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Cite this: *Chem. Sci.*, 2022, **13**, 14320

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 9th October 2022
Accepted 20th November 2022

DOI: 10.1039/d2sc05599f

rsc.li/chemical-science

Three-component carboformylation: α-quaternary aldehyde synthesis *via* Co(III)-catalysed sequential C–H bond addition to dienes and acetic formic anhydride†

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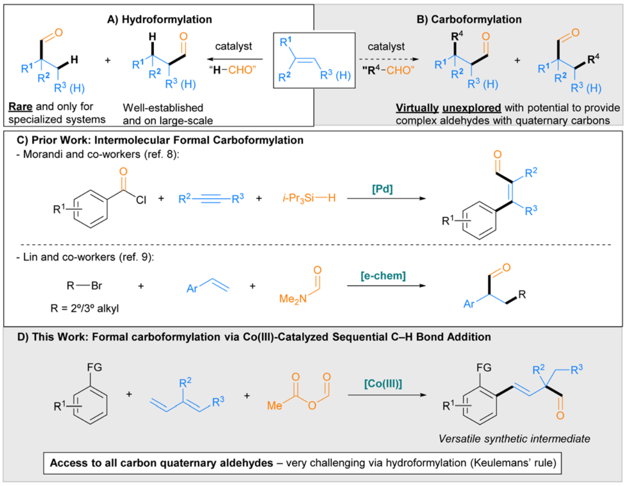
All carbon α-quaternary aldehydes are prepared *via* Co(III)-catalysed sequential C–H bond addition to dienes and acetic formic anhydride, representing a rare example of intermolecular carboformylation. A wide range of internally substituted dienes containing diverse functionality can be employed in this reaction, affording complex α-quaternary aldehydes that would not be accessible *via* hydroformylation approaches. Mechanistic investigations, including control reactions and deuterium labeling studies, establish a catalytic cycle that accounts for formyl group introduction with an uncommon 1,3-addition selectivity to the conjugated diene. Investigations into the role of the uniquely effective additive Proton Sponge® were also conducted, leading to the observation of a putative, intermediate Co(I) tetramethylfulvene complex at low temperatures *via* NMR spectroscopy. The synthetic utility of the aldehyde products is demonstrated by various transformations, including proline-catalysed asymmetric aldol addition, reductive amination, and the asymmetric synthesis of amines using *tert*-butanesulfinamide technology.

Introduction

Aldehydes are highly versatile synthetic intermediates due to the plethora of chemical transformations in which they can participate. Industrially relevant aldehydes are commonly produced on commodity scale using hydroformylation, a metal-catalysed process involving the formal addition of a hydrogen and a formyl group across an unsaturated C–C bond (Scheme 1A).[1] Hydroformylation has been studied extensively, with numerous developments for improving the chemoselectivity, regioselectivity and stereoselectivity of the reaction having been reported.[1,2] Despite these advances, a longstanding challenge in hydroformylation is the preparation of α-quaternary aldehydes from 1,1-disubstituted alkenes, which are generally considered to be prohibited according to the empirical Keulemans' rule, "Addition of the formyl group to a tertiary C atom does not occur, so that no quaternary C atoms are formed."[3] In keeping with this rule, examples of α-quaternary aldehyde synthesis from 1,1-disubstituted alkenes are limited to the use of highly specialized substrates, namely: alkenes containing electron-withdrawing substituents, including heteroatoms and fluorines (to form α-tetrasubstituted aldehydes);[4a,b,d,5a,b,e,g] strained exocyclic alkenes;[5b] and alkenes incorporating a directing group[4c,5f] or a functionality that reacts with a catalytic directing group.[5c,d]

Carboformylation whereby an R group and a formyl group are added across an unsaturated C–C bond has the potential to provide more complex value-added aldehydes given that two new C–C bonds are formed (Scheme 1B). Indeed, for 1,1-



