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Selective and synergistic cobalt(III)-catalysed three-component C–H bond addition to dienes and aldehydes

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Two-component C–H bond additions to a large variety of coupling partners have been developed with applications towards materials, natural product and drug synthesis. Sequential three-component C–H bond addition across two different coupling partners potentially enables the convergent synthesis of complex molecular scaffolds from simple precursors. Here, we report three-component Co(III)-catalysed C–H bond additions to dienes and aldehydes that proceed with high regio- and stereoselectivity, resulting in two new carbon–carbon σ-bonds and four to six new stereocentres. The reaction relies on the synergistic reactivity of the diene and aldehyde, with neither undergoing C–H bond addition alone. A detailed mechanism is supported by X-ray structural characterization of a Co(III)-allyl intermediate, observed transfer of stereochemical information, and kinetic isotope studies. The applicability of the method to biologically relevant molecules is exemplified by the rapid synthesis of the western fragment of the complex ionophore antibiotic lasalocid A.

Multicomponent reactions combine three or more coupling partners to enable the rapid generation of complex structures from simple precursors. The partners are combined in a precise way by the reaction of specific functional groups on the different coupling partners (Fig. 1a)[1–4]. Multicomponent reactions, as exemplified by the three-component Passerini reaction of aldehydes, isocyanides and carboxylic acids, have been extensively studied and employed in synthesis (see Fig. 1a)[1]. In transition metal-catalysed C–H functionalization, the ubiquitous C–H bond rather than a functional group serves as the site for reaction. Many transition metal-catalysed two-component additions of C–H bonds to a large variety of different coupling partners have been developed, such as additions to α,β-unsaturated carbonyl compounds (Fig. 1b)[5–10]. Sequential, three-component addition reactions of non-acidic C–H bonds to two different coupling partners could provide access to an enormous range of different products (top panel in Fig. 1c), promising examples of which have previously been reported by us[11,12]. For these reported transformations, at least two out of the three coupling partners are well-documented to undergo efficient two-component coupling with the metal catalyst used in the three-component coupling[8]. An even greater variety of useful structures might be achieved through synergistic three-component C–H bond addition. In this scenario, which is distinct from synergistic catalysis[13], the individual coupling partners do not undergo two-component transformations (middle panel in Fig. 1c).

Herein, we show that aromatic and α,β-unsaturated amides undergo Co(III)-catalysed β-C–H bond addition across dienes and aldehydes to provide a carbon framework with high regio- and stereocontrol that incorporates two new C–C σ-bonds and four or more new stereocentres[14,15]. Notably, neither the diene nor aldehyde partner individually undergoes Co(III)-catalysed two-component C–H addition (vide infra). Moreover, use of the bulk chemical feedstock butadiene[16,17] as the diene partner results in the introduction of vicinal α-methyl and hydroxyl asymmetric carbons that are commonly found in natural products.

Results

Optimization studies. A thorough exploration of conditions was conducted to determine the optimal reaction parameters for three-component coupling of benzamide **1a**, butadiene **2a** and isovaleraldehyde **3a** to provide alcohol **4a** in 87% yield (Fig. 2; see Supplementary Table 2). The most effective catalyst was found to be a cationic earth-abundant cobalt catalyst previously developed in our laboratory, $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (Co(III)L)[18,19]. Notably, this robust catalyst is completely air stable and is prepared by a straightforward and scalable salt metathesis without the use of any precious metals. Only acetic acid in sub-stoichiometric amounts was required as an additive with heating to 50 °C. In determining the reaction scope, 20 mol% of the robust earth-abundant catalyst (Co(III)L) was used. However, in preliminary studies on catalyst loading, the product alcohol **4a** was obtained with a modest reduction in yield to 70% when employing 5 mol% of (Co(III)L) with pivalic acid rather than acetic acid as an additive.

Scope and limitations of the reaction. Acetaldehyde also coupled in good yield to give alcohol **4b**, whose structure was rigorously confirmed by X-ray crystallography (see Supplementary Table 1 and Supplementary Fig. 3). Multiple linear aldehydes were evaluated to provide products **4c**–**h** in good-to-excellent yields. These aldehydes illustrate that a variety of functionalities are compatible with three-component coupling. A disubstituted alkene was incorporated without isomerization (**4d**), and a primary alkyl chloride was stable under the reaction conditions (**4e**). In addition, alcohol functionality could also be introduced when protected as either a benzyl (**4f**) or a silyl (**4g**) ether, although the *tert*-butyldiphenylsilyl (TBDPS) group was necessary to minimize silyl deprotection under

