How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202310639
doi.org/10.1002/anie.202310639

Photochemistry

Photoinduced Cobalt Catalysis for the Reductive Coupling of Pyridines and Dienes Enabled by Paired Single-Electron Transfer**

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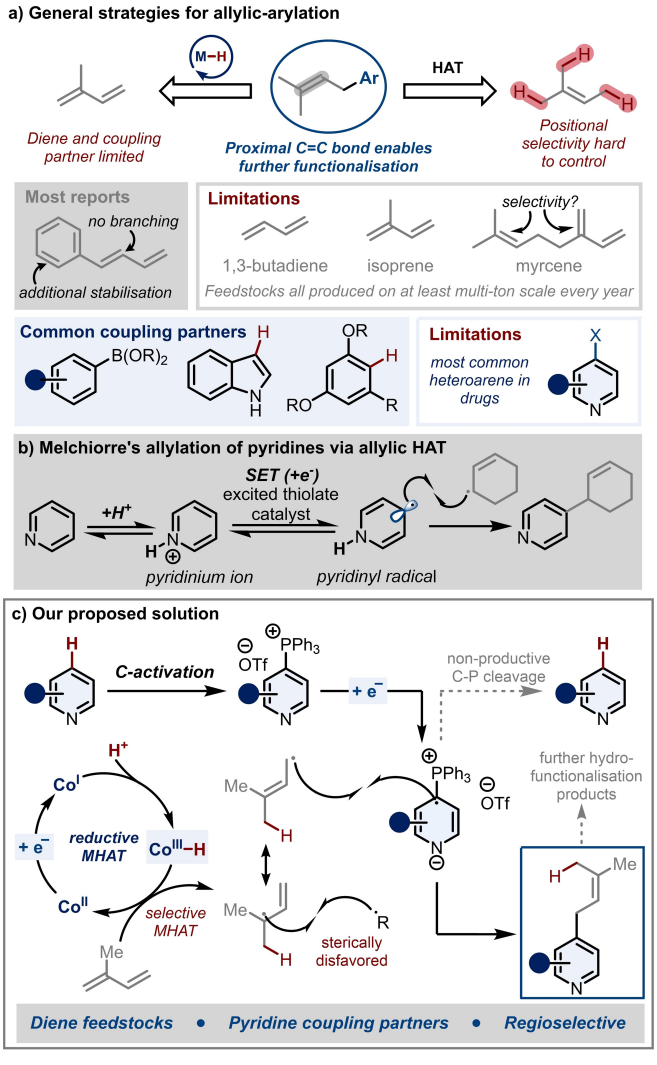
Abstract: Selective hydroarylation of dienes has potential to provide swift access to useful building blocks. However, most existing methods rely on dienes stabilised by an aromatic group and transmetallation or nucleophilic attack steps require electron-rich aryl coupling partners. As such, there are few examples which tolerate wide-spread heteroarenes such as pyridine. Whilst allylic C–H functionalisation could be considered an alternative approach, the positional selectivity of unsymmetrical substrates is hard to control. Here, we report a general approach for selective hydropyridylation of dienes under mild conditions using metal catalysed hydrogen-atom transfer. Photoinduced, reductive conditions enable simultaneous formation of a cobalt-hydride catalyst and the persistent radical of easily-synthesised pyridyl phosphonium salts. This facilitates selective coupling of dienes 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. Based on a combination of experimental and computational studies, we propose a mechanistic pathway which proceeds through non-reversible hydrogen-atom transfer (HAT) from a cobalt hydride species which is uniquely selective for dienes in the presence of other olefins due to a much higher relative barrier associated with olefin HAT.

Introduction

Dienes are readily-available feedstocks which are ideal starting materials for fine-chemical synthesis.[1] Their regioselective catalytic hydrofunctionalisation offers a potentially straight-forward, efficient route to a single product in a manner that cannot be matched by other approaches such as allylic hydrogen atom abstraction which face selectivity issues (Scheme 1a).[2–5] The resulting products are versatile building blocks which contain a C=C bond in proximity to



Scheme 1. Strategies for Markovnikov Hydroarylation.

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[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/10.26434/chemrxiv-2023-3rshq).

the newly formed bond, acting as an attractive handle for further derivatisation.