Scheme 1 Key issues and challenges of hydroformylation and carboformylation.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2sc05599f

disubstituted alkenes, either regioisomeric product necessarily incorporates a quaternary carbon, thereby overcoming Keulemans' rule for hydroformylation. However, approaches for achieving carboformylation are virtually unexplored. Initial reports relied on intramolecular transformations *via* Pd-catalysed cyclization-carboformylation cascades between alkene-tethered aryl iodides, carbon monoxide, and methyldiphenylsilane (as a terminal hydride source) to form indoline and 2,3-dihydrobenzofuran structures.[6,7] More recently, two formal intermolecular carboformylation processes have been disclosed. Morandi and co-workers[8] developed a procedure for the Pd-catalysed carboformylation of alkynes using aroyl chlorides as the carbon monoxide and ‘R’ source and triisopropylsilane as the terminal hydride source to form α,β-unsaturated aldehydes (Scheme 1C, top). Additionally, Lin and co-workers[9] developed a method for the carboformylation of styrenes using alkyl bromides and *N*,*N*-dimethylformamide as the formyl source to prepare α-branched aldehydes *via* an electrochemically mediated, radical-polar crossover mechanism (Scheme 1C, bottom). However, only two examples of α-quaternary aldehydes were synthesized using this method.

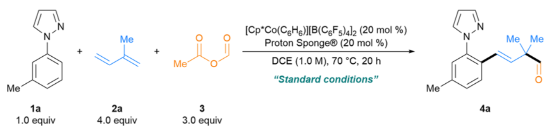
Recently, our group[10] and Zhou, Chen and co-workers[11] have developed Co(III)-catalysed sequential C–H bond additions to dienes and aldehydes, ketones, or an electrophilic cyanating reagent to prepare complex products with two new C–C σ-bonds in a single synthetic step.[12,13] Notably, reactions employing internally substituted dienes furnish a quaternary center. With this in mind, we hypothesized that leveraging the sequential C–H bond addition to dienes and an appropriate formylating agent might therefore grant access to complex all carbon α-quaternary aldehydes. Herein, we describe the development of a Co(III)-catalysed sequential C–H bond addition to dienes and acetic formic anhydride to efficiently prepare complex α-quaternary aldehydes *via* a formal intermolecular carboformylation process. The reaction proceeds with a wide range of internally substituted dienes, affording a broad scope of α-quaternary aldehydes that would not be accessible using existing hydroformylation methods. Mechanistic investigations support a proposed catalytic cycle consistent with the uncommon 1,3-addition to the conjugated diene and the unique effectiveness of Proton Sponge® as an additive. The versatility of the aldehyde products for further synthetic elaboration was illustrated by five distinct transformations, including efficient asymmetric transformations to alcohol and amine products.

Results and discussion

Identification of key reaction parameters towards reaction optimization

After examining a variety of reaction parameters, including catalyst counterion, additive, temperature, solvent, and formylating agent, optimized reaction conditions for the Co(III)-catalysed sequential C–H bond addition of 1-(*m*-tolyl)-1*H*-pyrazole (**1a**) to isoprene (**2a**) and acetic formic anhydride (**3**) to form aldehyde **4a** are presented in entry 1 of Table 1 (see Tables

Table 1 Examining the effects of different reaction parameters in the Co(III)-catalysed sequential C–H bond addition to isoprene (**2a**) and acetic formic anhydride[a] (**3**)



