Photoinduced cobalt catalysis for the reductive coupling of pyridines and dienes enabled by paired single-electron transfer

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Abstract

The development of methods to form C–C bonds from readily-available starting materials is essential in driving innovation of functional molecules. In this context, hydrofunctionalisation of feedstock alkenes via catalytic hydrogen atom transfer from an earth-abundant metal can be an effective and efficient approach. However, the range of amenable coupling partners for C–C bond formation is predominantly limited to strongly electrophilic radical traps. Here, we report an alternative approach: simultaneous formation of the key cobalt-hydride intermediate and the persistent radical of easily-synthesised pyridyl phosphonium salts is enabled through paired, photoinduced single-electron transfer. This facilitates selective coupling of dienes and styrenes in a traceless manner at the C4-position of a wide-range of pyridine substrates. The mildness of the method is underscored by its functional group tolerance and demonstrated by applications in late-stage-functionalisation of drugs. Based on a combination of experimental and computational studies, we propose a mechanistic pathway which proceeds through non-reversible hydrogen atom transfer from a cobalt hydride species which is uniquely selective for dienes in the presence of other olefins.

Introduction

Synthesis of complex molecules continues to play a transformative role in our lives, providing essential new materials,[1] agrochemicals[2] and medicines.[3,4] Concurrently, there is intensified focus on developing protocols that circumvent the need for lengthy synthetic manipulations, minimising energy usage and waste generation to access fine-chemicals in an efficient manner.[5] Transition metal catalysis plays a vital role in addressing this key challenge and a recent focus on earth-abundant metals,[6] in combination with photocatalysis, has revealed new reactivity with improved functional group tolerance that provides alternatives to classical synthetic disconnections.[7] One example that takes advantage of the unique properties of first-row transition metals – such as iron, manganese and cobalt – is metal catalysed hydrogen atom transfer (MHAT) to feedstock or easily-synthesised olefins.[8] This approach is a mild, highly chemoselective method for the generation of C–sp^3 radicals from simple, unsaturated starting materials and has been applied to a wide range of hydrofunctionalisation strategies.[9] These have predominantly relied on three main approaches: alkyl radical trapping with activated radicalophiles;[10–13] the merger with nickel catalysis for cross-coupling;[14–17] or radical-polar crossover reactivity with nucleophilic coupling partners.[18–24]

A transformation that has already drawn significant attention in this context, is the selective reductive coupling of olefins with pyridine derivatives (Fig. 1a).[25,26] As pyridine is the most-found heteroarene in drugs[27] as well as being commonplace in agrochemicals and ligand frameworks,[28,29] development of methods for its functionalisation with commodity coupling partners is of widespread interest.[30] The groups of Herzon[31,32] and Baran[33] have both reported pioneering Minisci-type reactivity to trap alkyl radicals formed *via* MHAT with pre-activated N-methoxypyridinium salts, pyridine N-oxides or quinolines complexed with Lewis Acids. These approaches all rely on electrophilic activation of the pyridine heterocycles through the nitrogen atom to increase their SOMOphilicity and propensity for radical trapping (Fig. 1c, left). However, modifying the parent heterocycle in this manner limits the functional group scope and leads to mixtures of C2 and C4 substitution. As C2 substitution is currently significantly more common than C4 in approved drug molecules (Fig. 1b),[27] it would be attractive to develop a selective method that increases availability of the latter substitution pattern.

