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Visible-light-mediated green synthesis of tertiary alcohols from dicarbonyl compounds and arylamines in water†

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Green organic synthesis mediated by visible-light chemistry is highly desired in academia and industry. Water is undoubtedly the most environmentally friendly medium. Herein, we report a mild and robust water-phase electron donor–acceptor (WEDA) platform by merging visible-light chemistry with the use of water. Carbonyl compounds and arylamines serve as electron acceptors and donors, enabling access to sterically hindered tertiary alcohols with quaternary sp^3-carbon centers through a green chemistry approach. The power of the transformation has been further demonstrated in the late-stage functionalization of a number of commercially available pharmaceutical compounds.

In the past decade, the use of electron donor–acceptor (EDA) complexes, which can be excited by visible light, has become a very powerful strategy for molecule construction without an exogenous photoredox catalyst.[1] Mechanistically, the inner-sphere electron transfer (k_{SET}) is triggered under light irradiation to generate a radical ion pair, leading to product formation (Fig. 1a). However, an unproductive back electron transfer (k_{BET}) process means that it is kinetically unfavorable to access the product, restoring the ground-state EDA complex. One recent solution depends on the incorporation of a suitable leaving group or redox auxiliary group, which can push the forward electron transfer *via* irreversible fragmentation (Fig. 1b). Obviously, this strategy inevitably brings synthetic complexity and practical limitations. Hence, it would be intriguing to develop a conceptual precedent to accelerate electron transfer inside the EDA complex by means of an extra regulator, synergistically bonding the donors and acceptors.

Water is the optimal reaction medium and conforms to green chemistry principles, as it is safe, nontoxic, cheap and readily available. In addition to this, the exclusive physicochemical properties of water in visible-light photoredox catalysis can unveil unconventional chemical behaviors.[2] For example, in natural photosystems, the CO_2–H_2O complex is a central species in the conversion of inorganic carbon to organic carbohydrates. The hydrogen-bonding transition state is formed inside the excited CO_2–H_2O complex, which can promote carbon dioxide activation with lower activation energy.[3] Moreover, the nicotinamide-dependent enzyme (NADPH) is an important electron and hydride donor in the CO_2 reduction reaction, concurrently delivering the NADP radical immediate.[4] Inspired by these natural systems, we recently questioned whether a water-phase electron donor–acceptor (WEDA) mechanism upon visible-light irradiation could be exploited to synthesize sterically hindered tertiary alcohols through a green chemistry approach. Indeed, merging

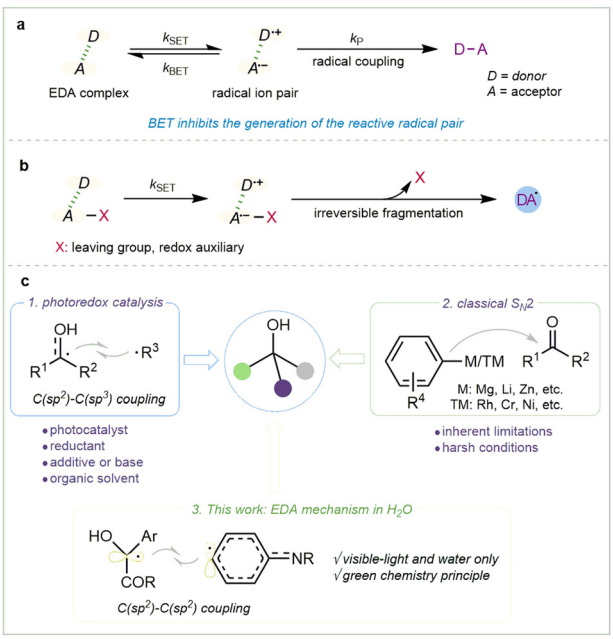

Fig. 1 (a) Classical electron donor–acceptor theory. (b) Current EDA state. (c) The designed concept of our work.