Entry	Variation from standard conditions	Yield of **4a**[b] (%)
1	None	71
2	$[Cp^*Co(C_6H_6)](PF_6)_2$ (20 mol%) in place of $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	20
3	$Cp^*Co(CO)I_2$ (20 mol%) + $AgSbF_6$ (40 mol%) in place of $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	50
4	$Cp^*Co(CO)I_2$ (20 mol%) + $AgNTf_2$ (40 mol%) in place of $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	45
5	No Proton Sponge®	51
6	Proton Sponge® (50 mol%)	0
7	HOAc (20 mol%) in place of Proton Sponge®	44
8	LiOAc (20 mol%) in place of Proton Sponge®	22
9	Performed at 90 °C	56
10	Performed at 50 °C	75
11	In 1,4-dioxane	62
12	In toluene	75
13	In PhCl	74
14	In CH_2Cl_2	76
15	No $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	0
16	$[Cp^*RhCl_2]_2$ (10 mol%) and $AgSbF_6$ (40 mol%) in place of $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), **3** (0.3 mmol), $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (20 mol%), Proton Sponge® (20 mol%) in DCE ([**1a**] = 1.0 M) at 70 °C. [b] Yield determined by crude ^1H NMR spectroscopic analysis relative to trimethyl (phenyl)silane as standard. Tf = triflyl, DCE = 1,2-dichloroethane, PhCl = chlorobenzene.

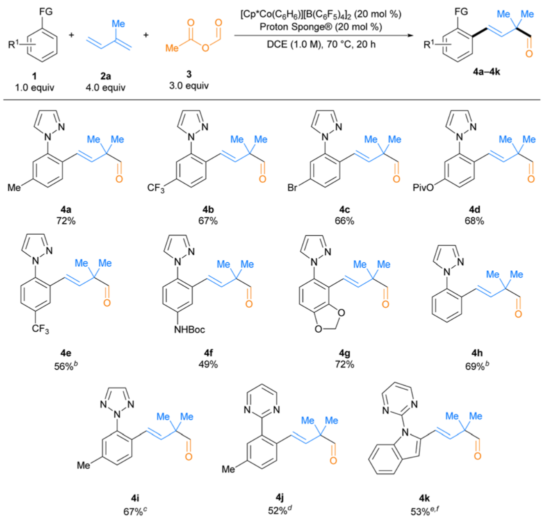
S1–S5 in the ESI for additional information†). $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$, developed by our lab,[14] proved to be a superior catalyst for this transformation because it is completely non-coordinating and provides for high solubility of the catalyst (entry 1). Other pre-formed Co(III) catalysts or catalyst mixtures containing minimally coordinating counterions gave lower yields (entries 2–4 and Table S1 in the ESI†). The addition of Proton Sponge® (1,8-bis(dimethylamino)naphthalene) proved to be uniquely beneficial to the reaction yield in comparison to a reaction run without additive (entry 5). However, the addition of excess Proton Sponge® completely inhibited catalytic activity (entry 6 and Table S2 in the ESI†). Other acidic or basic additives commonly used in two- and three-component C–H bond addition reactions such as HOAc and LiOAc were detrimental (entries 7 and 8). Moreover, in contrast to Proton Sponge®, a variety of other tertiary amines were ineffective (Table S2 in the ESI†).

Higher temperatures proved to be deleterious to the yield of **4a** (entry 9), although the reaction could be run with isoprene (**2a**) at 50 °C to afford the product with little change in yield (entry 10). Nevertheless, 70 °C was selected as the optimal reaction temperature because reactions at 50 °C with more sterically hindered dienes (*e.g.*, (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene) were not as effective (see Table S3 in the ESI†). A modest decrease in the yield of **4a** was observed when the reaction was conducted in 1,4-dioxane (entry 11), but yields in toluene, PhCl, and CH_2Cl_2 were comparable to those in DCE (entries 12–14 and Table S4 in the ESI†). Although DCE was selected as the standard solvent, toluene and PhCl were found to be superior to DCE for certain substrate combinations (*vide infra*). A control reaction in which the catalyst was omitted demonstrated that it is essential for this transformation (entry 15). Moreover, a closely related cationic Cp*Rh(III) catalyst did not provide any product (entry 16). Finally, acetic formic anhydride was found to be the optimal formylating agent, providing superior yields of aldehyde **4a** compared to formic pivalic anhydride, 4-nitrophenyl formate and 2,4,6-trichlorophenyl formate (see Table S5 in the ESI†).