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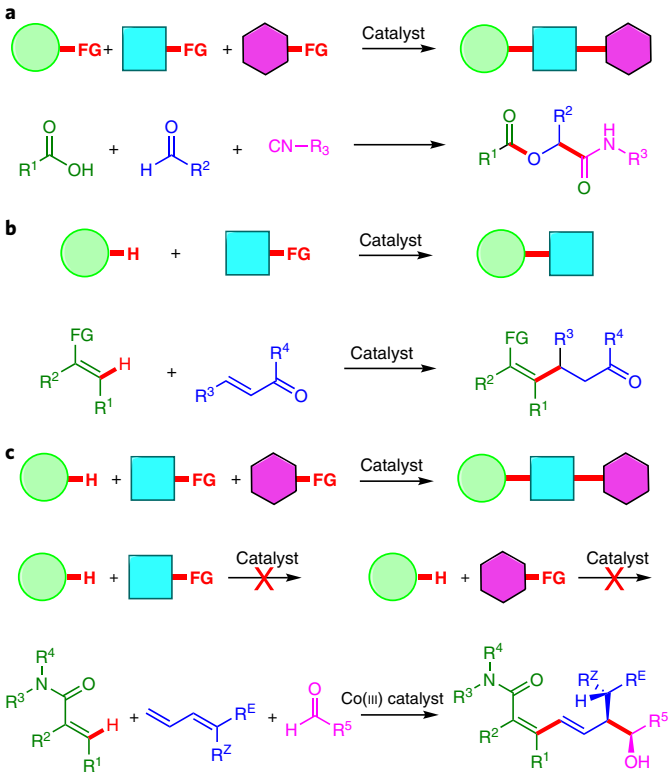

Fig. 1 | Three-component strategy for the rapid assembly of complex structures. a, Top, schematic of a multicomponent reaction. Bottom, the Passerini reaction is a well-known example of three-component coupling. **b**, Top, schematic of transition metal-catalysed two-component C–H bond addition. Bottom, representative C–H bond addition to α,β-unsaturated carbonyl compounds. **c**, Sequential three-component C–H bond additions. Top, transition metal-catalysed three-component C–H bond addition. Middle, as above, but for when corresponding two-component couplings do not occur. Bottom, in this work, successful three-component C(sp^2)–H bond additions to dienes and aldehydes lacking corresponding two-component reactions are achieved.

the reaction conditions. Finally, lactone **4h** was obtained in near-quantitative yield by coupling 4-oxo-butyric acid methyl ester with in situ cyclization of the initial alcohol product.

Several α-branched aldehydes were also evaluated, providing alcohol products **4i**–**k** in good-to-excellent yields. In particular, alcohol **4j** demonstrates incorporation of the privileged piperidine heterocycle motif[20] with the nitrogen protected by the popular Boc protecting group[21]. However, the highly sterically hindered α,α-dibranched aldehyde pivaldehyde provided little product under the standard reaction conditions; even at a 1 M concentration in benzamide **1a** and a 70 °C reaction temperature, it only provided **4l** in a 14% isolated yield as a single stereoisomer.

A broad range of aromatic aldehydes was also explored. Benzaldehyde (**4m**), along with a number of derivatives with electron-deficient groups at the *para*-position (**4n**–**q**) coupled in high yield. Moderately electron-rich *p*-tolualdehyde provided **4r** with a modest reduction in yield and diastereoselectivity. Aromatic aldehydes with substitution at the *ortho* site (**4s**) and at the *meta* site with electron-deficient (**4t**,**u**) and -rich (**4v**,**w**) substituents all coupled in high yields. The reactions performed with aromatic aldehydes further established the broad functional group compatibility of the transformation, with successful incorporation of electrophilic ester (**4p**) and ketone (**4u**) functionality, bromo (**4o**) and chloro (**4t**) substituents amenable to cross-coupling transformations, and acidic functionality exemplified by the introduction of a phenol (**4w**) and an *N*-Boc aniline (**4v**).

Different C–H bond substrates were also investigated (Fig. 3a). In addition to the pyrrolidine amide directing group, a number of other amide derivatives were also shown to be effective. Both the *N*,*N*-dimethyl and Weinreb[22] tertiary benzamides provided products **4x,y** in good yields, and the secondary amide *N*-methyl benzamide also coupled efficiently to give **4z**. A number of different functionalities were examined on the aryl portion of the pyrrolidine benzamide. A range of electron-donating and electron-withdrawing groups were well-tolerated, resulting in products **4aa**–**af** in good-to-excellent yield. With methylenedioxy substitution, alcohol **4ag** was obtained in 93% yield as a single regioisomer, presumably through coordination of the oxygen to the cobalt in the C–H activation step. Conversely, attachment of two methoxy groups on the *meta*- and *para*-positions resulted in product **4ah** as the major regioisomer, isolated as a single compound in 60% yield. Here, steric interactions between the two methoxy groups block the contiguous *ortho*-position. C–H functionalization was also successful for the heterocycle thiophene, giving alcohol **4ai** in 72% yield. Alkene C(sp^2)–H bonds also participated in the three-component reaction, generating products **4aj** and **4ak** in moderate yield and with high regio- and stereoselectivity for the introduction of six new stereocentres (four sp^2 and two sp^3) in a single transformation.