Construction of a new Csp^2–Csp^3 bond by hydroarylation of dienes has been explored using two primary approaches. The first relies on Ni or Pd hydride species which undergo concerted hydrometallation.[6–10] In these cases, the diene scope is usually limited to activated examples and heteroaromatic coupling partners are rare. Alternatively, π-acidic metal species or Lewis acids can activate the diene to nucleophilic attack by an electron-rich arene or heteroarene.[11–16] The lack of generality for reactive dienes and dearth of examples with Lewis-basic heteroarene coupling partners sparked our interest in developing a new strategy in this area. In particular, we were interested in opening up reactivity that was compatible with pyridines as these are the most-found heteroarenes in drugs[17] as well as being commonplace in agrochemicals and ligand frameworks.[18,19] As such, methods for their functionalisation are in high demand.[20]

During the course of this project, the Melchiorre group reported a novel photochemical organocatalytic functionalisation of pyridines with allylic radicals which can access similar motifs.[21] Their reaction proceeds via the generation of a C4-centred pyridyl radical originating from pyridinium ions upon single electron transfer (SET) with a highly reducing excited thiolate based organocatalyst (Scheme 1b). The organocatalyst can also function as an HAT catalyst, abstracting allylic C–H bonds to generate the coupling partner. Radical-radical coupling forms the new C–C bond and in cases without bulky groups at the C3 position, good C4 selectivity is obtained. Notably, their work does not require pre-functionalisation of the pyridine, however, some limitations arise with site-selectivity of the HAT and this approach is likely unsuitable for more complex polyolefins.

As an alternative, our proposed tactic relied on metal catalysed hydrogen atom transfer (MHAT) catalysis whereby a cobalt catalyst could selectively transfer a hydrogen atom to an unsaturated C–C bond.[22–24] We hypothesised that generation of this key cobalt hydride species under a photoinduced, reductive regime might allow us to pair this with reductive generation of a second radical,[25–29] ultimately leading to selective, sterically controlled coupling based on the persistent radical effect (Scheme 1c).[30] For the heteroarene synthon, we sought to exploit pyridyl phosphonium salts, easy-to-synthesise precursors which have been extensively researched by McNally and co-workers over the last years.[31–36] These versatile substrates can easily be applied for the late-stage-functionalisation of drug molecules[37–41] and the single report of coupling oxidatively generated benzylic radicals from trifluoroborate salts suggested the possibility of persistent radical formation via single electron reduction.[42]

However, we were conscious that we may face several problems with our envisaged reaction design. Firstly, unproductive, reductive cleavage of the C–P bond of the phosphonium salts could compete with productive C–C bond formation (Scheme 1c). Secondly, under reductive conditions, classical hydrogen evolution is a competing reaction.[43] Finally, it would be imperative to control the hydrogen atom transfer step to the diene both to control regioselectivity and also so that we would observe no reactivity of the resulting products, through further hydrofunctionalisation, reduction[44–49] or isomerisation[50,51] reactions which would nullify the proximal C=C functional handle.[52] Given that previous MHAT catalysed methods both for hydropyridylation[53–55] and other hydrofunctionalisation[56–73] reactions have demonstrated that alkenes are also prone to react under these conditions, selection of an appropriate catalytic species for this approach was crucial. We reasoned that the M–H bond strength may play a key role in allowing selective HAT for dienes over alkenes: a stronger bond may preclude formation of the unstabilised carbon radical from the alkene.[74] 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.