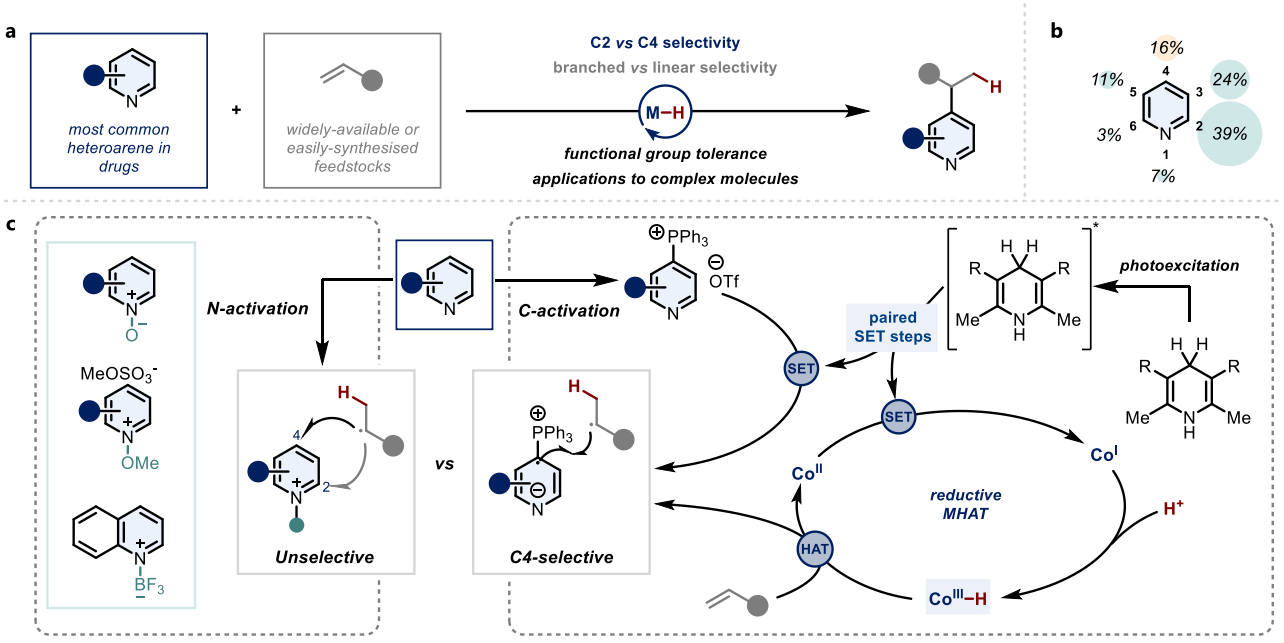


Figure 1| Reductive coupling of pyridines and alkenes. a, General scheme with the associated challenges. **b**, Degree of positional substitution of pyridine drugs. **c**, A comparison of selectivities for N-activation vs C-activation of pyridines. Our reaction design proposed that the required single electron reduction of the pyridyl phosphonium salt could be paired with a reductive metal hydride cycle enabling the merger of these two concepts for selective pyridine functionalisation.

Motivated by this goal, we sought an alternative method to combine pyridine derivatives and unsaturated C–C bonds under mild conditions. For the pyridine synthon, we directed our efforts towards a strategy that involved activation at carbon rather than at nitrogen such that radical density of a corresponding intermediate would be localised at the C4-position. We were drawn to pyridylphosphonium salts,[34] which have been extensively exploited by McNally and co-workers over the last years as easy-to-synthesise precursors with almost limitless availability.[35–38] In particular, they have highlighted their versatility, range of reactivity and how they can easily be applied for the late-stage-functionalisation of drug molecules.[39–43] For Csp^2–Csp^3 bond formation, cross-coupling with pre-functionalised starting materials is possible[44,45] and there is a single report of coupling oxidatively generated benzylic radicals from trifluoroborate salts with the persistent radical anion generated from single electron reduction of the pyridylphosphonium salt.[46]