Lastly, a number of mono- and disubstituted butadienes were explored to expand the range of products that are accessible while also providing stereochemical information useful for deciphering the reaction mechanism (Fig. 3b). Interestingly, both the (*E*)- and (*Z*)-isomers of 1,3-pentadiene furnished alcohol **4al**, with the (*E*)-isomer providing a slightly higher yield. Consistent with this stereochemical outcome, the pure (*E*)-isomer and a 1:1 mixture of (*E*)- and (*Z*)-isomers of hexa-3,5-dien-1-ylbenzene gave the same alcohol product **4am** and in nearly identical yields. Additionally, dienes containing linear alkyl chains or benzyloxy substituents furnished products **4an** and **4ao** in 83 and 80% yields, respectively. The monosubstituted butadiene with a phenyl group directly attached to the diene, 1-phenyl-1,3-butadiene, was also evaluated, but did not provide the three-component coupling product (data not shown).

The symmetrical 1,1-disubstituted butadiene, 4-methyl-1,3-pentadiene, provided three-component products **4ap** and **4aq** in 52 and 66% yields, respectively. Moreover, a stereochemically pure unsymmetrical 1,1-disubstituted butadiene coupled to give **4ar** with three asymmetric carbons and very high stereoselectivity. The relative stereochemistry for **4ar** was rigorously confirmed by X-ray structural analysis of an acylated derivative **4ar′** (see Supplementary Table 1 and Supplementary Fig. 4). Because the unsymmetrical 1,1-disubstituted butadiene used in the three-component reaction to give **4ar** required preparation, this diene was also evaluated as the limiting reagent for the three-component reaction and resulted in a comparable 54% yield. The added stereochemical complexity introduced by unsymmetrical 1,1-disubstituted butadienes not only has potential synthetic utility, but also provides useful mechanistic insight (vide infra).

Mechanistic studies. Experiments were conducted to help elucidate a mechanism for this three-component transformation (Fig. 4). First, butadiene and multiple aldehyde coupling partners were separately submitted to two-component coupling under standard reaction conditions (Fig. 4a). Butadiene resulted in only a 12% yield of the two-component coupling product diene **5**, with 85% recovery of **1a**. Diene **5** is presumably released from the cobalt after β-hydride elimination to give an off-cycle cobalt hydride species (vide infra). More forcing conditions (100 °C) or addition of the common stoichiometric terminal oxidant $Cu(OAc)_2$ resulted in less than 5% of diene **5** or any other type of two-component product. Attempted coupling of **1a** with alkyl and aryl aldehydes resulted in quantitative