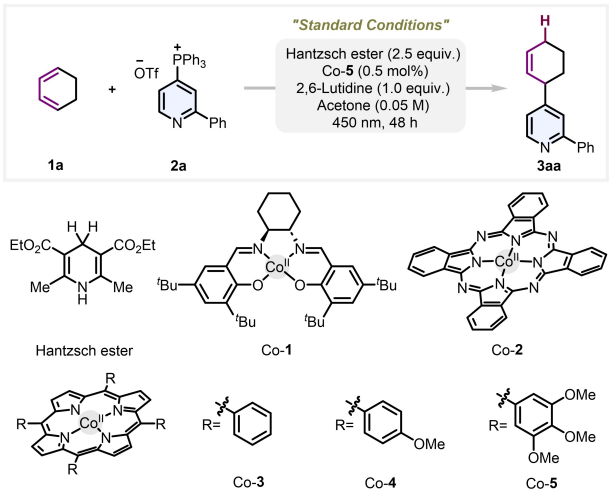
Results and Discussion

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 cyclic alkene poised for further derivatisation. Interestingly, the anticipated non-productive reductive cleavage of the C–P bond of the phosphonium salt was observed when using conditions previously developed by the Lin group (Mg as a chemical reductant and acetic acid as a proton source),[26] yielding solely 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,[75] nitrene formation[76] and alkane oxidation[77] - but are significantly less-explored in MHAT reactions.[78] After extensive investigation, our optimised conditions use just 0.5 mol% of Co-**5** under 450 nm light irradiation (Table 1). Hantzsch ester (2.5 equiv.) 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 Supporting Information for details). Interestingly, 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** (Table 1, entries 1, 4 and 5).

Control experiments demonstrated that the cobalt catalyst, the Hantzsch ester and light were all required for the

Table 1: Reaction optimisation.



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

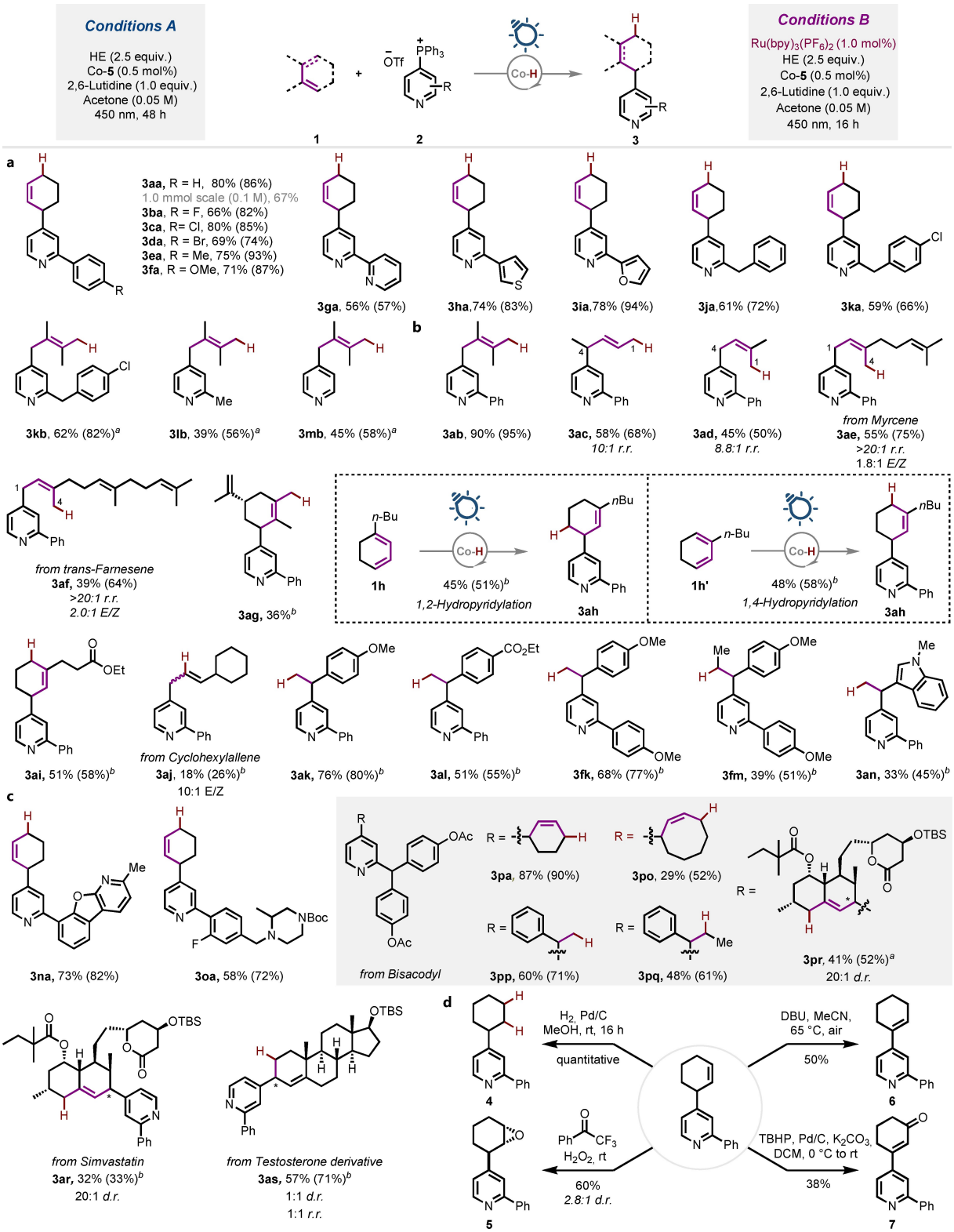
[a] Yields were determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yield.

