Dual-Catalysed Intermolecular Reductive Coupling of Dienes and Ketones

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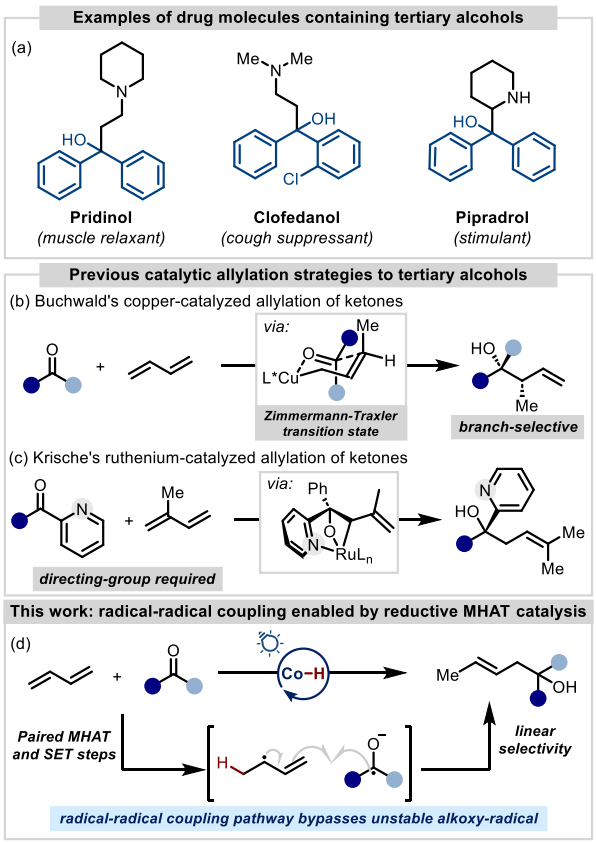
Abstract

We report a mild, catalytic method for the intermolecular reductive coupling of feedstock dienes and styrenes with ketones. Our conditions allow concomitant formation of a cobalt hydride species and single-electron-reduction of ketones. Subsequent selective hydrogen-atom-transfer from the cobalt hydride generates an allylic radical which can selectively couple with the persistent radical-anion of the ketone. This radical-radical coupling negates unfavourable steric interactions of ionic pathways and avoids the unstable alkoxy-radical of previous radical olefin-carbonyl couplings which were limited, as a result, to aldehydes. Applications of this novel and straightforward approach include the efficient synthesis of drug-molecules, key-intermediates in drug synthesis and site-selective late-stage-functionalisation.

Introduction

Tertiary alcohols containing two aryl groups and their ether derivatives feature across a number of pharmaceutical classes (Scheme 1a).[1] As such, the efficient synthesis of this motif draws wide-spread interest. Traditional approaches rely on nucleophilic addition of stoichiometric organometallic reagents to ketones.[2] However, these intermediates can be difficult to prepare and are frequently air and moisture sensitive. An alternative, streamlined strategy for construction of this motif from widely-available feedstocks would be the catalytic intermolecular hydrofunctionalisation of 1,3-dienes with carbonyl compounds.[3,4] Beyond minimizing stoichiometric metallic waste, this strategy can offer increased functional group tolerance with the products featuring a useful C=C bond in close proximity, poised for further functionalisation. A range of such reactivity has been investigated with aldehyde (or masked-aldehyde) coupling partners, initially by Mori[5] and Le Gendre and Moïse[6] before being extensively developed by the groups of Krische[7–13] and others[14,15] as a contemporary revolution of classical allylation chemistry. However, ketones remain challenging in all but a few limited cases (see below),[16] likely due to their lower electrophilicity and increased steric demands relative to aldehydes.

Two notable solutions to this problem have been developed. Buchwald and co-workers,[17–20] and also later Xiong and co-workers,[21] reported the copper-catalysed, enantioselective allylation of ketones with 1,3-dienes which proceeds through a Zimmerman-Traxler type transition state (Scheme 1b). As a result, branched rather than linear products are obtained. Krische and co-workers reported an alternative strategy that instead yields the linear product.[22] Relying on ruthenium-catalysis, this direct allylation of tertiary alcohols requires a coordinating Lewis-basic heterocycle to stabilize the intermediate metallocycle (Scheme 1c). Therefore, it is evident that a new tactic to allow entry to linear products with simple ketone coupling partners would be an attractive development for the field as an efficient approach to tertiary allylic alcohols which can be mapped onto key structures with linear carbon chains such as those in Scheme 1a.