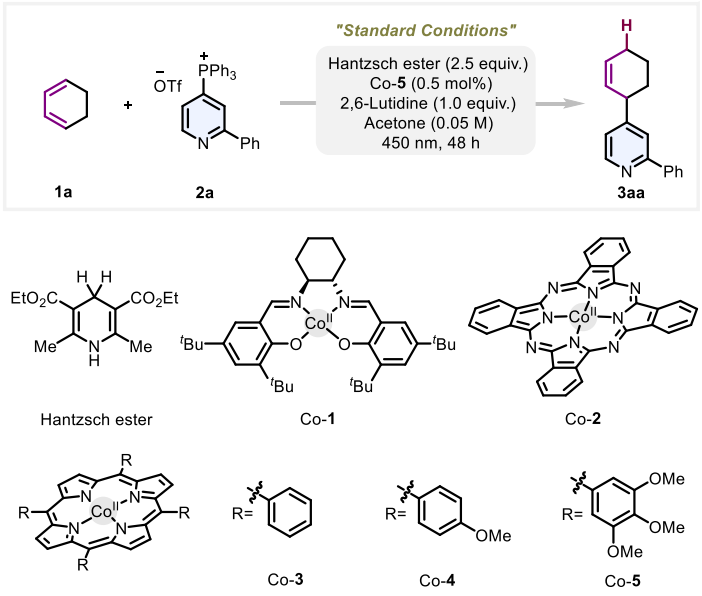
Inspired by this report, we hypothesised that we could potentially utilise such precursors in an MHAT reaction which involves radical-radical coupling. This would require single electron reduction of the phosphonium salts (E_{red} = −1.51 V vs. SCE)[46] to be merged with formation of a metal hydride species – a challenge under classical MHAT conditions which combine oxidants and silanes. However, our group[47] and others[48–52] have recently reported an alternative catalytic paradigm for MHAT catalysis whereby Co(III)–H is formed *via* single electron reduction of Co(II) to Co(I) and subsequent protonation. Our reaction design therefore centred around the pairing of two SET steps: concurrent reduction of Co(II) to Co(I) and of the C4 activated pyridyl phosphonium salt to the corresponding persistent radical coupling partner (Fig. 1c, right).[53] We envisaged achieving this through direct photoexcitation of a simple organic hydride donor, which would release electrons and protons for the reaction in a controlled manner.[54] To date, this approach had been limited to cyano-(hetero)arenes where preparation of heavily derivatised examples requires traditional cross-coupling chemistry with halogenated starting materials.[47,52] In contrast, pyridylphosphonium salts would be a vastly more generalised precursor due to their ease of synthesis from the parent pyridines, resulting in considerably broader applications. Herein we describe the realisation of this concept and demonstrate that this approach results in a uniquely selective catalytic platform for the reductive coupling of dienes and pyridines with applications to complex molecule synthesis.

Results

Reaction design and optimisation. We began by investigating the coupling of commercial 1,3-cyclohexadiene **1a** and pyridyl phosphonium salt **2a,** as the resulting product, **3aa**, would contain a useful alkene moiety for further functionalisation. However, from the outset, we were cognizant that we faced challenges with our envisaged reaction design: under reductive conditions, classical hydrogen evolution is a competing reaction[55] and we anticipated that non-productive reductive cleavage of the C–P bond of the phosphonium salt may rival productive C–C bond formation. This concern was underscored by the results obtained when using conditions previously developed by the Lin group (Mg as a chemical reductant and acetic acid as a proton source).[52] This resulted solely in reductive cleavage of the C–P bond, returning 2-phenylpyridine. Turning next to photoinduced reactions, with the hope that a more controlled release of electrons and protons may favour productive C–C bond formation, we performed extensive screening of photocatalysts, solvents and bases with cobalt-salen catalysts but were unsuccessful in obtaining the desired product **3aa** in more than traces of yield.

As such, we became interested in exploring cobalt porphyrin catalysts which have a wide-range of applications – for example in CO_2 reduction,[56] nitrene formation[57] and alkane oxidation[58] – but are significantly less-explored in MHAT reactions.[59] After extensive investigation, our optimised conditions rely on just 0.5 mol% of Co-**5** under 450 nm light irradiation (Fig. 2). Hantzsch ester (2.5 equivalents) is used as a photoactive electron (and proton) donor and 2,6-lutidine as a base. A number of solvents performed well but acetone was the best (see supplementary information for details). Interestingly, cobalt-salen Co-**1** resulted in no product formation under these conditions whereas cobalt-phthalocyanine Co-**2** gave product, albeit in a lower yield (Table 1, entries 2 and 3). The ease of porphyrin synthesis allowed us to vary the electronics of the pendant aryl group for cobalt tetraphenylporphyrin (TPP) derivatives. Notably, the more electron-rich cobalt catalyst Co-**5** gave slightly better results than others tested, Co-**3** and Co-**4** (Fig. 2, entries 1, 4 and 5).

Control experiments demonstrated that the cobalt catalyst, the Hantzsch ester and light were all required for the reaction to proceed (Fig. 2, entries 6, 7 and 8). In contrast, removal of the 2,6-lutidine species did not significantly impede the reaction, and the desired product was observed in 72% yields (Fig. 2, entry 9) which may plausibly be as a result of similar basic pyridine species arising during the course of the reaction from oxidation of the Hanztsch Ester and also from product formation. Finally, replacement of the pyridylphosphonium salt with 4-iodopyridine did not yield any desired product, whereas 2-cyano-4-phenylpyridine gave a low 29% yield of product. These results are consistent with this reaction proceeding *via* a radical-radical coupling mechanism rather than radical substitution.