C–H bond substrate and diene scope

Having identified optimized reaction conditions, we first explored the scope of this transformation with respect to C–H bond substrate (Table 2). C–H bond substrates containing a variety of substituents, including trifluoromethyl (**4b** and **4e**), bromo (**4c**), pivalate-protected phenol (**4d**), and Boc-protected amine (**4f**) groups, were effective reactants. Moreover, a C–H bond substrate without any substituent provided the desired product in a good yield (**4h**). Heterocyclic C–H bond substrates with benzodioxole (**4g**) or indole (**4k**) cores were also successfully employed in this transformation. In addition to substrates containing a pyrazole directing group (**4a–4h**), those with other *N*-heterocyclic directing groups such as 1,2,3-triazole (**4i**) and pyrimidine (**4j** and **4k**) could be used. However, substrates with less basic directing groups such as amides or ketoximes did not afford the corresponding aldehyde product under the standard reaction conditions.

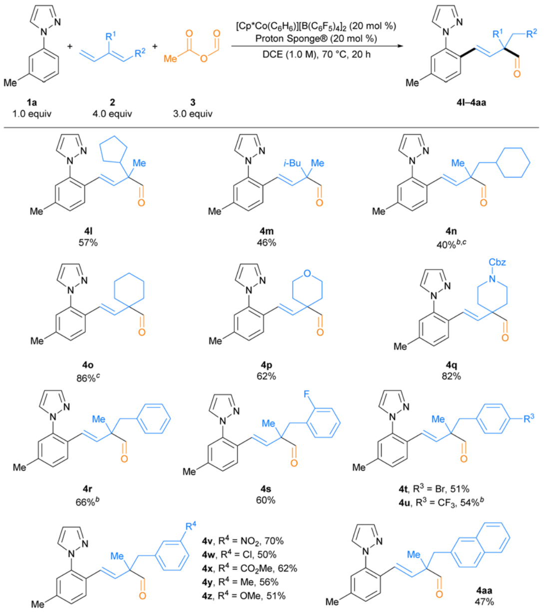
Table 2 C–H bond substrate scope[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), 3 (0.6 mmol), $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (20 mol%), Proton Sponge® (20 mol%) in DCE ([1] = 1.0 M) at 70 °C. Isolated yields reported. [b] Conducted at 50 °C. [c] 1,2-dichlorobenzene as solvent. [d] PhCl as solvent. [e] Toluene as solvent. [f] **2a** (1.2 mmol, 6.0 equiv.). Piv = pivalate.

We then surveyed the diene scope of this transformation (Table 3). A wide range of 2-substituted and 1,2-disubstituted dienes were successful inputs. Moderate to good yields were observed for 2-substituted dienes with cyclopentyl (**4l**) and

Table 3 Diene scope[a]



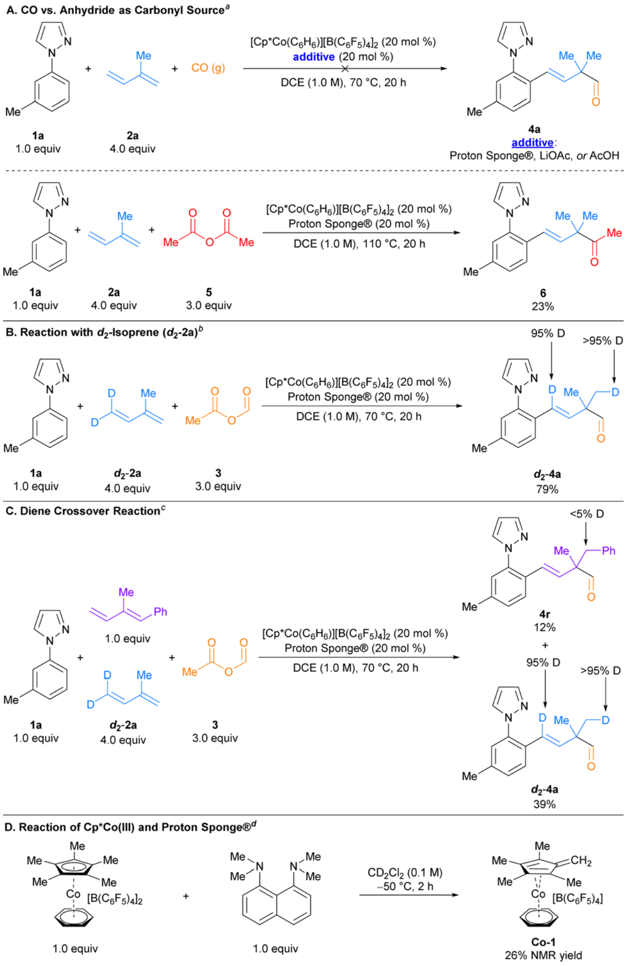
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.8 mmol), **3** (0.6 mmol), $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (20 mol%), Proton Sponge® (20 mol%) in DCE ([1] = 1.0 M) at 70 °C. Isolated yields reported. [b] **2** (1.2 mmol, 6.0 equiv.). [c] PhCl as solvent.