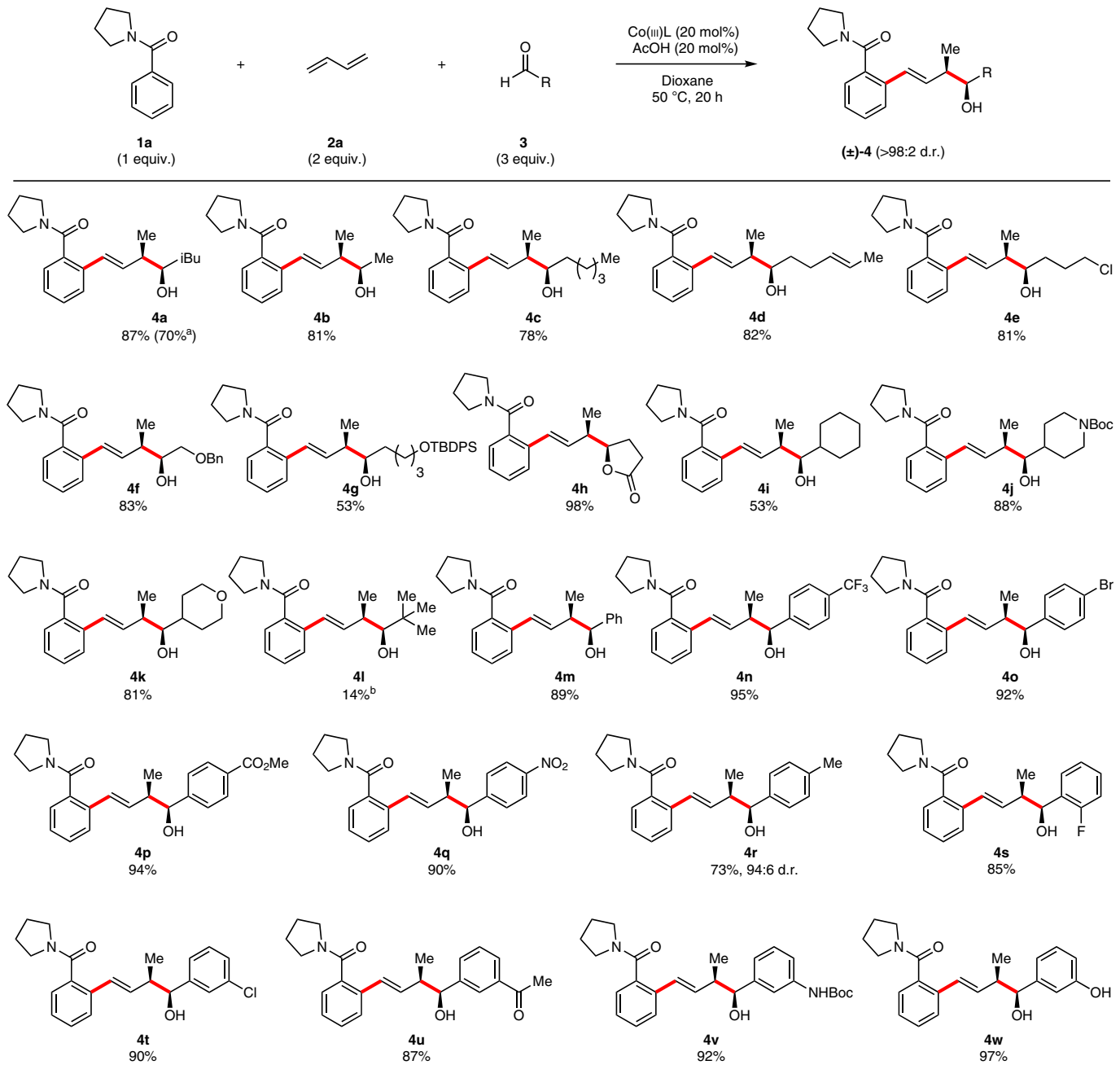

Fig. 2 | C–H functionalization with benzamide 1a, butadiene 2a and diverse aldehydes 3. Reactions were performed on a 0.2 mmol scale with **1a** at 0.4 M and proceeded with >98:2 d.r. unless otherwise noted. Isolated yields of products after purification by chromatography are reported. See Supplementary Methods for experimental details. [a]Reaction performed with 5 mol% of (Co(III)L) and 20 mol% of pivalic acid in place of acetic acid. [b]Reaction performed with **1a** at 1.0 M and at 70 °C.

recovery of **1a** without formation of any two-component product **6**. This reaction outcome is expected because arene C(sp^2)–H additions to standard aromatic and alkyl aldehydes are well-documented to be thermodynamically disfavoured[23,24].

To trap possible intermediates along the catalytic cycle, substrate **1a** was reacted with butadiene without any aldehyde but with stoichiometric amounts of the cobalt catalyst, resulting in isolation and rigorous X-ray structural characterization of the coordinatively saturated Co-allyl species **8a** with η^3-allyl binding (Fig. 4b, Supplementary Table 1 and Supplementary Fig. 5). Notably, the isolation and structural characterization of Cp*Co(III)-intermediates via direct C–H functionalization pathways has proven to be very challenging[25]. To ascertain whether the isolated Co-allyl species **8a** is an intermediate along the reaction pathway, a reaction was conducted using **8a** as the catalyst for the coupling of **1a** with butadiene and isovaleraldehyde (Fig. 4c). Using the standard reaction conditions, a 77% NMR yield of the desired alcohol **4a** was obtained. This result establishes that **8a** is a competent catalyst, and is consistent with this allyl species serving as an intermediate along the reaction pathway.

Experiments with the deuterated substrate **1a-D** also defined key features of the reaction (Fig. 4d). When substrate **1a-D** was subjected to the standard reaction conditions for only 2 h, no deuterium exchange was observed in either the product or the starting material