Entry	Variations to the standard conditions	Yield (%)[a]
1	none	86 (80%)[b]
2	Co-**1** instead of Co-**5**	0
3	Co-**2** instead of Co-**5**	66
4	Co-**3** instead of Co-**5**	73
5	Co-**4** instead of Co-**5**	78
6	w/o [Co]	0
7	w/o Hantzsch ester	0
8	w/o light	0
9	w/o 2,6-lutidine	72

Figure 2| Reaction optimisation. Notes: [a]Yields were determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yield.

Substrate scope. With the optimised conditions in hand, we next investigated the reaction scope (Fig. 3). The methodology proved to be general to 2-arylpyridine phosphonium salts as both electron-withdrawing halogen atoms and electron-donating groups gave the corresponding functionalised pyridines in good to excellent yields (**3ba-3fa**).[60] Despite the reductive conditions used, aryl halides are fully tolerated, highlighting the selectivity of the single electron reduction step. Heteroaromatic moieties were also well tolerated: the strategy of preactivation at carbon facilitates desymmetrisation of bipyridine leading to **3ga** in 56% yield and providing swift access to interesting ligand derivatives. In addition, both pyridyl-thiophene **3ha** and pyridylfuran **3ia** could be isolated in good yields. Pyridines bearing a benzyl group on the C2 position,

3ja and **3ka**, could also be synthesised using our protocol. We were interested in employing a non-cyclic diene with some substrates to explore the regioselectivity of the process with regards to the diene. Linear products from 1,4-hydropyridylation were obtained which provides frameworks which contrast with typical branch-selectivity obtained in MHAT catalysis with alkenes. For these reactions it was necessary to use $Ru(bpy)_3(PF_6)_2$ as photocatalyst (conditions B). In doing so, we were able to isolate **3kb** in 62% yield and simple 2-alkylpyridine and non-substituted pyridine phosphonium salts led to the corresponding allylated products **3lb** and **3mb**, respectively.

Next, we focussed our attention on the scope of the olefinic coupling partner (Fig. 3b). When employing the optimised conditions with the model 2-phenyl pyridine **2a** and diene **1b**, the corresponding product **3ab** was isolated in excellent yield. Unsymmetrical dienes could be used in the reaction leading to the desired products, **3ac** and **3ad**, with excellent regioselectivity. Experimentally, it has been observed that the MHAT step occurs predictably on the more electron-rich and less hindered terminus of the diene. Remarkably, the process is extremely chemoselective: only the diene system reacts even in the presence of other simple olefins. For instance, complex terpene polyolefins myrcene and *trans*-farnesene, which are frequently used in the fragrance industry, react with complete regioselectivity to yield **3ae** and **3af**, respectively. This contrasts to our attempts with the previously reported hydropyridylation method from Herzon and co-workers[31] on this substrate whereby a complex mixture of products was obtained. Notably, we also never observed reactivity of the product olefins in the reaction and the same regio- and chemoselectivity can be emphasised with a carvone derivative where pyridine **3ag** was obtained as a mixture of diastereoisomers. The pendant isopropene group, which is unreactive under our conditions, is usually highly prone to react under classical MHAT conditions,[61] demonstrating the unique selectivity of our photoinduced approach and orthogonality to previously reported methods.

Introducing substitution on the 1,3-cyclohexadiene moieties allowed us to further probe the selectivity of the hydrofunctionalisation. Interestingly, the pyridine **3ah** could be obtained as a single regioisomer when employing either 1-*n*-butylcyclohexadiene **1h** or 2-*n*-butylcyclohexadiene **1h'**. These experiments highlight that HAT from the Co(III)–H occurs at the sterically less-hindered, more electron rich terminus of the diene – a pattern that is discussed further in the computational part of this study. The resulting delocalised, allylic radical then couples with the radical anion of the phosphonium salt through the least-hindered C–atom. As such, 1,2-hydropyridylation occurs for diene **1h**, however 1,4-hydrofunctionalisation occurs for **1h'**. MHAT catalysis is proposed to be an extremely chemoselective methodology for hydrogen-atom transfer and, as such, other reducible functional groups such as esters are also fully tolerated under the reaction conditions, with **3ai** obtained in moderate yield. Beyond dienes, cyclohexylallene was reactive under the conditions giving a low yield of **3aj** and styrenes could also be employed. In these cases, an additional photocatalyst was required to obtain good conversion into the desired products. The corresponding C4-functionalised pyridines could be isolated in moderate to good yields and included β-substitution on the styrene (**3fm**). Finally, the methodology was not limited to aryl-styrenes and the heteroaromatic styrene **1n** led to the desired product **3an** in moderate yield.