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water as a medium with visible-light catalysis has received little attention so far in the field of sustainable chemical synthesis.[5]

Along this line, radical sp^2 nucleophilic addition and radical–radical coupling *via* photoredox catalysis are great approaches to synthesize sterically hindered alcohols, in which photocatalysts, metal catalysts, strong bases and other additives are necessary, as well as organic solvent as the reaction medium.[6,7] These transformations usually involve the formation of $C(sp^3)$–$C(sp^3)$ bonds by highly reactive alkylates and carbonyl compounds (Fig. 1c.1). Nonetheless, a highly effective protocol for the preparation of tertiary alcohols through $C(sp^2)$–$C(sp^2)$ cross-coupling of aromatic compounds and carbonyl compounds driven by visible light has remained elusive. Among the most well-established methods for carbonyl arylation are to employ stoichiometric organometallic agents (*e.g.*, Mg, Li, Zn) or transition metal catalysts (*e.g.*, Rh, Cr, Ni).[8–10] These methods impose inherent limitations on synthetic applications due to the relatively harsh conditions, particularly when aldehyde carbonyl substrates are employed (Fig. 1c.2). On this basis, we envisioned a green strategy for carbonyl arylations *via* radical cross-coupling in water under visible-light conditions (Fig. 1c.3).

With the hypothesis in mind, we initially investigated a photocatalyst-free radical cross-coupling protocol between ethyl benzylformate **1** and diphenylamine **2** under visible light irradiation (see ESI section 2†). We found that the starting materials always remained with only about 40% conversion when the reactions proceeded in polar or nonpolar organic solvents, giving the quaternary carbon-bearing alcohol **3** in an average yield of 30%. Here, a larger ratio of the *para*-selectivity product of **3** was observed, probably due to the stable *para*-radical in the sluggish electron transfer step. This experimental phenomenon is consistent with classical EDA theory. Intriguingly, the reaction can reach 80% conversion in water. A reasonable explanation for this is water-accelerated inner-sphere electron transfer, which promotes the reaction equilibrium forward. Moreover, the yields of the model reaction were 13% and 24% respectively when running under white light and green light, indicating that the excitation light source is also an important factor. Additionally, the control experiment indicated that light is essential for this transformation.

Having established the optimized reaction conditions, we next explored the generality of our green protocol, starting with diversely functionalized benzylformates (Table 1). Methyl, ethyl and benzyl esters all provided good yields of the desired tertiary alcohols (**3–5**). To our delight, halogen substituents (I, Br, and F) on the phenyl scaffold were also very compatible, giving the corresponding halogenated alcohols in excellent yields (**6–12**). No dehalogenations occurred under our mild paradigm. These products would also serve as very valuable precursors for organometallic reactions.[11] In addition, a range of substituted ketoesters with electron-deficient and electron-donating substituents, such as cyano (**13**), alkyl (**14**, **15**), phenyl (**16**), and methoxyl (**17**, **18**), were good substrates as well. Furthermore, ketoesters with naphthalene and thiophene substituents can also readily convert to the cross-coupling alcohols (**19**, **20**). Beyond that, diketones were also suitable substrates to afford α-hydroxyketones (**21**, **22**), which are ubiquitous structural motifs emerging in many natural products and biologically active molecules.[12] It is worth mentioning that imines (**23**, **24**) were readily tolerated and yielded valuable amine frameworks, further expanding the application space of this green methodology.