isobutyl (**4m**) groups; however, 2-aryl substituted dienes (*e.g.*, 2-phenyl-1,3-butadiene) only provided trace amounts of the desired aldehyde product (<5% NMR spectroscopic yield). While the 1,2-dialkyl substituted diene 1-cyclohexyl-2-methyl diene (**4n**) coupled in only 40% yield, 1,2-dialkyl substituted dienes with an endocyclic alkene gave much higher yields to provide aldehydes incorporating α-quaternary cyclohexyl (**4o**), tetrahydropyranyl (**4p**), and Cbz-protected piperidinyl (**4q**) ring systems. Various 1-aryl-2-methyl dienes containing diverse functional groups were also effective substrates. Fluoro (**4s**), bromo (**4t**), trifluoromethyl (**4u**), nitro (**4v**), chloro (**4w**), methyl ester (**4x**), methyl (**4y**), and methoxy (**4z**) substituents, including at the *ortho*-, *meta*-, and *para*-positions on the aryl ring, could all be incorporated into the carboformylation products. Finally, a 1-naphthyl-2-methyl diene provided aldehyde **4aa** in a synthetically useful yield. Butadiene and terminally mono-substituted dienes did not give rise to aldehyde products under these conditions, perhaps because the putative α-tertiary aldehyde products would be readily deprotonated and/or form enol tautomers that could undergo side reactions (see Chart S3 in the ESI for unsuccessful diene substrates†).

Mechanistic studies and proposed mechanism

Several experiments were conducted to gain more insight into the mechanism of this reaction (Scheme 2). Because acetic formic anhydride is known to release carbon monoxide spontaneously and in the presence of base,[15,16] we were interested in determining whether carbon monoxide was the source of the formyl carbonyl in this transformation. Reactions employing carbon monoxide gas in place of acetic formic anhydride under optimized reaction conditions did not afford any aldehyde product, and neither omitting Proton Sponge® nor replacing it with equimolar amounts of HOAc or LiOAc had any effect on the reaction outcome (Scheme 2A, top). Furthermore, a reaction where acetic formic anhydride was replaced with acetic anhydride, which cannot serve as a carbon monoxide surrogate, provided the corresponding three-component methyl ketone product **6** (Scheme 2A, bottom). More forcing conditions were likely required for this reaction due to the reduced electrophilicity and increased steric hindrance of acetic anhydride *vs.* acetic formic anhydride. Taken together, the carbonyl source in this reaction is unlikely to be carbon monoxide.

We also performed a deuterium labelling experiment in which isoprene (**2a**) was replaced with terminally deuterated d_2-isoprene (***d*₂-2a**; Scheme 2B). Under the standard reaction conditions, quantitative deuterium incorporation occurred at the sp^2-benzylic position as well as at one of the geminal methyl groups in the resulting aldehyde, ***d*₂-4a**, consistent with the proposed β-hydride elimination/intramolecular hydride reinsertion pathway that accounts for the observed regioselectivity of the products (*vide infra*). An alternative mechanism involving intermolecular hydride reinsertion was also considered and probed *via* a crossover experiment where 1.0 equiv. of (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene was added to the reaction of **1a**, ***d*₂-2a**, and **3a** under standard conditions (Scheme 2C). No significant deuterium incorporation into product **4r** was observed, suggesting the intermolecular pathway is not operative.