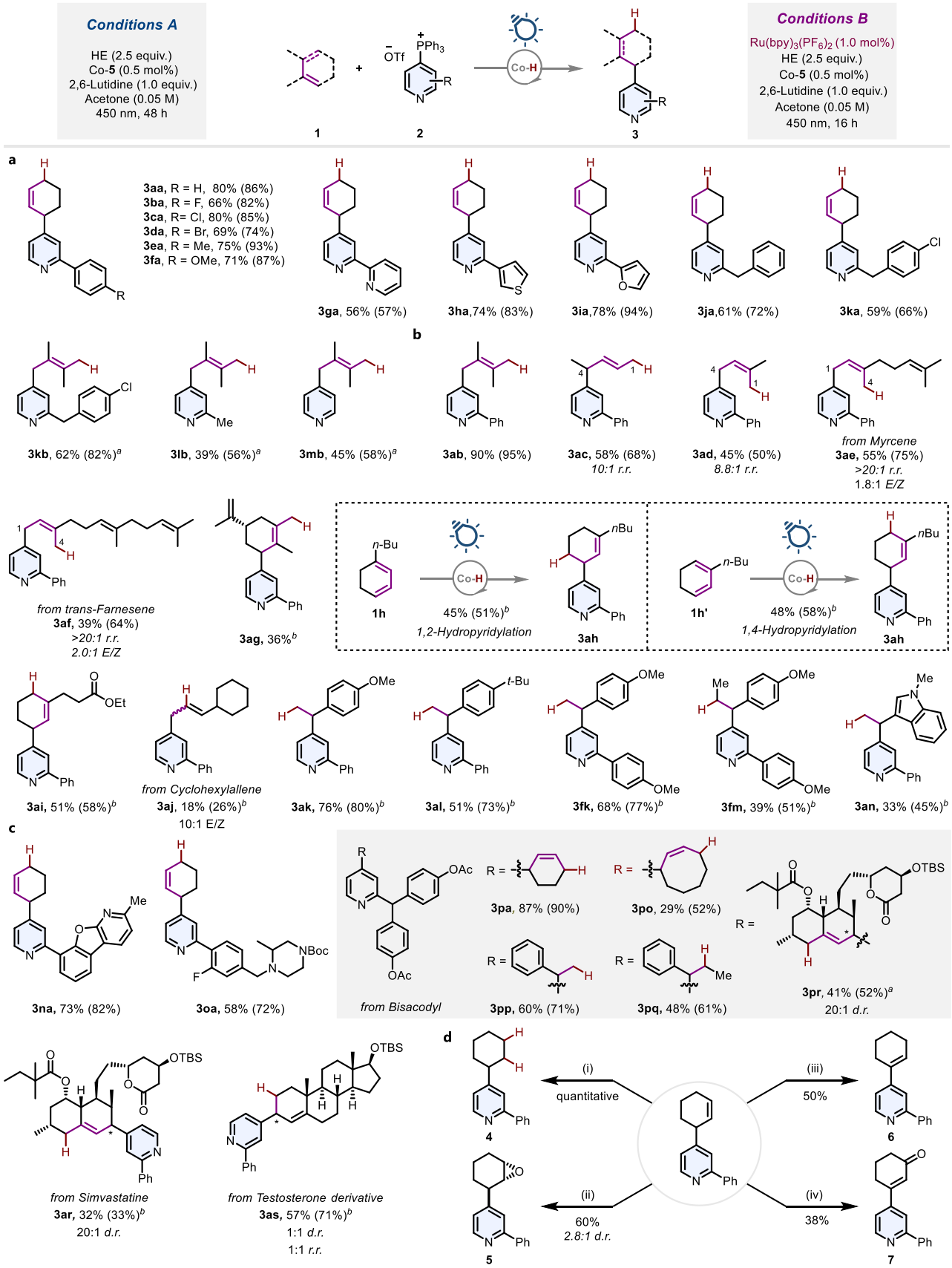


Figure 3| Substrate scope and applications. a, Variation in the pyridine substitution pattern. **b**, Diversity of dienes and styrenes that can be employed in the reaction. **c**, Applications to drugs and drug-like molecules. **d**, Synthetic transformations of product: (i) H_2, Pd/C, MeOH, rt, 16 h; (ii) 1,1,1-trifluoroacetophenone, H_2O_2, MeCN, *t*-BuOH, aq. Buffer

