Synthetic methodology

https://doi.org/10.1038/s44160-023-00400-9

Carbene- and photocatalysis redefine arene acylation

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Combined *N*-heterocyclic carbene and photoredox-catalysed strategies for the acylation of arenes offer regiocontrol that is complementary to Lewis-acid-mediated Friedel–Crafts approaches.

Arene acylation is a fundamental transformation with extensive industrial applications in the preparation of pharmaceuticals, agrochemicals and materials. The most common strategy, especially on a large scale, for such transformations is to use Friedel–Crafts reactions, reacting arenes with acyl chlorides in the presence of a Lewis acidic activating reagent, for example aluminium chloride (Fig. 1a, left). The regioselectivity of Friedel–Crafts reactions is typically determined by the electron-rich substituents on the arene substrate, with acylation occurring at the arene carbon atoms that are *ortho*- or *para*- to the electron-rich substituent. The development of new strategies for the acylation of arenes with different regioselectivity would complement Friedel–Crafts-based approaches. Current progress in this direction mainly comes from transition-metal-catalysed carbon–hydrogen bond functionalizations by preinstalling directing groups, which are not necessarily desired substituents on the target products, on the arene substrates[1].

Now, writing in *Nature Synthesis* and *Angewandte Chemie International Edition*, respectively, Ohmiya, Sumida and co-workers[2] and Studer and co-workers[3] independently report the development of (hetero)arene acylation reactions that offer regioselectivity not readily attainable using Friedel–Crafts methods (Fig. 1a, right). Both methods involve the combined use of *N*-heterocyclic carbene (NHC) catalysis and photoredox catalysis, placing the acyl groups onto the *meta*-positions of arene substrates. A key step in both studies is the coupling of NHC-catalyst-derived ketyl radical intermediates[4] with arene-derived radical intermediates, generated in the presence of light and a photocatalyst. Similar NHC-bound ketyl radical intermediates have previously been obtained through the oxidation of the Breslow intermediate[5–7] and have recently been accessed via single-electron-transfer (SET) reduction of acyl azolium ester intermediates[8–10]. The persistence of these ketyl radicals provides opportunities to trap these highly reactive radical species in radical–radical cross-coupling reactions, enabling access to valuable ketone products that are difficult to obtain using traditional methods[11].

Studer and co-workers found that reacting 2-methoxynaphthalene **1a** with benzoylfluoride **2a** in the presence of a triazolium salt NHC pre-catalyst, a photocatalyst **PC1** and caesium carbonate as a base, under blue light irradiation (456 nm) gave acyl arene product **3a**, with exclusive *meta*-regioselectivity (Fig. 1b). Studer and co-workers also showed that reacting the same substrates under Friedel–Crafts conditions (with aluminium chloride as a Lewis acid activator) gives the acyl arene product with predominantly *ortho*-selectivity.

Similarly, Ohmiya, Sumida and co-workers found that reacting 1,3-dimethoxybenzene **1b** with picolinic-acid-derived acyl imidazole **2b** in the presence of a triazolium salt NHC pre-catalyst, photocatalyst **PC2** and base and additive caesium 1,2,4-triazolide under blue light irradiation (440 nm) gives acyl arene **3b**, in good yield with exclusive *meta*-regioselectivity (Fig. 1b). Both studies showed encouraging substrate scope, tolerating arenes bearing halogen, ether, alkyl or ester substituents, heteroarenes, and complex molecules with arene units. With respect to the acyl substrate, although aryl acyl substrates are mostly used, Ohmiya, Sumida and co-workers' method is also compatible with alkyl acyl substrates.

Mechanistically, both studies are proposed to start with single-electron transfer (SET) oxidation of the electron-rich arenes by the photoexcited state of the photocatalyst, **PC1** or **PC2**, to form a transient arene radical cation species, **A1** or **A2** respectively, and a reduced photocatalyst (Fig. 1c). The reduced photocatalyst then undergoes SET to deliver one electron to the acyl azolium intermediate, **B1** or **B2**, which is generated through reaction of the NHC catalyst with the acyl fluoride or acyl imidazole substrates, to give NHC-bound ketyl radicals, **C1** or **C2**, and regenerate the respective photocatalyst, **PC1** or **PC2**.

The mechanistic difference between the two studies is thought to arise in the subsequent steps, leading to differing origins of regioselectivity (Fig. 1c). Studer and co-workers' method is proposed to proceed through coupling of radical cation intermediate **A1** with ketyl radical **C1** to generate an NHC-bound cyclohexadienyl cation **D1**. This radical coupling step is thought to be reversible and so does not affect the regioselectivity of the reaction. Isotopic labelling experiments reveal that the regioselectivity of the process probably originates from the deprotonation step, **D1** to **3a**.

In contrast, mechanistic and computational studies reveal that Ohmiya, Sumida and co-workers' method involves nucleophilic addition of an azolide anion, 1,2,4-triazolide, from caesium 1,2,4-triazolide or imidazolide released in the formation of **B2**, to the arene-derived radical cation intermediate **A2** to form neutral radical intermediate **D2**. Subsequent coupling of **D2** with NHC-bound ketyl radical **C2** leads to intermediate **E2**. During this step, **D2** to **E2**, the azolide unit on **D2** serves to block the *para*-position of the arene temporarily, and therefore forces the acylation reaction to occur on the *meta*-carbon of the arene substrate. The azolide moiety in intermediate **E2** then behaves as a leaving group, and *meta*-acyl arene product is formed.