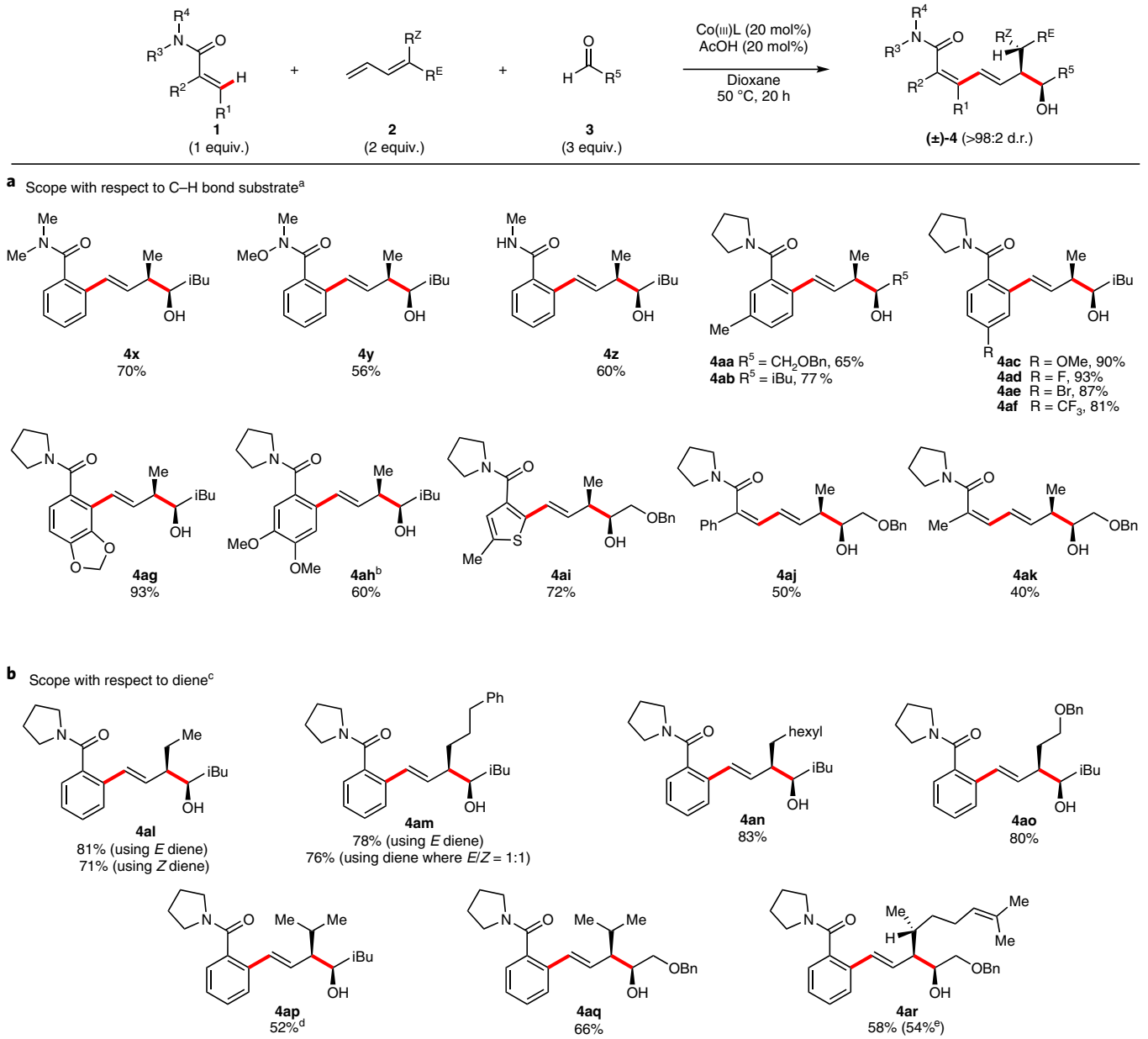

Fig. 3 | C–H functionalization with dienes and aldehydes. Reactions were performed on a 0.2 mmol scale and proceeded with >98:2 d.r. unless otherwise noted. Isolated yields of products after purification by chromatography are reported. See Supplementary Methods for experimental details. **a**,**b**, Scope of products with respect to C–H bond substrates (**a**) and dienes (**b**). [a]**1a** = 0.4 M. [b]20% of the minor regioisomer was observed by NMR analysis. [c]**1a** = 1.0 M. [d]Isolated yield of major diastereomer; crude d.r.: 92:8. [e]Benzamide **1a** (2.0 equiv.), diene **2ar** (1.0 equiv.) and benzyloxyacetaldehyde (3.0 equiv.).

(see Supplementary Methods). A primary kinetic isotope effect of 2.90 ± 0.20 was observed (Fig. 4d and Supplementary Figs. 1 and 2), which is consistent with orthometallation as a rate-determining step[26].

A mechanism consistent with all of the experimental data is shown in Fig. 5. First, rate-determining C–H metallation of substrate **1a** generates 5-membered metallocycle **7**, which inserts into the terminal carbon of diene partner **2** to form Co-allyl species **8**. This step is supported by the isolation and X-ray structural characterization of **8a** (see Fig. 4b). Formal migration of a hydrogen from carbon 1 to 4 in allyl intermediate **8** must occur to achieve the bond connectivity observed in the final product. *Syn* β-hydride elimination at carbon 1 in **8** would give the Co-diene complex **9**, which is supported by the isolation of diene by-product **5** when no aldehyde is present (Fig. 4a). Reversible stereospecific syn-insertion of the Co-hydride from the same face but at carbon 4 would provide Co-allyl species **10** (ref. [27]). Reaction of aldehyde **3** by the chair transition state depicted in **11** would provide the stereochemistry observed in product **4**, which is obtained upon protonolysis with concomitant release of the cobalt catalyst.