reaction to proceed (Table 1, 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 (Table 1, 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.

With the optimised conditions in hand, we next investigated the reaction scope (Scheme 2). 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**). To evaluate the synthetic potential of our method, we also carried out a 1.0 mmol-scale preparation of **3aa** and 67 % isolated yield was obtained. 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, 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-methylpyridine and non-substituted pyridine phosphonium salts led to the corresponding allylated products **3lb** and **3mb**, respectively.

Next, we focused our attention on the scope of the olefinic coupling partner (Scheme 2b). 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, both 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[53] 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,[79] demonstrating the unique selectivity of our photoinduced approach and also highlighting orthogonality to the previously reported method by Melchiorre and co-workers.[21]

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 again highlight that HAT from the Co(III)-H occurs at the sterically less-hindered, more electron rich terminus of the diene. 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′**. These results emphasise the power of this approach for selective product formation over allylic HAT approaches.



Scheme 2. 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. 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.

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 both with electron-donating and electron-withdrawing substitution on the aromatic ring (**3ak** and **3al**). 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.

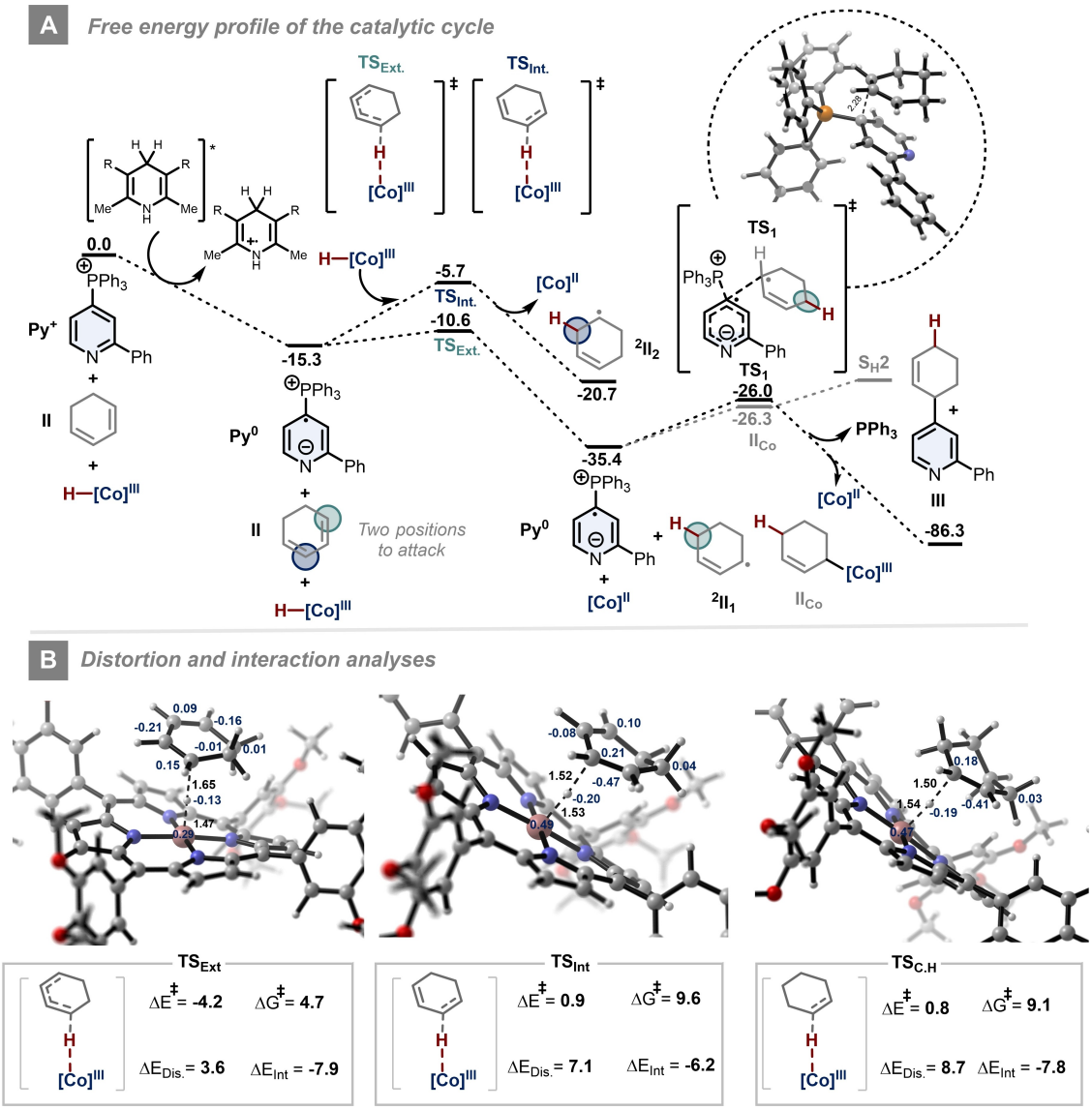
To further probe the robustness of the process and demonstrate applicability, late-stage functionalisation of drugs, or drug-like molecules, was attempted (Scheme 2c). The product **3na**, containing a benzofuran-pyridine moiety, was obtained selectively in high yields again thanks to the selective C-activation 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 underlines that our methodology is 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** (Scheme 2d).