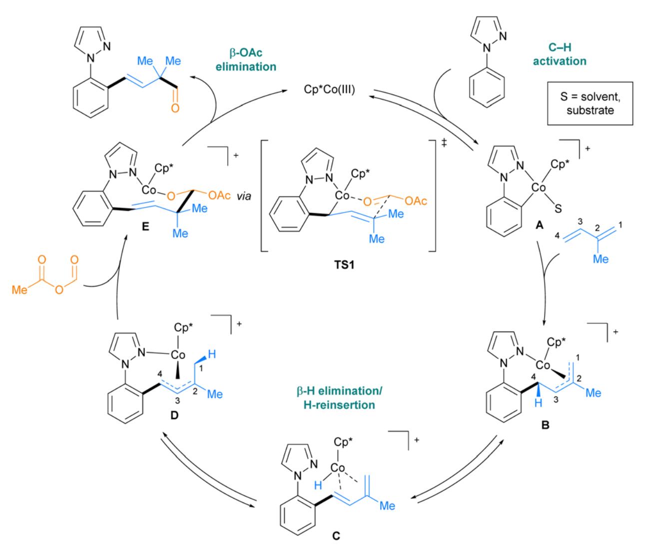


Scheme 2 Mechanistic experiments. ^{a}(A) Top, reaction conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), [Cp*Co(C$_6$H$_5$)][B(C$_6$F$_5$)$_4$]$_2$ (20 mol%), additive (20 mol%), in DCE ([**1a**] = 1.0 M) at 70 °C. (A) Bottom, **1a** (0.2 mmol), **2a** (0.8 mmol), **5** (0.6 mmol), [Cp*Co(C$_6$H$_5$)][B(C$_6$F$_5$)$_4$]$_2$ (20 mol%), Proton Sponge® (20 mol%), in DCE ([**1a**] = 1.0 M) at 110 °C. Isolated yield reported. ^{b}(B) Reaction conditions: **1a** (0.2 mmol), ***d*₂-2a** (0.8 mmol), **3** (0.6 mmol), [Cp*Co(C$_6$H$_5$)][B(C$_6$F$_5$)$_4$]$_2$ (20 mol%), Proton Sponge® (20 mol%), in DCE ([**1a**] = 1.0 M) at 70 °C. Isolated yield reported. ^{c}(C) **1a** (0.2 mmol), ***d*₂-2a** (0.8 mmol), (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene (0.2 mmol), **3** (0.6 mmol), [Cp*Co(C$_6$H$_5$)][B(C$_6$F$_5$)$_4$]$_2$ (20 mol%), Proton Sponge® (20 mol%), in DCE ([**1a**] = 1.0 M) at 70 °C. Isolated yields reported. ^{d}(D) Reaction conditions: [Cp*Co(C$_6$H$_5$)][B(C$_6$F$_5$)$_4$]$_2$ (0.04 mmol), Proton Sponge® (0.04 mmol) in CD$_2$Cl$_2$ ([Cp*Co] = 0.1 M) at −50 °C.