The stereochemistry observed for substituted dienes provides critical support for the proposed hydride migration from **8** to **10**. (*Z*)- and (*E*)-monosubstituted dienes would be expected to provide the same intermediate **10** because a stereocentre is not introduced during hydride migration. Consequently, both (*Z*)- and (*E*)-monosubstituted dienes would be expected to provide the same product, as was observed for both **4al** and for **4am**. Moreover, the high stereoselectivity and relative stereochemistry observed for **4ar** is consistent with stereospecific hydride migration[28] on coupling with the unsymmetrical 1,1-disubstituted butadiene.

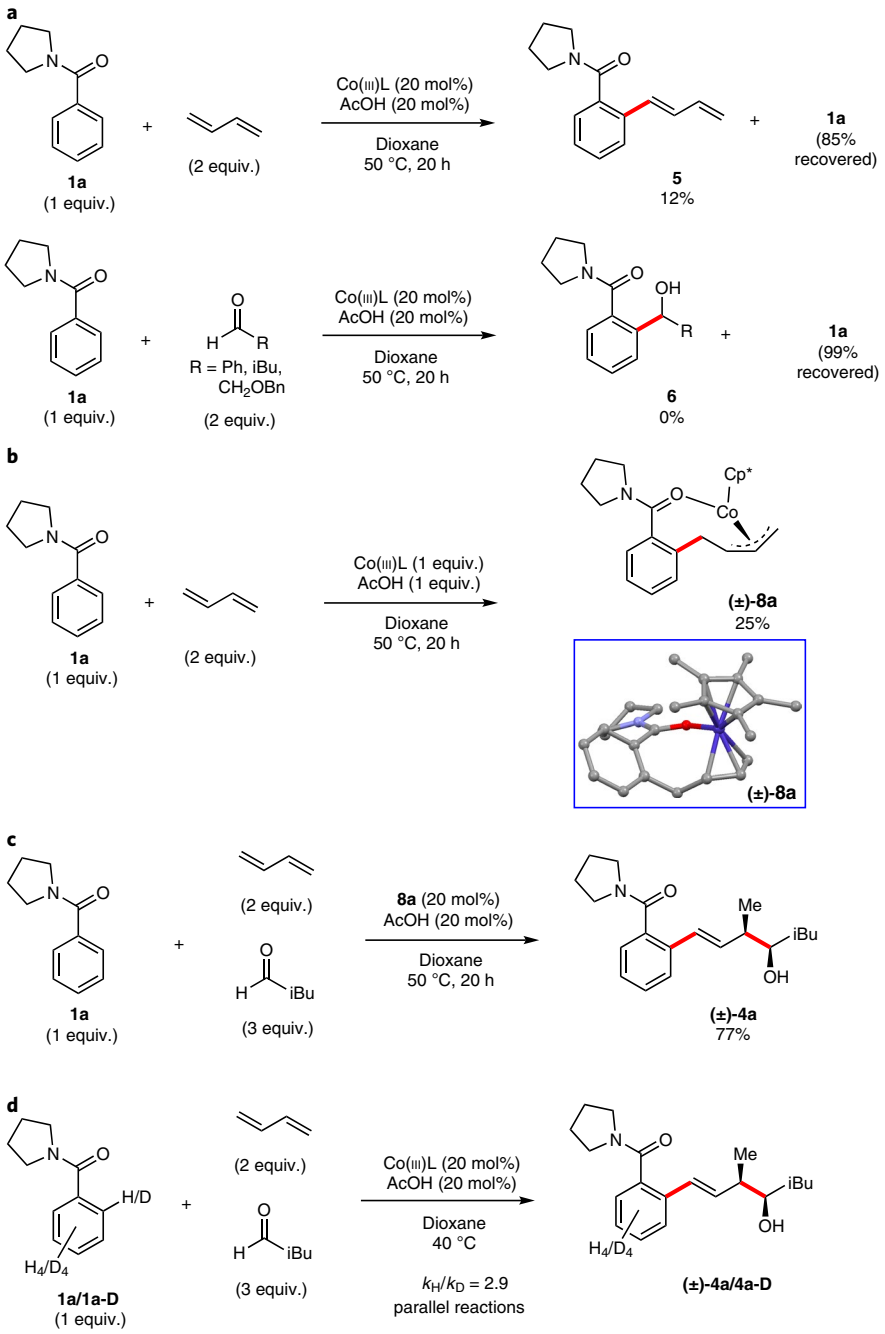

Fig. 4 | Mechanistic experiments. a, Evaluation of two-component coupling reactions with either a diene (top) or aldehyde coupling partner (bottom). Benzamide **1a** = 0.4 M. **b**, Synthesis of Co-allyl species **8a**. **c**, Co-allyl species **8a** as the catalyst in the three-component reaction. **1a** = 0.4 M. **d**, Kinetic isotope effect determined from parallel reactions of **1a** and **1a-D**. Benzamides **1a** and **1a-D** = 0.4 M. The ratio of the rates of the reaction for **1a** and **1a-D** is defined as k_H/k_D.