Scheme 1| Tertiary alcohol synthesis through catalytic hydrofunctionalisation of dienes.

We became interested in developing a solution to this problem using metal-catalysed hydrogen atom transfer (MHAT) catalysis.[23–26] Previous methods have been reported in this area by Bradshaw and Bonjoch which rely on iron catalysis to couple olefins and carbonyl compounds.[27–31] However, the intermolecular examples are restricted to aldehyde carbonyls due to the propensity of the alkoxy-radical intermediate from ketone to undergo reversible β-fragmentation and revert to the more stable C-centred radical.[32–35] Shenvi and co-workers have reported an alternative approach which proceeds *via* transmetallation to chromium to generate an anion-equivalent species.[36] However, similar to examples discussed earlier, this intermediate is only able to react with aldehydes and aldimines.

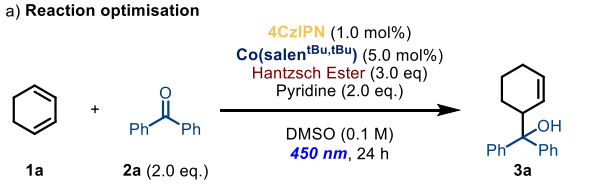
Our group[37,38] and others[39–46] have recently exploited a reductive route to generating the key cobalt hydride which performs hydrogen atom transfer (HAT). This proceeds *via* sequential single electron reduction of Co(II) to Co(I) and subsequent protonation. We recognized that this – in contrast to traditionally used oxidative conditions[47–53] – might enable us to also reduce ketone coupling partners under the same conditions to their corresponding radical anion.[54,55] Following HAT to a diene to generate an allylic radical, radical-radical coupling *via* the persistent radical effect[56] could then occur, bypassing the unproductive O-centred radical that was problematic in previous approaches (Scheme 1d).

Herein, we report the realisation of this approach and the development of a methodology that enables the mild, reductive coupling of dienes and styrenes with ketones and imines. Using this platform, we showcase a streamlined and practical route for the construction of molecular complexity from abundant starting-materials through applications in the synthesis and late-stage-functionalisation of drug molecules.

Results

Reaction design and optimisation. Our investigation began with the examination of the reaction between 1,3-cyclohexadiene **1a** and benzophenone **2a.** We hypothesized that Hantzsch Ester (HEH), upon visible light irradiation, could function both as a sacrificial reductant and proton donor.[37,57] With three equivalents, 5 mol% of commercially available [Co(salen^{tBu,tBu})] as the catalyst, and pyridine as the base, product was formed in a range of solvents. DMSO was found to be optimal, however, without addition of 4-CzIPN as a photocatalyst, efficiency of the reaction was low (Scheme 2a, entries 1 and 2), though this could be increased by lowering the wavelength of light (entry 3). Notably, the reaction did not proceed in the absence of the cobalt catalyst (Scheme 2a, entry 4), HEH (entry 5), or light (entry 6). Additionally, excluding pyridine led to lower yields (entry 7). Interestingly, the reaction could also be conducted under aerobic conditions using DMSO from a bottle without any membrane seal (entry 8), albeit with moderate yields, demonstrating the potential utility of this method.