The uniqueness of Proton Sponge® as an additive in this transformation (and indeed in the realm of C–H functionalisation in general) prompted us to investigate its role in facilitating this reaction. Reacting equimolar amounts of [Cp*Co(C$_6$H$_6$)][B(C$_6$F$_5$)$_4$]$_2$ and Proton Sponge® in CD$_2$Cl$_2$ at −50 °C generates appreciable amounts (26% NMR yield) of a putative Co(I) tetramethylfulvene complex **Co-1** of the form [(η^4-C$_5$Me$_4$CH$_2$)Co(C$_6$H$_6$)][B(C$_6$F$_5$)$_4$] (Scheme 2D). Proton Sponge® has been shown to deprotonate methyl groups on the Cp* ligand of cationic, piano stool Rh(III) complexes,[17] and Co(I) tetramethylfulvene complexes generated from Cp*Co(III) precursors and a suitable base (*e.g.*, KO*t*-Bu or KHMDS) have been characterized spectroscopically.[18] Complex **Co-1** displays NMR signals consistent with the proposed structure, as well as related tetramethylfulvene complexes (see Fig. S10–S15 in the ESI†). Attempts to characterize **Co-1** crystallographically or by high-resolution mass spectrometry (HRMS) were unsuccessful, consistent with prior efforts to obtain crystallographic or HRMS characterization of Co(I) tetramethylfulvene complexes due to their instability.[18] A catalytic amount of complex **Co-1** gave comparable yields of product relative to our standard conditions (see Scheme S2 in the ESI†). Additionally, the Co(I) tetramethylfulvene complex **Co-1** forms in lower yield when $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ is reacted with 2.0 equiv. of Proton Sponge® in CD_2Cl_2 at −50 °C (see Fig. S16 in the ESI†). This result correlates with the lower observed yield when excess Proton Sponge® is added (see entry 6, Table 1).

These experiments suggest the combination of $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ and Proton Sponge® generates a catalytically competent species *via* an intermediate Co(I) tetramethylfulvene that might be superior in facilitating the sequential C–H bond addition to dienes and acetic formic anhydride than $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ alone (see Section 6 in the ESI for additional experiments†). However, further investigations are needed to definitively establish the relevance of **Co-1** in the catalytic cycle.

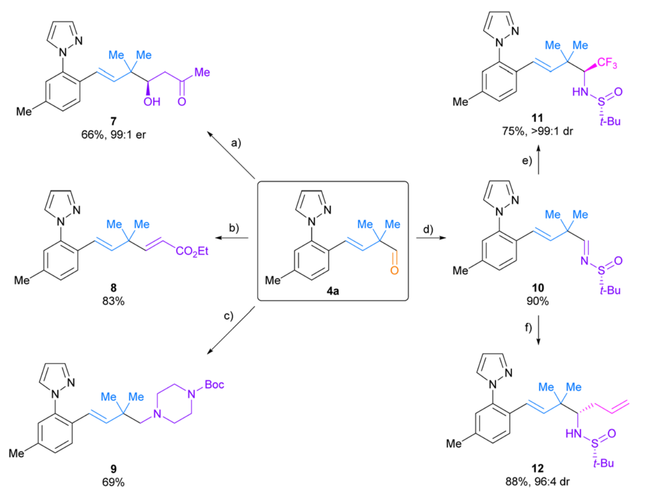
On the basis of these collective mechanistic studies, as well as those performed for other Co(III)-catalysed sequential C–H bond addition reactions with conjugated dienes,[10a,c,d,11] a proposed mechanism for this transformation is shown in Scheme 3. Firstly, reversible C–H activation by the cationic Co(III) catalyst *via* concerted metalation-deprotonation, possibly facilitated by Proton Sponge or another equivalent of **1a**,[19] gives rise to the cobaltacycle **A** (see Scheme S1 in the ESI for reversibility experiments†). Next, diene insertion into the Co–C bond affords the Co(III)-allyl species **B.** This complex then undergoes a reversible β-hydride elimination/hydride reinsertion *via* Co(III)-hydride species **C** to give an isomerized Co(III)-allyl complex **D**, in which one of the diene hydrogens at C4 has been transposed to C1. Evidence for this isomerization pathway is provided by the deuterium incorporation observed in ***d*₂-4a** when using ***d*₂-2a** (Scheme 2B). Acetic formic anhydride can then undergo direct nucleophilic attack from complex **D,** possibly through the six-membered transition state **TS1**, to afford complex **E.** Finally, β-OAc elimination from complex **E** furnishes the aldehyde product **4** and regenerates the active Co(III) catalyst.



