Direct α-Acylation of Alkenes via N-Heterocyclic Carbene, Sulfinate, and Photoredox Cooperative Triple Catalysis

Kun Liu and Armindo Studer*

ABSTRACT: N-Heterocyclic carbene (NHC) catalysis has emerged as a versatile tool in modern synthetic chemistry. Further increasing the complexity, several processes have been introduced that proceed via dual catalysis, where the NHC organocatalyst operates in concert with a second catalytic moiety, significantly enlarging the reaction scope. In biological transformations, multiple catalysis is generally used to access complex natural products. Guided by that strategy, triple catalysis has been studied recently, where three different catalytic modes are merged in a single process. In this Communication, direct α-C=H acylation of various alkenes with aryl fluorides using NHC, sulfinate, and photoredox cooperative triple catalysis is reported. The method allows the preparation of α-substituted vinyl ketones in moderate to high yields with excellent functional group tolerance. Mechanistic studies reveal that these cascades proceed through a sequential radical addition/coupling/elimination process. In contrast to known triple catalysis processes that operate via two sets of interwoven catalysis cycles, in the introduced process, all three cycles are interwoven.

N-Heterocyclic carbene (NHC) catalysis has drawn considerable attention over the past decades. For example, umpolung of aldehydes via NHC catalysis to provide acyl anion equivalents has led to the development of important processes, including the benzoin condensation and the Stetter reaction. Most of these reactions proceed via a single catalysis cycle (Figure 1A), and there are limitations associated with the use of single NHC catalysis. In recent years, NHC catalysis has witnessed an expansion by a move toward dual catalysis in which NHC catalysis is merged with acid catalysis, expansion by a move toward dual catalysis in which NHC catalysis is merged with acid catalysis, hydrogen-bond catalysis, transition-metal catalysis, or others (Figure 1B). In these processes, the NHC catalysis cycle is interwoven with a second catalysis cycle, where the two cycles have a common intermediate. The construction of complex natural products in biological systems generally proceeds via a multiple catalysis approach, and by following nature’s strategies, multiple catalysis on the basis of combining three or more distinct catalysts has emerged as an appealing opportunity for the development of novel reactions. However, triple catalysis involving an NHC catalysis cycle is still in its infancy. The challenges lie in the many compatibility issues between catalysts and intermediates if two additional catalysis cycles have to be considered along with the NHC cycle. The few examples reported operate via two sets of interwoven catalysis cycles with the first and second cycles coupled and the second and third cycles coupled. However, the first and third cycles are not interwoven in these systems, and overall, two common intermediates are observed (Figure 1C).

Herein we present an unprecedented mode of NHC triple catalysis in which NHC catalysis is merged with cooperative sulfinate and photoredox catalysis. In contrast to known triple catalysis processes that operate via two sets of interwoven catalysis cycles, all three cycles are interwoven, resulting in three common intermediates (Figure 1D).

The conceptual novel triple catalysis could be realized in a direct α-C=H acylation of various alkenes with aryl fluorides. The reaction design and mechanistic rationality are depicted in Scheme 1. The sulfinate catalysis cycle starts with single electron transfer (SET) oxidation of an aryl sulfinate by an excited photoredox catalyst *PC* to give an aryl sulfonyl radical along with a PC−1 complex. Radical addition of the sulfonyl radical to substrate alkene 1 leads to adduct radical A. On the other hand, the reaction between aryl fluoride 2 and the NHC catalyst gives acyl azolium ion B, which undergoes SET reduction with the reduced photoredox catalyst (PC−) complex to generate ketyl-type radical C and the starting PC* complex, thereby closing the photoredox cycle. Radical/radical cross-coupling between C and radical A followed by NHC fragmentation leads to intermediate D, closing the NHC catalysis cycle. Such radical/radical cross-couplings are steered by the persistent radical effect and have recently been successfully used by Ohmiya and others, other groups, and us in NHC-catalyzed radical processes. Base-mediated elimination of the aryl sulfinate eventually delivers α-acylated alkene 3, closing the sulfinate catalysis cycle. Notably, acylation of substituted alkenes with acyl electrophiles usually affords the corresponding β-acylation products.