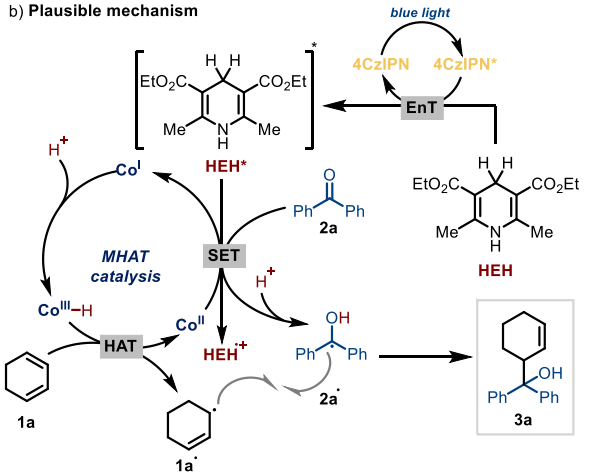
a) **Reaction optimisation**



entry	deviation from standard conditions	yield, %[a]
1	none	90 (81)[b]
2	without 4CzIPN	25
3	without 4CzIPN, 365 nm light	50
4	without Co(salen^{tBu,tBu})	0
5	without Hantzsch Ester	0
6	without light	0
7	without pyridine	28
8	wet-DMSO/air atmosphere	69

[a]Yield determined by ^{1}H NMR by comparison with internal standard.
[b]Isolated yield

b) **Plausible mechanism**



Scheme 2| Reaction optimisation and proposed mechanism.

Based on previous work and on our investigations, we propose the following mechanism (Scheme 2b): photoexcitation of the photocatalyst, 4CzIPN, at 450 nm results in energy transfer to HEH. Irradiation at a lower wavelength where HEH absorbs (Scheme 2a, entry 3) also results in product formation which is consistent with an energy transfer step in preference to electron transfer from 4CzIPN. Alternatively, quenching could occur from a cage complex, formed between the photocatalyst and HEH.[58] Notably, Stern-

Volmer quenching experiments have revealed that 4CzIPN* is quenched by HEH[59] but not by benzophenone. The resulting excited state Hantzsch Ester, HEH*, is a highly reducing species (E_{ox}^{*} = -2.28 V vs SCE in DMF)[60] that can be quenched by benzophenone, **2a** (E_{red} = -1.83 V vs SCE in DMF)[61] and subsequently protonated[58,62] to generate the corresponding persistent radical, **2a**•. At the same time, Co(II) can be reduced to Co(I) (E_{red} = -1.60 V vs SCE)[41] *via* SET from HEH*. Subsequent protonation from the reaction media will form the Co(III)–H species which notably undergoes selective HAT to cyclohexadiene (**1a**) rather than reacting with the benzophenone. The resulting allylic radical can couple with **2a**• at the carbon center[63,64] yielding product **3a**. We consider reduction of the allylic radical **1a**• to the corresponding anion (E_{red} = -2.3 V vs SCE) and subsequent addition to the ketone to be less likely due to the more negative reduction potential.[65]