(pH 11), rt; (iii) DBU, MeCN, 65 °C, air; (iv) TBHP, Pd/C, K_2CO_3, DCM, 0 °C to rt. Notes: yield determined by ^{1}H NMR by comparison with an internal standard is given in parentheses. d.r. was determined by analysis of ^{1}H NMR of the crude reaction mixture. Reactions were performed under conditions A unless otherwise indicated. [a]performed under condition B [b]conditions B were used but with 48 h reaction time.

To further probe the robustness of the process and demonstrate applicability, late-stage functionalisation of drugs, or drug-like molecules, was attempted (Fig. 3c). The product **3na**, containing a benzofuran-pyridine moiety, was obtained selectively in high yields again thanks to the selective C-activation approach. Other functionality such as tertiary amines and Boc-protected amines were also fully tolerated under the reaction conditions, with **3oa** isolated in moderate yield. The phosphonium salt **2p**, derived from Bisacodyl, could be coupled with a range of different diene and styrene partners to give late-stage-functionalisation products in moderate to good yields (**3pa, 3po**–**3pr**). This includes coupling with larger ring dienes (**3po**) and highly-functionalised Simvastatin (**3pr**), uniquely enabling the stitching together of two separate drug moieties. This highlights that our methodology is also unusually amenable to late-stage-functionalisation from both sides of the scope. Simvastatin **1r** could also be coupled with **2a**, resulting in a product, again, as a single, predictable regio- and diastereoisomer. A testosterone derivative could also be used in the reaction, however in this case, a mixture of diastereoisomers, as well as isomerised products, were obtained upon purification of the crude mixture. Finally, a significant advantage of using dienes over alkenes is that the product contains an alkene within close proximity of the newly formed C–C bond to the pyridine. The synthetic versatility of this functionality to undergo a range of further oxidation and reduction reactions allows product **3aa** to be transformed into diverse structures, **4**–**7** (Fig. 3d).

Mechanistic studies. Next, we turned our attention to investigating the mechanism and selectivity of this reaction by carrying out a DFT computational study of the proposed catalytic cycle (Fig. 4A; see supplementary information for computational details). As is consistent with the experimentally measured reduction potentials, 2-phenyl-pyridylphosphonium, $\mathbf{Py}^+$ (E_{red} = −1.51 V vs SCE),[46] can be easily reduced by the excited state of the Hantzsch Ester (E_{red}^* = −2.28 V vs SCE)[62] to form the zwitterionic radical $\mathbf{Py}^0$ exergonically. This persistent radical can be accumulated in the reaction media to react rapidly with the allyl radical once it is generated.[53] This step involves reaction of Co(III)–H with 1,3-cyclohexadiene through HAT whereby the metal is reduced to Co(II) and the diene is transformed to the corresponding allylic radical, through a broken-symmetry singlet transition state (as confirmed by the spin density distribution in Fig. 4B). As expected, HAT is selective at the external position of the diene due to the larger stability of the resulting allyl radical $\mathbf{^2II_1}$ **(-35.4 kcal/mol)** compared to unconjugated radical $\mathbf{^2II_2}$ (-20.7 kcal/mol). The free energy barrier for the transition state of HAT from Co(III)–H to the diene, was calculated to be 4.7 kcal/mol for the external position ($\mathbf{TS_{Ext.}}$) compared to 9.6 kcal/mol for the internal position ($\mathbf{TS_{Int.}}$) – which is almost identical for cyclohexene (see Fig. S9 in the supplementary information). This significantly higher value – a $\Delta\Delta G^‡$ of 4.9 kcal/mol – explains why experimentally only dimeric and reduced products from the pyridyl phosphonium salt, **2a** are observed with cyclohexene as the olefin substrate (Fig. 4C (i)). There is insufficient concentration of the cyclohexyl radical for productive bond formation and so non-productive radical reactions occur from the radical anion of the pyridylphosphonium, $\mathbf{Py}^0$. This points to a more general rationale for the unique selectivity of stabilised alkenes under these conditions.