Synthesis of fragment of the ionophore antibiotic lasalocid A. The carbon framework and stereochemistry obtained with this three-component reaction provide an opportunity to access structural motifs present in natural products, as exemplified by the western fragment of the ionophore antibiotic lasalocid A[29,30], which is used to treat coccidiosis in cattle (Fig. 6). Three-component coupling of benzamide **12**, butadiene and isovaleraldehyde as a model aldehyde, provided alcohol **13** in good yield regardless of whether benzamide **12** (70% yield) or isovaleraldehyde (77%) was employed as the limiting reagent. Moreover, this reaction was also performed on the benchtop under an N_2 atmosphere with benzamide **12** as the limiting reagent, and gave a comparable 68% yield. In addition, when the reaction was performed on the benchtop with only 5 mol% of (Co(III)L) and with pivalic acid as the additive, the product was obtained with only a slight reduction in the yield to 60%. Alkene hydrogenation[31] to provide **14** was followed by amide *N*-nitrosylation[32], saponification and benzyl group cleavage to furnish alcohol **15** in excellent overall yield.

Conclusion

These studies establish a general Co(III)-catalysed three-component transformation for the synergistic, sequential C–H bond additions across dienes and aldehydes to form two new carbon–carbon σ-bonds and up to six stereocentres with high regio- and diastereoselectivity.

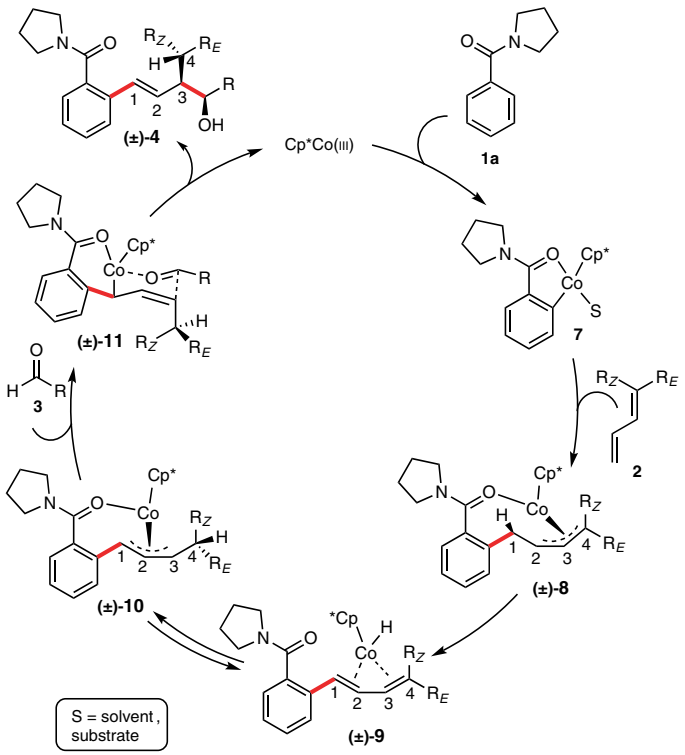

Fig. 5 | Proposed mechanism for the three-component transformation. The transformation proceeds through formation of Co-allyl species **8**, which is supported by isolation of species **8a**. *Syn* β-hydride elimination and hydride reinsertion leads to a new Co-allyl species **10**, which can coordinate with the aldehyde to produce the chair transition state **11**. Aldehyde addition and protonolysis yields the product **4**. The depicted mechanism is consistent with the stereochemical outcomes observed for the substituted butadienes.