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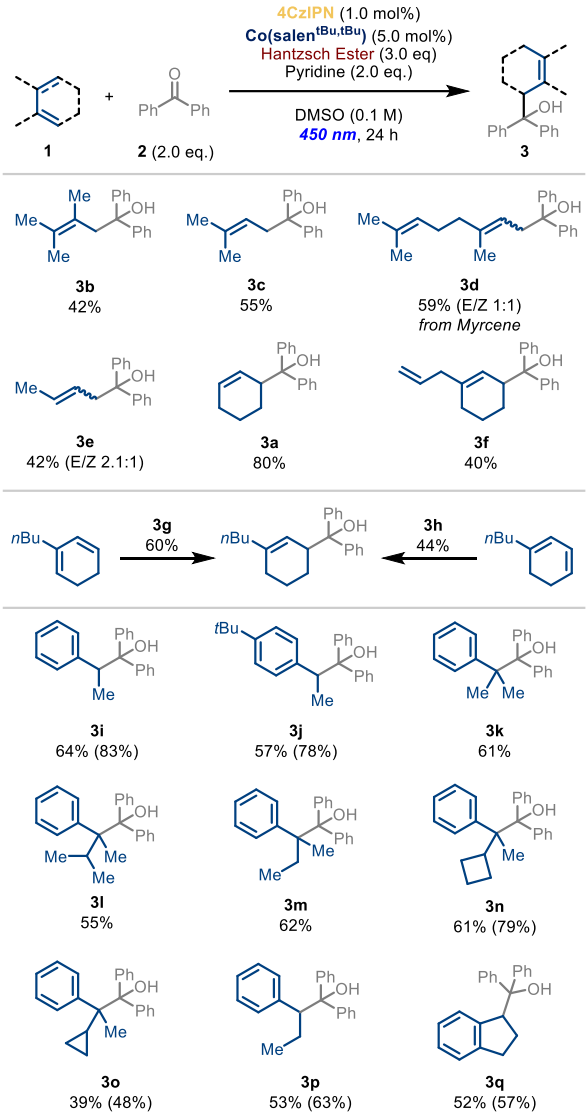
Substrate scope. Next, we explored the substrate scope of the reaction (Scheme 3) beginning first with evaluation of different unsaturated C=C bonds with benzophenone. Linear dienes such as 2,3-dimethyl-1,3-butadiene and feedstocks isoprene, myrcene and 1,3-butadiene all functioned well under our reaction conditions to form products **3b**, **3c**, **3d** and **3e**. Notably, the regioselectivity of the reaction is excellent and follows a predictable pattern as we have recently reported, ascribed to selective HAT at the more electron-rich and less hindered terminus of the diene.[57] As such, regioconvergence is observed in the case of two differently substituted cyclohexadiene starting materials to form a single product **3g**/**3h**. Interestingly, allyl-substituted cyclohexadiene reacts to form product **3f** without any notable functionalisation or isomerisation of the terminal alkene, consistent with our previous reports of photoinduced MHAT catalysis.[37,38] The lack of reactivity of unstabilised olefins is another notable point of this reaction platform that enables selective functionalisation of complex polyolefins (see **3d**). On this basis, we next investigated styrenes, believing they too might work under these conditions. Styrene itself and the *para*-^{t}Bu substituted example both yielded the corresponding branched product in good yield (**3i** and **3j**). Using α-substituted styrenes, we were able to construct congested quaternary centres – a motif that still challenges synthetic chemists – adjacent to the tertiary alcohol in one straightforward step (**3k** to **3o**). Finally, β-methyl styrene and indene yielded the corresponding products, **3p** and **3q**, in moderate yields.

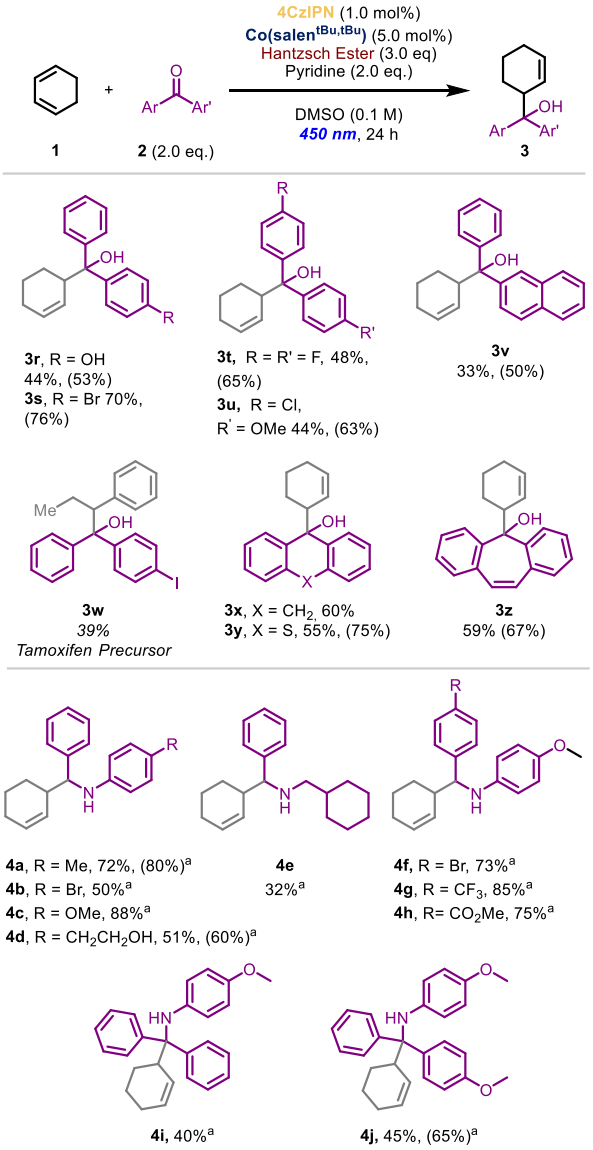


Scheme 3| Substrate scope of diene and styrene substrates**.** Conditions: diene (0.1 mmol, 1 equiv.), ketone (2 equiv.), 4CzIPN(1 mol %), [Co(salen^{tBu,tBu})] (5 mol %), Hantzsch ester (3 equiv), pyridine (2 equiv), DMSO (0.1 M). Diastereomeric ratio is 1:1 unless otherwise stated.