For 1,3-cyclohexadiene, the HAT step was calculated to be very exergonic (-20.1 kcal/mol), indicating a non-reversible process. We probed this experimentally by carrying out a reaction between excess styrene-d_8 and

2a (Fig. 4C (ii)). In this case, the product was obtained with the full incorporation of H at the terminal position (2:1 ratio of D:H) and no loss of deuterium was observed in the recovered styrene starting material which is consistent with irreversible HAT. Further deuterium labelling studies (Fig. 4C (iii)) showed conclusively that HAT occurs at the terminus of the alkene, in particular the least hindered position for substituted substrate **1h**. Computational probing of **1h** and **1h'** (see Fig. S8 in the supplementary information) confirmed that in **1h** the favoured position of HAT is the less hindered external position and in **1h'**, the external position next to ^{n}Bu is favoured, in accord with the experimentally observed convergence to the same radical-radical coupling product, **3ah** (Fig. 3). Interestingly, the largest incorporation of deuterium (Fig. 4C (iii)) occurred through use of excess D_2O, which is in agreement with Co(III)–H being formed through reduction of protic species with Co(I).[59]

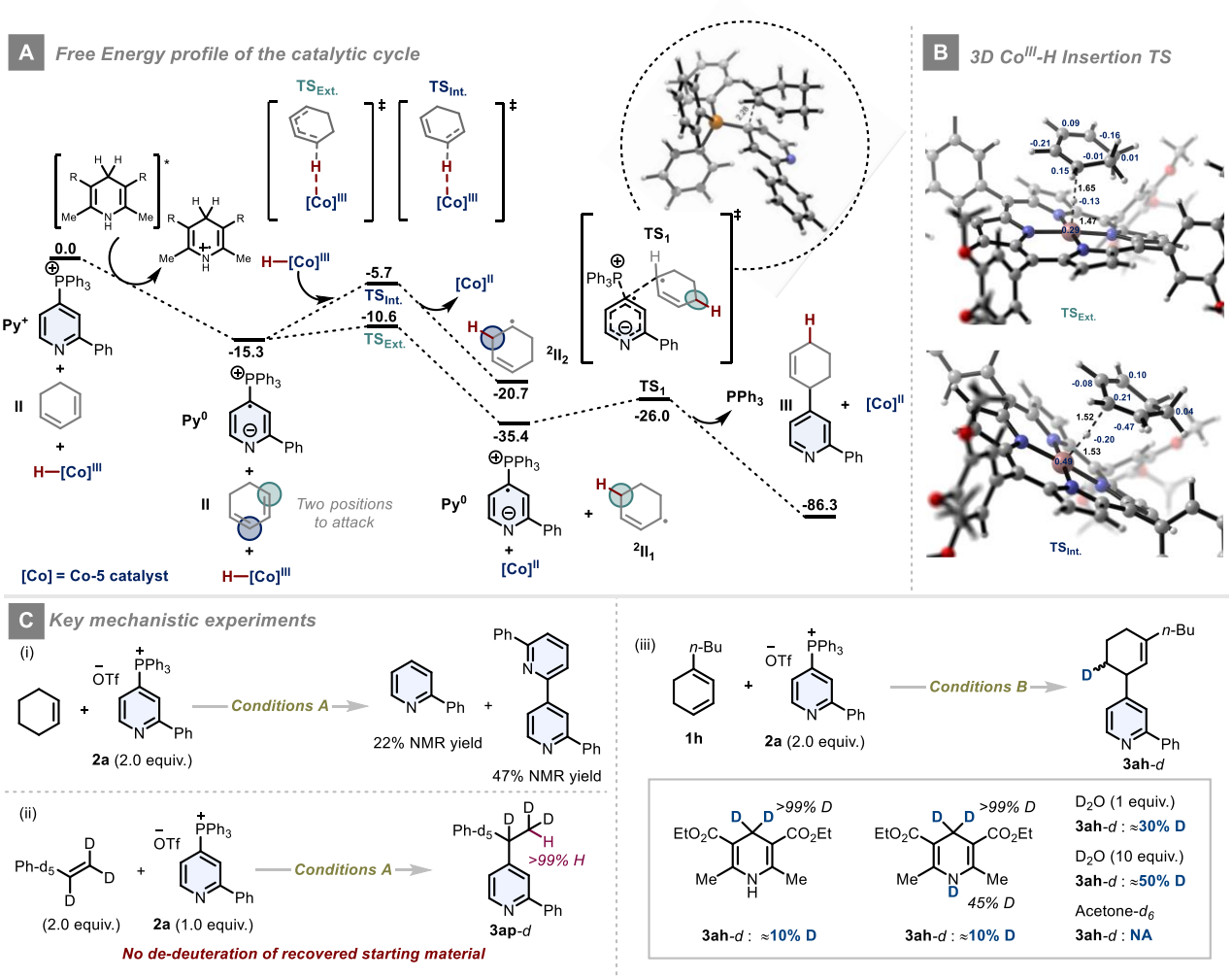


Figure 4| Mechanistic studies. A) Free energy profile of the proposed catalytic cycle (Energies in kcal/mol). B) 3D structures of Co(III)-H Hydrogen Atom Transfer to cyclohexadiene (black: bond distances in Å; blue: spin densities in a.u.) C) Deuterium labelling mechanistic experiments.

Next we turned to the proposed radical-radical coupling through concerted **TS1**. The free energy barrier is relatively high for a radical process (9.4 kcal/mol)[53] which is due to the large distortion of the PPh_3 leaving group which must move out of the plane, resulting in additional steric interactions in the transition state. The concentration of radical species in solution would make the actual rate of coupling even lower as the persistent radical needs to be accumulated in solution, explaining the observed reaction times and lack of

productive reactivity with unstabilised olefins where insufficient concentration of the radical coupling partner is formed. For comparison of the radical-radical coupling on other pyridine substrates, we recalculated the process using unsubstituted pyridylphosphonium and 3-phenyl-pyridylphosphonium radicals. The free energy barrier is increased by 2.9 kcal/mol when the highly hindered 3-substituted pyridine is used, which does not react