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On the basis of our design, we began the investigations with 4-methylstyrene (1a) and benzoyl fluoride (2a) as the model substrates. PhSO₂Na was chosen as the sulfinate catalyst (25 mol %) in combination with [Ir(ppy)₂(dtbbpy)]PF₆ (1.5 mol %) as the photoredox catalyst. Triazolium salt A was selected as the NHC precatalyst (15 mol %) for initial base screening. Experiments were conducted in acetonitrile at room temperature under irradiation with a compact fluorescent lamp.

**Figure 1.** General representation of NHC-catalyzed transformations proceeding via single, double, and triple catalysis.

**Scheme 1. Reaction Design and Proposed Mechanism**

| Table 1. Reaction Optimizationᵃ  |
|----------------------------------|
| entry | PC  | NHCᵇ  | sulfinate | base (equiv) | yield of 3a (%) |
| 1     | PC-I A | PhSO₂Na | Cs₂CO₃ (2) | n.d. |
| 2     | PC-I A | PhSO₂Na | KOtBu (2) | n.d. |
| 3     | PC-I A | PhSO₂Na | DBU (2) | n.d. |
| 4     | PC-I A | PhSO₂Na | Cs₂CO₃ (1) + KOtBu (1) | trace |
| 5     | PC-I A | PhSO₂Na | Cs₂CO₃ (1) + DBU (1) | 8 |
| 6     | PC-I A | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 26 |
| 7     | PC-I B | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 39 |
| 8     | PC-I C | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 17 |
| 9     | PC-I D | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 22 |
| 10    | PC-II B | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 43 |
| 11    | PC-III B | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 28 |
| 12    | PC-IV B | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 35 |
| 13    | PC-V B | PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | n.d. |
| 14    | PC-II B | 4-OMe-PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 10 |
| 15    | PC-II B | 4-Cl-PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 56 |
| 16    | PC-II B | 4-CN-PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 48 |
| 17    | PC-II B | MeSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 4 |
| 18    | PC-II B | 4-Cl-PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | 81 (78)ᵇ |
| 19    | PC-II B | 4-Cl-PhSO₂Na | Cs₂CO₃ (0.5) + MTBD (1.3) | n.d.ᵇ |

ᵃReaction conditions: 1a (0.15 mmol), 2a (0.3 mmol), NHC (15 mol %), photoredox catalyst (1.5 mol %), PhSO₂Na (25 mol %), base (2.0 equiv), and MeCN (1.5 mL) under irradiation with a 23 W CFL for 24 h.ᵇPhotoredox catalysts and NHCs: PC-I: [Ir(ppy)₂(dtbbpy)]PF₆, PC-II: [Ir(ppy)₂(CF₃ppy)₂]PF₆, PC-III: [Ir(ppy)₂(dtbbpy)]PF₆, PC-IV: 4-CI-2PzN, PC-V: [ppy]₅.ᶜGC yields using biphenyl as an internal standard. The yield of the isolated product is given in parentheses.ᵈ20 mol % NHC, 30 mol % 4-Cl-PhSO₂Na, and 2.5 equiv of 2a were applied. ᵉWithout photoredox catalyst, NHC, sulfinate, or irradiation.

On the basis of our design, we began the investigations with 4-methylstyrene (1a) and benzoyl fluoride (2a) as the model substrates. PhSO₂Na was chosen as the sulfinate catalyst (25 mol %) in combination with [Ir(ppy)₂(dtbbpy)]PF₆ (1.5 mol %) as the photoredox catalyst. Triazolium salt A was selected as the NHC precatalyst (15 mol %) for initial base screening. Experiments were conducted in acetonitrile at room temperature under irradiation with a compact fluorescent lamp.
(CFL). Disappointingly, with Cs₂CO₃, KOt-Bu, or DBU (2 equiv), the target 3a was not formed (Table 1, entries 1–3). A small amount of side product 4, corresponding to intermediate D (see Scheme 1), was identified in the presence of Cs₂CO₃. It is obvious that the base plays a crucial role.