Investigation of the structural diversity of ketone coupling partners followed (Scheme 4). Unsymmetrical benzophenone derivatives with *para*-hydroxy or *ortho*-bromo substitution gave products **3r** and **3s**, respectively. Similarly, fluoro, chloro and methoxy substitution were all tolerated on the aromatic rings of the benzophenone derivatives (**3t** to **3u**), as was an extended aromatic in the case of **3v**. Replacing 1,3-cyclohexadiene with β-methyl styrene and carrying out the reaction with an iodo-substituted benzophenone yielded product **3w** which is a reported precursor of Tamoxifen, a hormone therapy used to treat breast cancer.[66] Encouragingly, tricyclic aromatic ketones, anthrone, thioxanthone (which yields a motif found in Meprotixol, a cough suppressant) and dibenzosuberenone, also performed well in the reaction yielding products **3x** to **3z**.

Based on these promising results, we expanded our exploration to include imines in place of ketones allowing formation of amines in a straightforward manner. Slight adjustments to the reaction conditions were required to obtain satisfactory: Co(salen^{OMe,Br}) (5 mol%) and (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (1 mol%) were used. Aldimines substituted at the 4-position of the *N*-phenyl with methyl, bromo, methoxy and ethyl alcohol

groups were all good substrates for the reaction (**4a** to **4d**). However, alkyl substitution on the nitrogen resulted in a lower yield (**4e**). Different substitution patterns on the aryl group all resulted in good yields (**4f** – **4h**) and it was possible to vary the diene used as a coupling partner (**4k**, Scheme 5). Interestingly, ketimines also functioned as substrates under our reaction conditions, enabling formation of congested quaternary centres adjacent to an amine (**4i** and **4j**).



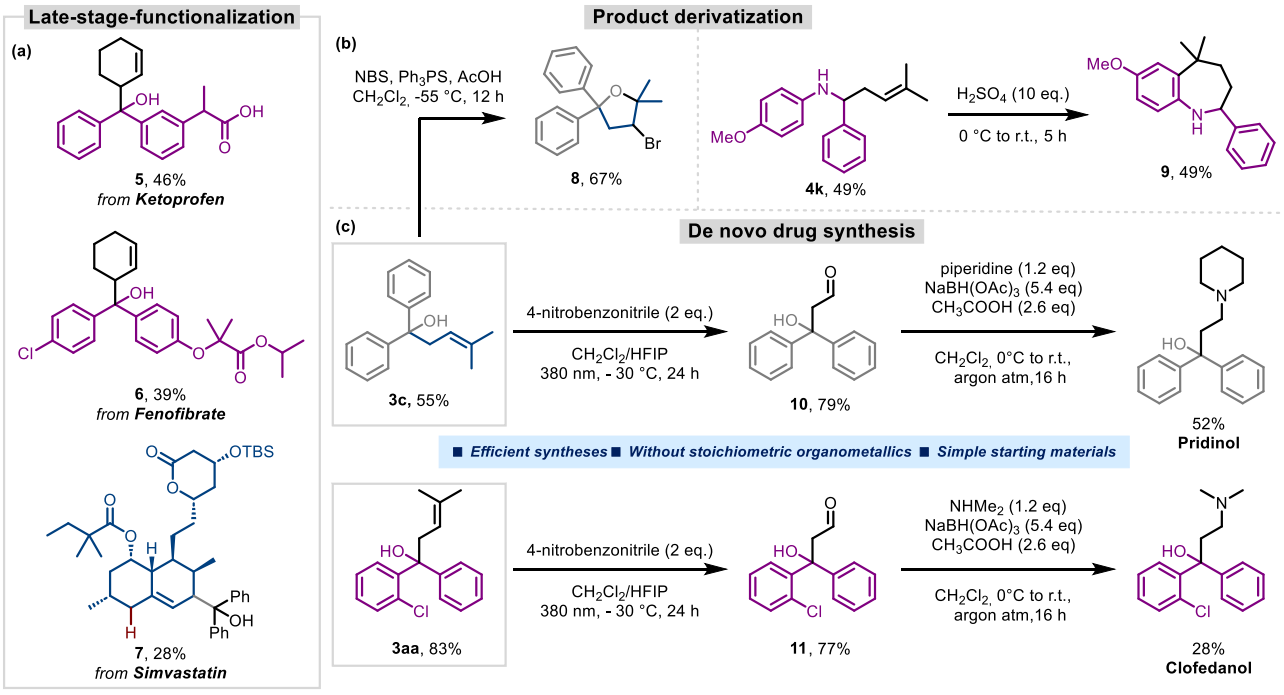
Scheme 4| Scope of ketones and imines. [a]Conditions used for imines: imine (0.1 mmol, 1 equiv.), diene (3 equiv.), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (1 mol %), [Co(salen^{OMe,Br})] (5 mol %), Hantzsch ester (3 equiv), pyridine (2 equiv), DMSO (0.2 M). Diastereomeric ratio is 1:1 unless otherwise stated.