Next, we turned our attention to investigating the mechanism and selectivity of this reaction by carrying out a density-functional theory (DFT) computational study of the proposed catalytic cycle (Scheme 3A; see Supporting Information for computational details). In addition, the absorption and emission spectra of various reaction components were measured. These suggest that some interaction between the cobalt catalyst and Hantzsch Ester might occur,[80] however, are broadly consistent with the proposed pathway outlined below (see Supporting Information for more information).

As is consistent with the experimentally measured reduction potentials, 2-phenyl-pyridylphosphonium, $\mathbf{Py}^+$ ($E_{red} = -1.51$ V vs SCE),[42] can be easily reduced by the excited state of the Hantzsch Ester ($E_{ox}^* = -2.28$ V vs SCE)[81] to form the zwitterionic radical $\mathbf{Py}^{\mathbf{0}}$ exergonically. This persistent radical can be accumulated in the reaction media to react rapidly with the allyl radical once it is generated.[30] This step involves reaction of Co(III)-H - itself formed through reduction of Co(II) to Co(I) by SET and protonation from the reaction mixture[25,78,80] - with 1,3-cyclohexadiene through HAT. Here, 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 Scheme 3B left).

As expected, HAT is selective at the external position of the diene due to the larger stability of the resulting allyl radical $^2\mathbf{II}_1$ (−35.4 kcal/mol) compared to unconjugated radical $^2\mathbf{II}_2$ (−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 ($\mathbf{TS}_{\mathbf{Ext.}}$) compared to 9.6 kcal/mol for the internal position ($\mathbf{TS}_{\mathbf{Int.}}$) - which is almost identical for cyclohexene (see Scheme 3B, right). The origin of the larger free energy barrier was analysed by Distortion-Interaction analysis. While the interaction energy is similar in all the three cases, due to the similar bond strength of the Co–H and C–H bonds, the distortion energy is considerably higher for cyclohexene and the internal position of the diene due to the loss of conjugation in the transition state. This significantly higher value - a $\Delta\Delta G^{\ddagger}$ 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 (Scheme 4(i)). There will be insufficient concentration of the cyclohexyl radical for productive bond formation and so non-productive radical reactions occur from the radical anion of the pyridylphosphonium, $\mathbf{Py}^{\mathbf{0}}$. 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** (Scheme 4(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 (Scheme 4(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 Figure S18 in the Supporting Information) confirmed that in **1h** the favoured position of HAT is the less hindered external position and in **1h′**, the external position next to ″Bu is favoured, in accord with the experimentally observed convergence to the same radical-radical coupling product, **3ah** (Scheme 2). Interestingly, the largest incorporation of deuterium (Scheme 4(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).[78]