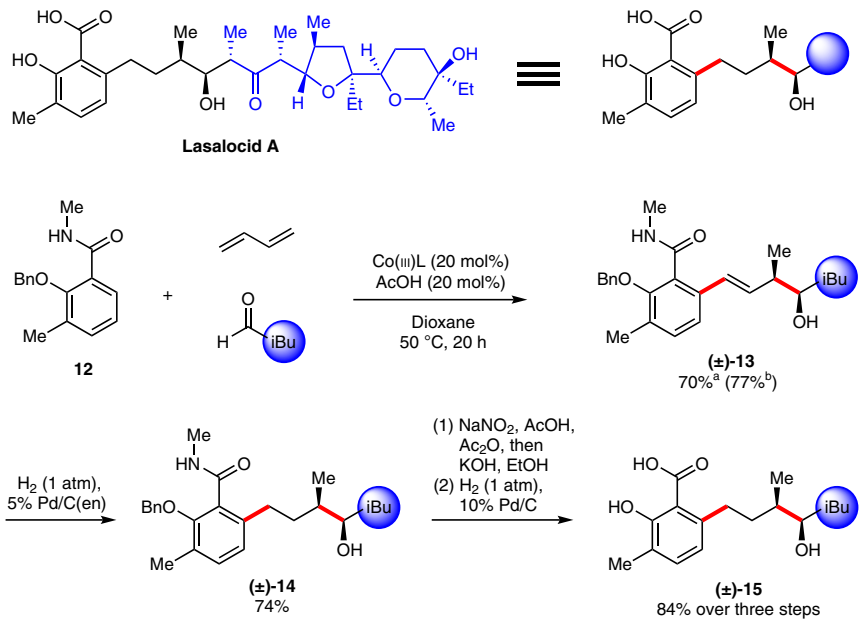

Fig. 6 | Synthesis of the core scaffold in lasalocid A. Isolated yields are shown. [a]Benzamide **12** as the limiting reagent: benzamide **12** (1 equiv.), butadiene (2 equiv.) and isovaleraldehyde (3 equiv.). [b]Aldehyde as the limiting reagent: benzamide **12** (2 equiv.), butadiene (2 equiv.) and isovaleraldehyde (1 equiv.).

A mechanism is proposed that involves stereospecific hydrogen migration and is supported by product connectivity and stereochemistry, X-ray structural characterization of a Co(III)-allyl intermediate, and isotope labelling studies. The utility of the three-component reaction is demonstrated by the rapid assembly of the western fragment of lasalocid A. Asymmetric variants of this three-component reaction might be possible using either enantiomerically pure coupling partners or chiral catalysts. Given the success of the disclosed three-component reaction, the discovery of additional synergistic three-component processes is anticipated.

Methods

General procedure for aldehyde and C–H bond substrate scope. In an N_2-filled glove box, a 0.5–2.0 ml microwave vial was charged with $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (65.2 mg, 0.0400 mmol, 0.20 equiv.), the indicated C–H bond partner (**1**) (0.200 mmol, 1.0 equiv.) and the corresponding aldehyde (**3**) (0.600 mmol, 3.0 equiv.). Following this, 67 µl of a 0.6 M stock solution of acetic acid in 1,4-dioxane, followed by 333 µl of 1,4-dioxane were added. Finally, 100 µl of a 4 M stock solution of 1,3-butadiene in tetrahydrofuran (0.400 mmol, 2.0 equiv.) was added (the use of a commercial solution of butadiene in tetrahydrofuran works equally well; for full details, see Supplementary Table 2 and Supplementary Methods for the synthesis of the lasalocid A fragment **15**). The reaction vial was then equipped with a magnetic stir bar, sealed with a microwave cap and taken outside the glove box. The reaction mixture was stirred at 50 °C in a preset oil bath for 20 h. The reaction mixture was allowed to cool to room temperature and then filtered through a small celite plug (1 cm long in a pipette) that was washed with ethyl acetate. The resulting mixture was then concentrated and purified by the corresponding chromatographic method to afford the desired product. Full experimental details and characterization of new compounds are provided in the Supplementary Methods.

General procedure for diene substrate scope. In an N_2-filled glove box, a 0.5–2.0 ml microwave vial was charged with $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ (65.2 mg, 0.0400 mmol, 0.20 equiv.), the indicated C–H bond partner (**1**) (0.200 mmol, 1.0 equiv.) and the corresponding aldehyde (**3**) (0.600 mmol, 3.0 equiv.). Following this, 67 µl of a 0.6 M stock solution of acetic acid in 1,4-dioxane was added to the solid mixture, followed by 133 µl of 1,4-dioxane. Finally, diene (**2**) was added (0.400 mmol, 2.0 equiv.). The reaction vial was then equipped with a magnetic stir bar, sealed with a microwave cap and taken outside the glove box. The reaction mixture was stirred at 50 °C in a preset oil bath for 20 h. The reaction vial was allowed to cool to room temperature. The reaction mixture was filtered through a small celite plug (1 cm long in a pipette) that was washed with ethyl acetate. The resulting mixture was then concentrated and purified by the corresponding chromatographic method to afford the desired product. Full experimental details and characterization of new compounds are provided in the Supplementary Methods.

Data availability. The data that support the findings of this study are available within the paper and its Supplementary Information. X-ray crystallography data for structures 4b, 4ar′, and 8a are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers CCDC 1812525, CCDC 1826301 and CCDC 1812526, respectively.

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Author contributions

J.A.B. co-conceived the concept and developed the reaction conditions. J.A.B. also completed the scope with respect to C–H bond substrates, including the lasalocid A derivative, conducted the mechanistic experiments and co-prepared the manuscript. S.M. helped with the development of the reaction conditions and completed the scope with respect to both aldehyde and diene coupling partners. S.M. also helped with the preparation of the manuscript. S.K.W. helped with the completion of the scope with respect to C–H bond substrates. B.Q.M. solved the X-ray crystal structures of compounds **4b, 4ar′** and **8a**. J.A.E. co-conceived the concept and co-prepared the manuscript with feedback from J.A.B. and S.M.

Competing interests

The authors declare no competing interests.

Additional information

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