Encouraged by the functional group tolerance of our method, we then sought to apply our method to more complex molecules (Scheme 5a). The diarylketone motif is frequently found in drug molecules[67] and so we sought to demonstrate the reactivity of some examples under our developed conditions. Both Ketoprofen (an anti-inflammatory medication) and Fenofibrate (a treatment for abnormal lipid levels) successfully underwent late-stage-functionalisation to yield **5** and **6** demonstrating excellent functional group tolerance, for instance, of carboxylic acids. Dienes can also be found in drug molecules and Simvastatin, a commercial lipid-lowering

medicine, could undergo selective hydrofunctionalisation with benzophenone to yield product **7**. Although the yield is low, the selectivity of the reaction is excellent.

One advantage of using dienes, beyond their wide-availability, is the resulting C=C bond in proximity to the newly formed C–C bond. To demonstrate the utility of the products that we had synthesized, we further reacted two examples (Scheme 5b). We were able to form the highly-substituted 5-membered heterocycle **8** upon bromonium-induced cyclisation.[68] It was also possible to form the seven-membered heterocycle **9** through an acid-promoted intramolecular Friedel-Crafts type mechanism from **4k** (itself formed on 1 mmol scale).[69]

Finally, we noted the potential to transform the products which we had formed into drug-molecules in a concise manner. **3c** and **3aa** could be formed in good yields on 1 mmol scale by increasing the duration of the reaction.[70] Subsequent oxidative cleavage of these two molecules using the photocatalytic procedure of the Leonori group[71] led to **10** and **11**, respectively. Reductive amination[72] with either piperidine or dimethylamine formed two drug molecules, each in just three steps: Pridinol (a treatment for Parkinson's) and Clofedanol (a cough suppressant). Not only are these syntheses short in number of steps but they avoid all use of stoichiometric organometallic intermediates, minimizing waste streams and thus showcasing the utility of our method in developing modern, streamlined routes to key chemicals. Additionally, this same route could easily be adapted for analogue synthesis by changing the benzophenone and secondary amine in the final step.



Scheme 5| Applications to late-stage-functionalisation and synthesis of drug molecules.

Conclusions

To conclude, we have presented a dual-catalysed method that enables, for the first time, the linear-selective reductive intermolecular coupling of dienes with ketones. This approach has successfully been extended to styrenes and imines. The mild reaction conditions and broad functional group tolerance allows swift

construction of complex molecules and the practical utility has been showcased both in the de novo synthesis and for the late-stage-functionalisation of drug molecules.

Data availability

All of the data are available within the main text or Supporting Information.

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Competing interests

The authors declare no competing interest.

Additional information

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Supporting information contains all data and information required to verify and repeat the conclusions reported in the text.

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