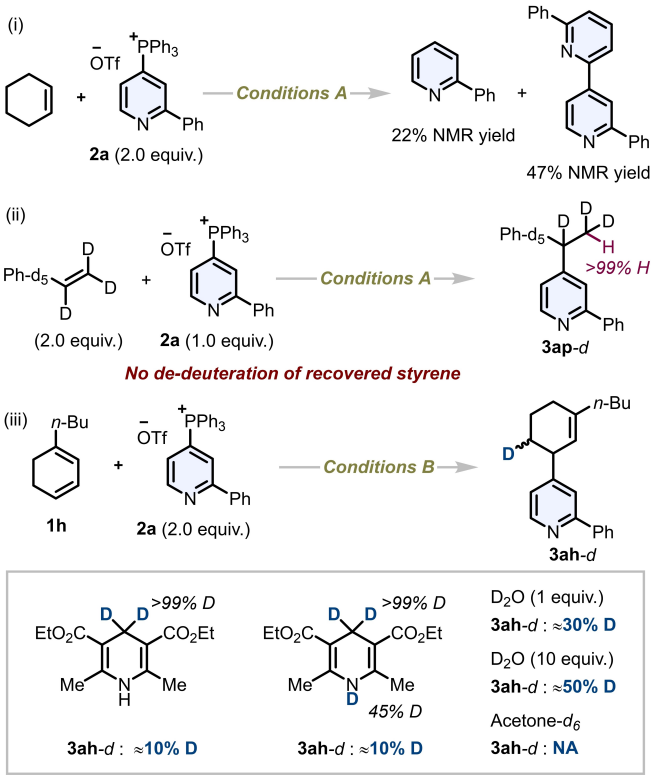


Scheme 3. Mechanistic studies. A) Free energy profile of the proposed catalytic cycle (Energies in kcal/mol). B) 3D structures of Co(III)-H Hydrogen Atom Transfer to cyclohexadiene (black: bond lengths in Å; blue: spin densities in a.u.) and cyclohexene.

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)[30] which is due to the large distortion of the PPh_3 leaving group which must move out of the plane, resulting in additional steric hindrance in the transition state (see Fig S22 for Distortion-Interaction analysis). 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, due to the larger distortion in the transition state (see Figure S22 in the Supporting 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 Figure S23 in the Supporting Information). Finally, the resulting product **III** is formed irreversibly, releasing triphenylphosphine as side product.

Conclusion

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



Scheme 4. Deuterium labelling mechanistic experiments.

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.

Acknowledgements

C.J.T. thanks the Fonds der Chemischen Industrie (Liebig Fellowship), the DFG (Grant number 497336511) and the Boehringer Ingelheim Stiftung (Exploration Grant) for funding of this research. J.Q. is grateful to the CSC for a PhD scholarship. I.F.A. and N.S. thank the financial support for project "PID2021-126075NB-I00" financed by the Spanish MCIN/AEI/10.13039/501100011033 FEDER, UE and the "Ministerio de Ciencia e Innovación" for the Juan de la Cierva-Incorporation (IJC2020-045125-I). We also acknowledge the University of La Rioja for financial support and thank the "Beronia" cluster at University of La Rioja for computational resources. Finally, we are thankful to Enrico Bergamaschi for initial investigations into this project, to Daniele Leonori for helpful discussions and to Franziska Schoenebeck for her continuing support. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cobalt · Density Functional Calculations · Heterocycles · Hydrogen-Atom Transfer · Reaction Mechanisms

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Manuscript received: July 25, 2023
Accepted manuscript online: September 7, 2023
Version of record online: September 27, 2023