experimentally (see Fig. S11 in the supplementary information). An alternative pathway based on the protonation of radical $\mathbf{Py^0}$ before the radical-radical coupling was also calculated and the free energy barrier was found to be very similar (10.2 kcal/mol, see Fig. S12 in the supplementary information). Finally, the resulting product **III** is formed irreversibly, releasing triphenylphosphine as side product.

Conclusions

We have reported a catalytic reactivity platform to reductively couple dienes and pyridyl phosphonium salts under mild, photochemical conditions. Exquisite site-selectivity and functional group tolerance are hallmarks of this method which can be applied in the late-stage-functionalisation of both pyridine- and diene-containing drug molecules. Detailed mechanistic investigations have shed light on the unique regioselectivity that we observe in this reaction leading to a predictable platform that enables new routes to complex molecules from simple starting materials.

Methods

General procedure for the reductive coupling of dienes with pyridylphosphonium salts.
In an oven-dried 4 mL vial equipped with a magnetic stirring bar were added the phosphonium salt (0.20 mmol, 2.0 equiv.), Hantzsch ester (63.33 mg, 0.25 mmol, 2.5 equiv.), and Co-**5** (0.52 mg, 0.5 µmol, 0.5 mol%). A plastic cap with rubber septum was used to close the vial and the system was degassed with a stream of argon for 15 minutes. Acetone (2.0 mL, 0.05 M) was added followed by the diene or styrene (0.10 mmol, 1.0 equiv.) and 2,6-lutidine (11.6 µL, 0.10 mmol, 1.0 equiv.). The vial was then placed in the PhotoRedOx Box (see Materials and Methods for more details about the photochemical setup) and irradiated at 450 nm for 48 hours. The crude was then filtered on a plug of silica (EtOAc as eluent) and concentrated under reduced pressure.

Data availability

All of the data are available within the main text or supplementary information.

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Author contributions

C.J.T. and J.Q. designed the project. J.Q. and M.B. performed the optimisation. Further synthetic work including scope and mechanistic investigations were performed by J.Q., M.B. and S.J.. I.F.-A. and N.S. performed all computational experiments. I.F.-A. and C.J.T. directed the work and wrote the manuscript with contributions from all authors.

Competing interests

The authors declare no competing interest.

Additional information

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

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