We next explored mixed-base systems by combining Cs₂CO₃ with KOt-Bu or DBU, where the second base was expected to facilitate the elimination of the aryl sulfinate (Table 1, entries 4 and 5). Gratifyingly, the Cs₂CO₃/DBU couple provided ketone 3a in an encouraging 8% yield, whereas the Cs₂CO₃/KOt-Bu mixture was not efficient. The base system containing 0.5 equiv of Cs₂CO₃ and 1.3 equiv of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) led to an improved yield (26%; Table 1, entry 6). Without base, this cascade did not proceed (not shown). Optimization was continued by screening of different NHCs. The steric and electronic nature of the NHCs showed a measurable effect, and the use of B as the precatalyst provided an improved 39% yield, whereas the NHCs derived from C and D led to lower yields (Table 1, entries 7–9). Next, different photocatalysts were investigated, and Ru(bpy)₃(PF₆)₂ afforded an improved yield (Table 1, entry 10). [Ir[dF(CF₃)ppy]₂(dtbbpy)]PF₆ gave a worse result, and no product was identified with Ir(ppy)₃ (Table 1, entries 11 and 13). Replacing the Ru photocatalyst with 4-CzIPN led to a success, but the yield was modest (20%).

Reactions were conducted on a 0.15 mmol scale. Yields are of the isolated materials after purification, Bz = benzoyl. "4-CF₃-PhSO₂Na." "4-CN-PhSO₂Na." "trans-Anethole." "cis-Anethole." Half of 2a and MTBD were added at the beginning, and the rest was added after 12 h. Cs₂CO₃ (0.8 equiv).
to a slightly lower yield (Table 1, entry 12). Knowing that electron-poor aryl sulfonates show better leaving group ability in elimination reactions, we also varied the sulfonate. p-Methoxyphenyl sulfonate showed decreased efficiency compared with PhSO2Na (Table 1, entry 14). Pleasingly, a 56% yield of the target 3a was obtained with p-chlorophenyl sulfonate (Table 1, entry 15). The more electron-deficient p-cyanophenyl sulfonate gave a minor improvement (Table 1, entry 16). Of note, an aliphatic sulfonate was not an efficient cocatalyst (Table 1, entry 17). Some styrene remained unreacted in the best run (Table 1, entry 15), and we therefore increased the amount of NHC, sulfonate, and benzoyl fluoride. A significant improvement was achieved with 2.5 equiv of 2a, 20 mol % NHC, and 30 mol % sulfonate, which provided 3a in 78% yield (Table 1, entry 18). Control experiments revealed that the photoredox catalyst, NHC, sulfonate, and irradiation are all indispensable (Table 1, entry 19).

Under the optimized conditions, we explored the generality of the protocol by first varying the alkene component while keeping fluoride 2a as the acylation reagent (Scheme 2). The effect of substituents on the benzene ring in various styrenes was investigated. Acceptors bearing a halogen atom or electron-donating groups at the para position reacted smoothly to afford the products 3a–f in good yields (65–78%). Lower reaction efficiency was noted for the p-CF3 and p-ETO2C-substituted congeners (3g and 3h), where a significant amount of the alkene remained unreacted. The radical α-acylation also worked with ortho- and meta-substituted styrenes, and 3i–l were isolated in 60–73% yield. Ester and amide functionalities were tolerated, as documented by the preparation of 3m (85%) and 3n (68%). The fluoroalkylamine entity and a base-sensitive primary alkyl chloride were tolerated (3o and 3p). For substrates containing both an aryl alkene and a terminal aliphatic alkene moiety, the reaction occurred at the activated aryl alkene position (3q). Alkenes substituted with biologically important heteroarenes such as thiazole, benzothiophene, benzofuran, indole, and carbazole engaged in the α-benzoylation, and ketones 3r–x were obtained in 55–76% yield. Along with terminal alkenes, internal alkenes like 1,2-dihydronaphthalenes were α-acylated with complete regioselectivity (3z–aa, 76–81%). For the noncyclic system 3y, good E/Z selectivity (6.7:1) was obtained from trans-anethole when p-cyanophenyl sulfonate was used as the cocatalyst. A similar result was obtained with cis-anethole. With regard to aliphatic alkenes, only a trace amount of product was detected when the standard conditions were applied. We assumed that a more electron-deficient sulfonate catalyst might facilitate the radical addition and elimination steps. Indeed, when p-cyanophenyl sulfonate was used instead of p-chlorophenyl sulfonate, allylbenzene and 1-octene reacted to give the α-alkylated vinyl ketones (3ba and 3ca), albeit in lower yields. Next, the
aryl fluoride component was varied using 4-methyl styrene as the coupling partner. Electron-rich (3ab and 3ah) and electron-poor (3ac, 3ai, and 3aj) aryl fluorides reacted well, and the product ketones were obtained in 51−75% yield. Halogen substituents were tolerated (3ad−ag), and aryl fluorides bearing an extended π system or heteroarenes like thiophene and furan reacted to afford ketones 3ak−am in 52−70% yield. Of note, no product was identified with benzoyl chloride or benzoyl bromide instead of benzoyl fluoride. The potential of the process was further documented by late-stage functionalization of more complex activated alkenes. For example, alkenes derived from D-phenylalanine, hormone, natural product, and marketed drugs bearing an indole ring or functional groups such as ketone, amide, halide, and ester could all be aroylated at the α-position (3da−ha). Thus, our process offers a good platform to access more complex α-substituted vinyl ketones.