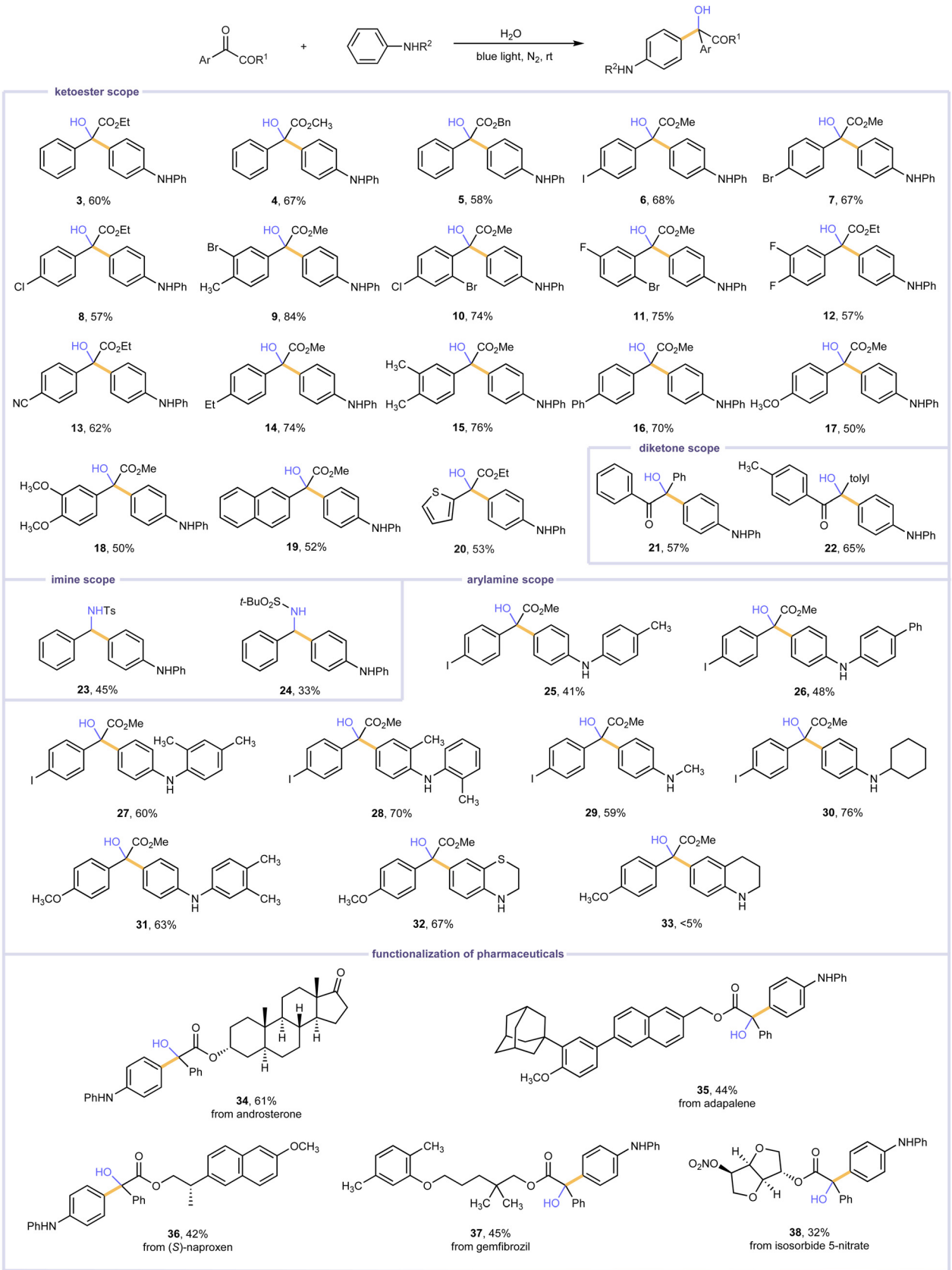
We next explored a series of arylamine coupling partners. Substituted diarylamines reacted to furnish the respective products in good yields. High regioselectivity was shown for the *para*-position of unsubstituted aromatic rings, indicating that steric hindrance might play a dominant role compared to electronic factors (**25–28**), favoring the formation of the stable EDA complex. Notably, the alkyl–aryl amines, including *N*-methylaniline (**29**) and *N*-cyclohexylaniline (**30**), were also found to readily deliver the target alcohols in good yields. For the ketoester with an electron-rich substituent (–OCH_3), the electron-rich arylamines (dimethyldiphenylamine and dihydrobenzothiazine *vs.* tetrahydroquinoline) were more favorable for electron transfer, exhibiting good reactivity (**31–33**).

The synthetic value of this practical technology was further tested in the late-stage modification of complex drug-like molecules (Table 1). For example, the direct incorporation of tertiary alcohol motifs into pharmaceutical derivatives, such as androsterone (**34**), adapalene (**35**), naproxen (**36**), gemfibrozil (**37**), and isosorbide 5-nitrate (**38**), was feasible in a modular way, for conveniently building a library of compounds for drug screening.

We subsequently moved forward to gain more insights into the mechanism. Specifically, a radical-trapping experiment was performed with TEMPO under standard conditions, and the reactivity decreased dramatically, indicating a radical pathway (Fig. 2a). Furthermore, UV–vis spectroscopy of the reaction components revealed that the EDA complex could be formed due to the appearance of a charge-transfer (CT) band (Fig. 2b). A further bathochromic-shift of the CT band was observed after mixing with water, possibly resulting in a new EDA molecular aggregation. A description of our proposed mechanism is outlined in Fig. 2c. Ketone **1** and arylamine **2** could be assembled reversibly to forge the ground-state EDA complex **I**, within which the water molecules might bridge the carbonyl and amido groups through weak hydrogen bonding. Meanwhile, the oxidation potential of ketone **1** was enhanced.[13,14] Visible-light promoted electron transfer and rapid proton conduction would productively afford the neutral radical pair **II**, including a persistent ketyl radical and a transient allyl radical.[15] These factors enable selective radical cross-coupling, avoiding radical homo-dimerization. Subsequent radical cross-coupling can give the imine intermediate **III** upon aromatization, providing the product **3**.