Scheme 3 Proposed mechanism for the Co(III)-catalysed sequential C–H bond addition to dienes and acetic formic anhydride.

Synthetic elaboration of aldehyde 4a

Various transformations were conducted on aldehyde **4a** to showcase the synthetic versatility of the products generated through Co(III)-catalysed sequential C–H bond addition to dienes and acetic formic anhydride (Scheme 4). A proline-catalysed asymmetric aldol addition of acetone to aldehyde **4a** produced β-hydroxy ketone **7** with excellent enantioselectivity (99 : 1 er). A Horner–Wadsworth–Emmons olefination of aldehyde **4a** with triethyl phosphonoacetate and sodium hydride gave rise to alkene **8** with complete (*E*)-selectivity. Additionally, tertiary amine **9** was prepared *via* reductive amination of aldehyde **4a** using 1-Boc-piperazine. Finally, *tert*-butanesulfinyl imine **10** was synthesized from aldehyde **4a** and (*R*)-*tert*-butanesulfinamide[20] and subsequently reacted with $TMSCF_3$ and TBAT (tetrabutylammonium difluorotriphenylsilicate)[21] and allylmagnesium bromide[22] to furnish the corresponding α-branched amines **11** and **12** with high diastereoselectivities (>99 : 1 and 96 : 4 dr, respectively). These transformations highlight the utility of the aldehyde products **4** for the



Scheme 4 Diversification reactions of aldehyde **4a**. (a) (*S*)-proline, acetone, $CHCl_3$, 30 °C. (b) Triethyl phosphonoacetate, NaH, Et_2O, 25 °C. (c) 1-Boc-piperazine, $NaBH(OAc)_3$, MeCN, 25 °C. (d) (*R*)-*tert*-butanesulfinamide, $Ti(Oi\text{-}Pr)_4$, THF, 50 °C. (e) $TMSCF_3$, TBAT, THF, −55 °C. (f) Allylmagnesium bromide, CH_2Cl_2, −40 °C. TMS = trimethylsilyl. TBAT = tetrabutylammonium difluorotriphenylsilicate. For complete experimental details, see the ESI.†

straightforward and stereoselective introduction of useful functionality.

Conclusions

We have developed a Co(III)-catalysed sequential C–H bond addition reaction to dienes and acetic formic anhydride for the synthesis of all carbon α-quaternary aldehydes *via* a three-component process. A wide variety of substituted dienes are successful inputs in this reaction, affording a broad range of complex aldehyde products that are inaccessible *via* the hydroformylation of specialized 1,1-disubstituted alkenes. Mechanistic studies support that acetic formic anhydride directly provides the formyl group, explain the uncommon 1,3-functionalization of the conjugated diene, and provide insight into the role of the uniquely effective Proton Sponge additive. The versatility of the aldehyde products was also demonstrated through several diversification reactions, including proline-catalysed asymmetric aldol addition, olefination, reductive amination, and nucleophilic additions to the corresponding *tert*-butanesulfinyl imine derivative. Overall, this procedure highlights the synthetic potential of sequential C–H bond addition reactions for the modular and efficient preparation of complex, value-added products incorporating all carbon α-quaternary aldehyde functionality.

Data availability

The data that support the findings of this study are available in the ESI† for this article.

Author contributions

J. P. T. and J. A. E. conceptualized the project. J. P. T. and J. Y. performed the experiments and collected the data. J. P. T. wrote the original draft of the manuscript, and all authors contributed to the revision and editing of the manuscript. J. A. E. supervised the project and acquired funding for the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the NIH (R35GM122473). J. P. T. is grateful to the NSERC of Canada for a Postdoctoral Fellowship. We also thank Dr Robert Berry and Dr Fabian Menges of the Yale University Chemical and Biophysical Instrumentation Center for technical assistance in the acquisition of NMR and HRMS data.

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