue LEDs: 456 and 467 nm. CFL = compact fluorescent lamp. Yields were determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [a] In benzene at 95 °C for 6 h. Addition of tin hydride by syringe pump over 2 h. Yield of isolated oxindole 3a: 38%. [b] Yield of isolated product. [c] In the dark. n.i. = not identified.
and 2b were also achieved upon simple UV irradiation in the absence of the catalyst and additive (Method B, 82 and 63%). The transformation of sulfonamide 1a to amide 2a was also feasible on a gram scale (59% yield). The sterically less hindered N-methyl amide 2d afforded the targeted 3d in 77% using method A. However, the catalyst-free variant did not provide a good result in this particular case (13%). In contrast, the N-benzyl-substituted sulfonamide 1e was not a good substrate for the Ir-catalyzed process (24%), whereas method B afforded an acceptable yield (56%). The N-phenyl sulfonamide 1f delivered only 24% product 2f using method A and with method B, 2f was not identified. Conformational effects exerted by the N substituents likely play a role in these transformations. Along these lines, the unsubstituted sulfonamide 1f did not provide the target 2g using either method A or B and the same result was noted for the Weinreb-type substrate 1h.

To investigate the effect of the migrating aryl moiety on the reaction efficiency, various N-isopropyl sulfonamides 1i–s were prepared (see SI). For this study, only method A was chosen (Scheme 3). We could show that meta- and para-mono-substituted phenyl groups bearing electron-donating (methyl and methoxy) and -withdrawing (chloro and trifluoromethyl) substituents engaged in the transformation and the products 2i–2m were isolated in 48–79% yield. Arylsulfonamides 1n–1p containing doubly substituted phenyl groups could be transformed to the corresponding α-arylated amides 2n–2p (62–72%) and also the α-naphthyl-substituted amides 2q (73%) and 2r (68%) were accessible via this approach. The latter also shows the compatibility of amine functional groups with the applied conditions. The amide core of the anti-nausea agent Netupitant® 2s (56%) has also been prepared following our approach. However, the 2-pyridyl derivative 2t and the thienyl amide 2u were formed in traces only. The targeted migration product was not observed for the para-imide substrate 1v. Instead, N,S heterocycle 2v was formed in 76% yield via 1,6-HAT followed by a homolytic aromatic substitution reaction.

Next, we studied the effect of the α-substituents in amides of type 1 on the novel cascade using method A (Scheme 4). Switching from the parent α,α-dimethyl derivative 1a to the α-methyl-α-propyl congener 1w did not affect the yield and 2w was isolated in 81% yield. With the sterically even more hindered α-isopropyl-α-methyl amide 1x, the yield remained good (2x, 72%) and a similar result was obtained for the cyclic amide 1y. We also addressed the synthesis of α,α-diarylated amides using α-aryl-α-methyl amides 1z–1ad as substrates. For steric and also for electronic reasons (reactions proceed through more stabilized α-amide radicals) these α-arylations are even more challenging. We were pleased to find that all tested transformations proceeded, albeit with slightly lower efficiencies. Electronic effects of the α-aryl substituent could be observed. Better yields were achieved with the more electron-rich para-alkyl-phenyl amides and products 2ac and

\[ \text{Scheme 3. Substrate scope—variation of the radical translocating arylating group. Reaction scale: 0.1 - 0.25 mmol. Yields of isolated product.} \]

\[ \text{Scheme 4. Substrate scope—primary, secondary, and tertiary α-amide radicals. Reaction scale: 0.1-0.15 mmol. Yields of isolated product.} \]
2ad were isolated in 64% yield. Notably, substrate 1ad is a readily prepared Ibuprofene®-derived amide. Lower yields were noted for the para-fluoro and para-chloro derivatives (43–48%), whereas the corresponding bromide 2ab was isolated in 62% yield. Our method also tolerates an α-methoxy substituent as documented by the successful preparation of 2ae (63%).

We continued the studies by addressing the α-arylation of α-mono-substituted amides. α-Phenylation with amide 1ag occurred highly efficiently and targeted 2ag was isolated in excellent 93% yield. A lower yield was obtained for the α-phenoxyl derivative 2af, likely due to the increased stability of the corresponding intermediate α-amide radical. Not surprisingly, steric effects at the α-position play a role and the highest yield was obtained for the α-unsubstituted amide 1ah where the product 2ah was isolated in 95% yield. This is in line with the fact that only traces of the sterically highly hindered product 2ai were observed by GC–MS and ESI-MS. Moreover, the large stabilization of the corresponding intermediate bisbenzyl α-amide radical also contributes to the suppression of the attempted α-phenylation in 1au.[15]

Plausible mechanisms for methods A and B are presented in Scheme 5. Considering method A, the aryl radical R-1 is reductively generated by oxidative quenching of the photoexcited Ir[III]-catalyst.[14] Stern–Volmer fluorescence quenching experiments with model substrate 1a and the photocatalyst support the oxidative quenching of the photocatalyst (see SI). Radical R-1 then undergoes a selective 1,6-HAT to give the translocated α-amide radical R-2. In method B, the aryl radical R-1 is generated by UV-induced homolysis of the C–I bond in 1a. As for method A, 1,6-HAT is followed by 1,4-aryl migration to give the amidyl radical R-4.[11a,c,12] Reduction of the amidyl radical by the excited [Ir[III]] catalyst and protonation by traces of water which is present in the reaction mixture eventually provide product 2a.

In method B, the aryl radical R-1 is generated by UV-induced homolysis of the C–I bond in 1a. As for method A, 1,6-HAT is followed by 1,4-aryl migration to give, after SO2 extrusion, the amidyl radical R-4. Reduction by acetonitrile via intermolecular HAT finally provides product 2a.[12,18] This reduction step could be further supported experimentally: UV-light (254 nm) irradiation of 1a in deuterated acetonitrile provided amide 2a-D with >95% deuterium incorporation (see SI).

In summary, two protocols for arylation of α-C(sp3)–H bonds in amides starting from easily accessible substrates are introduced. Reactions proceed in good to excellent yields via a 1,6-HAT/1,4-aryl migration/desulfonylation sequence. These radical translocation arylation cascades show broad substrate scope. Importantly, the introduced method allows for the construction of all-carbon quaternary centers but secondary and primary α-amide C(sp3)–H bonds can also be functionalized. Considering the Ir-catalyzed process, inexpensive and environmentally benign cesium carbonate acts as the terminal reductant. Although less general and not as mild, a transition-metal free variant for this transformation was also developed.

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Conflict of interest

The authors declare no conflict of interest.

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