As a final practical test of the green protocol, the scalability was evaluated on a 1 g scale using a batch setup to yield the desired alcohol in 72% yield (Fig. 2d). In medicinal chemistry, tertiary amine-hydroxy-ester building blocks are the representative pharmacophores of the muscarinic receptor antagon-

Table 1 The substrate scope and functionalization of drugs[a]



[a] Isolated yields are indicated. See ESI† for experimental details.

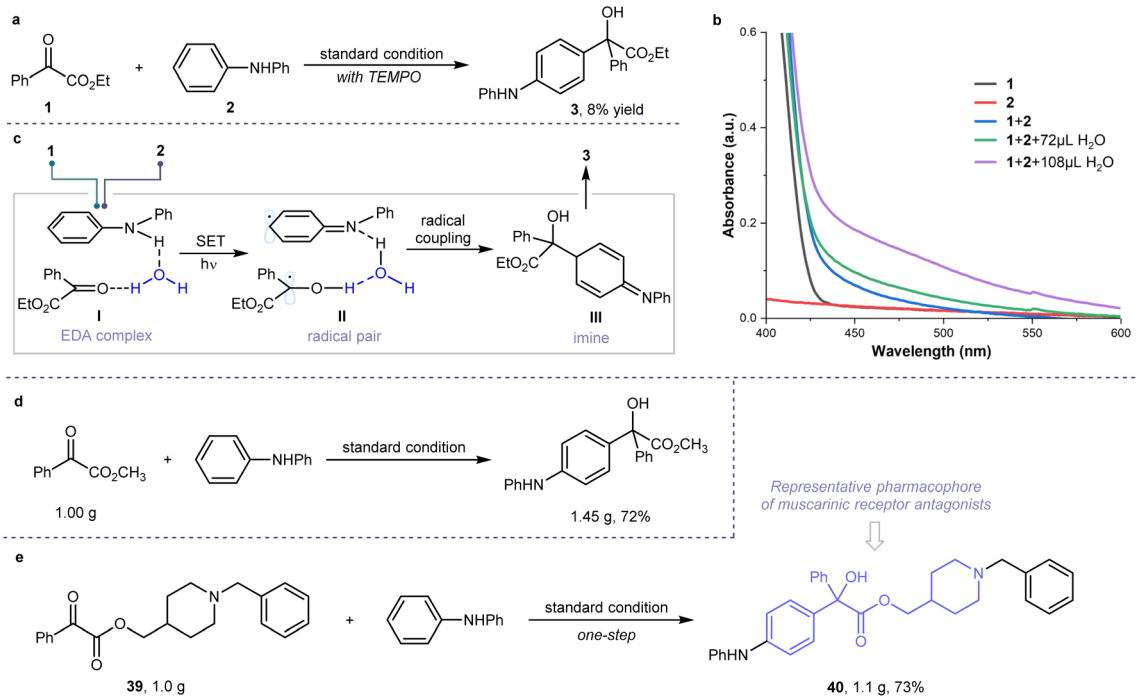


Fig. 2 (a) Radical-trapping experiment with TEMPO. (b) UV/Vis absorption spectroscopy of the reaction system. (c) Proposed WEDA mechanism. (d) Scaled-up synthesis. (e) Green process for the promising lead compounds of muscarinic receptor antagonists.

ists,[16] whereas the construction of this kind of useful pharmacophore often needs harsh conditions according to the reported methods.[17] Intriguingly, we herein developed a green process to prepare a type of drugs with excellent performance (Fig. 2e).

Conclusions

In summary, we have developed a green protocol for the synthesis of tertiary alcohols and secondary amines by visible-light-mediated carbonyl arylations in water. This mild synthesis approach can be easily scaled-up and exhibits a broad substrate scope under environmentally benign conditions. The tertiary alcohol building blocks can be easily incorporated into many pharmaceutical compounds, which is very valuable in the pharmaceutical industry. Mechanistic studies indicate that a water-assisted EDA mechanism might be responsible. Therefore, we anticipate that this powerful platform has good application prospects in green organic synthesis. Additionally, due to its excellent water compatibility and clean nature, this approach could also be developed into a useful photo-controllable biological orthogonal reaction.[18]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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