To illustrate the synthetic value of these α-substituted vinyl ketones, a gram-scale reaction of 1m was conducted with reduced amounts of the catalysts, and a comparable yield was obtained (Scheme 3a). Furthermore, [3 + 2] annulation of vinyl ketone 3a with N-acetylhydrazone provided dihydro-1H-pyrazole 5 in 75% yield (Scheme 3b). Photoredox-catalyzed hydroaclylation of 3ai with α-oxocarboxylic acid gave 1,4-diketone 6 (Scheme 3c), and epoxidation of enone 3a afforded oxirane 7 in 71% yield (Scheme 3d).

To support the mechanism suggested in Scheme 1, additional experiments were conducted. With acyl azolium ion 8 as the substrate in the absence of the NHC, 4-methyl styrene reacted in 51% yield to give vinyl ketone 3a, indicating that acylazoliums B (see Scheme 1) are competent intermediates (Scheme 4a). The reaction between α-methyl styrene and benzoyl fluoride with 1 equiv of p-chlorophenyl sulfinate furnished the three-component coupling product 9 in 48% yield (Scheme 4b). The absence of an acidic proton at the position β to the sulfone moiety prevents the sulfinate elimination, showing that three-component products of type D are intermediates in these cascades.

Furthermore, to investigate the sulfinate elimination from D, a parallel kinetic isotope effect (KIE) experiment was carried out using 1z and [D]-1z as substrates (Scheme 4c). The two reactions were stopped after 40 min, and on the basis of the individual conversions, a KIE value of 2.8 was calculated. A competition KIE experiment using equal amounts of 1z and [D]-1z (0.5 equiv each) was stopped after 40 min, and analysis of the unreacted starting alkene revealed a KIE value of 2.2 (Scheme 4d). These results indicate that the deprotonation process might be involved in the rate-determining step. Moreover, when the model reaction was conducted in the presence of 2 equiv of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the α-acylation was not observed. Instead, benzoyl-TEMPO adduct 10 was isolated in 19% yield, suggesting ketyl radical C as an intermediate (Scheme 4e). On the other hand, the formation of adduct radical A was supported by a radical probe experiment using styrene 11 as the acceptor to give ring-opening product 12 (44% yield; Scheme 4f). Finally, fluorescence quenching experiments revealed that only sodium sulfinates quench the excited state of Ru* (II) (see Figure S2 for details), supporting the reductive quenching pathway. Thus, all of these experiments are in line with our suggested mechanism.

In conclusion, we have developed the first example of triple catalysis involving a carbene catalyst in which all three catalysis cycles are interwoven. Along with the carbene, a photoredox catalyst and a sulfinate catalyst are used for α-acylation of aryl fluorides with acyl fluorides to access α-substituted vinyl ketones. The cascade exhibits high functional group tolerance. Successful late-stage modification shows the potential of the method, and useful follow-up chemistry on the product ketones further documents the value of the process. Notably, existing methods for acylation of aryl alkenes usually afford the β-acylation products. Mechanistic studies indicate that the reaction proceeds through a radical addition/coupling/elimination cascade. We are confident that multiple catalysis proceeding through NHC-catalyzed radical transformations will enable the discovery of other novel transformations in the future.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01022.
Experimental procedures, characterization data, and copies of 1H and 13C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author
Armido Studer — Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, 48149 Münster, Germany; orcid.org/0000-0002-1706-513X; Email: studer@uni-muenster.de

Author
Kun Liu — Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, 48149 Münster, Germany

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c01022

Notes
The authors declare no competing financial interest.

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