Overall, the two methods offer a valuable approach for the acylation of arenes. Although the mechanistic pictures remain to be further explored, and important synthetic applications and substrate scopes wait to be demonstrated, the methods provide possibilities not readily available using Friedel–Crafts or transition-metal-catalysed

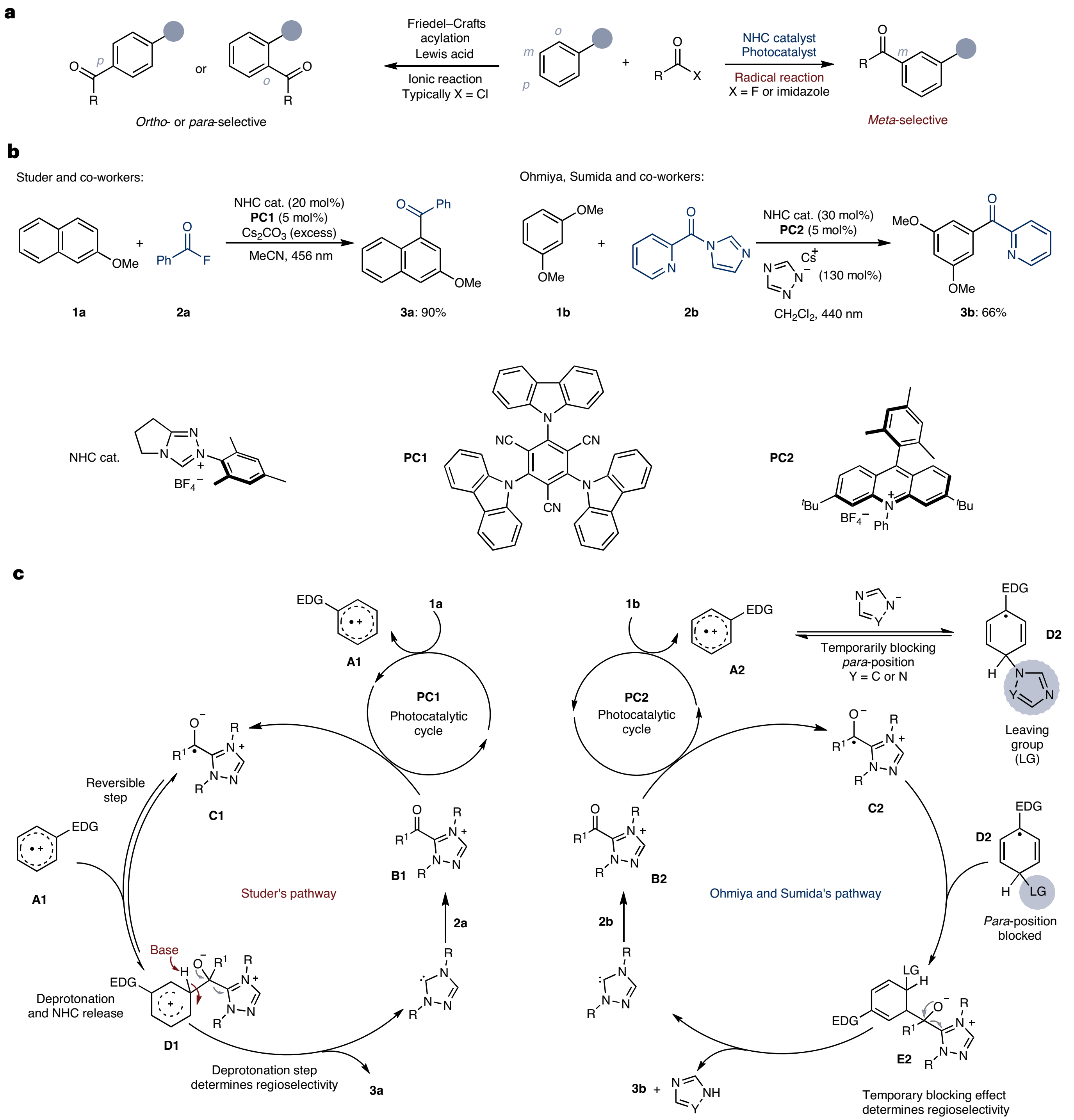

Fig. 1 | Combined *N*-heterocyclic carbene and photoredox-catalysed regioselective acylation of electron-rich arenes. a, Regioselective acylation of (hetero)arenes. **b**, Model regioselective arene acylation reactions from Studer and co-workers, and from Ohmiya, Sumida and co-workers. **c**, Proposed mechanistic pathways. EDG, electron-donating group; NHC, *N*-heterocyclic carbene.

C–H activation reactions. Additionally, in the field of NHC catalysis, these studies constitute a clear advancement by expanding NHC-catalysed reactions to the functionalization of arenes, an arena that is currently underdeveloped. The findings of these two studies may inspire revision of fundamental challenges in synthetic chemistry by creatively using emerging catalytic tools.

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Competing interests

The authors declare no competing interests.