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Syngas-Free Rhodium-Catalyzed Highly Regioselective Transfer Hydroformylation of Alkynes to *α,β*-Unsaturated Aldehydes

Guangying Tan, Yimin Wu, Yang Shi and Jingsong You*

Abstract: The hydroformylation of alkynes is a fundamental and important reaction in both laboratory and industry. Conventional methods are concentrated on the conversion of alkynes, CO and H_2 into *α,β*-unsaturated aldehydes but often suffer from problems associated with operation, regioselectivity and chemoselectivity. Herein, we disclose an operationally simple, mild and syngas-free rhodium-catalytic method for the hydroformylation of alkynes via the transfer of formyl and hydride from an alkyl aldehyde. The current synthetic version uses inexpensive and easy-to-handle *n*-butyraldehyde to overcome the challenge posed by the use of syngas in traditional approaches and employs commercially available catalyst and ligand to transform a broad range of internal alkynes, especially for alkynyl-containing complex molecules, into versatile stereodefined *α,β*-unsaturated aldehydes with excellent chemo-, regio- and stereoselectivity.

α,β-Unsaturated aldehydes are fundamental synthetic intermediates for the preparation of agrochemicals, pharmaceuticals, biologically active molecules, and fine chemicals.[1] Among various synthetic approaches to *α,β*-unsaturated aldehydes, the hydroformylation of alkynes is generally regarded as one of the most efficient and rapid methods and has been of great interest to synthetic chemists.[2] Over the past few decades, a lot of catalytic systems have been reported, as exemplified by the pioneering works of Buchwald,[3] Hidai,[4] Alper,[5] Beller,[6] Breit,[7] and Zhang,[8] all of which are concentrated on the conversion of alkynes, CO, and H_2 into aldehydes (Scheme 1a). Despite strenuous effort, two fundamental issues might plague the further application of the hydroformylation reaction. First, although "syngas", a 1:1 mixture of CO and H_2, is inexpensive and abundant, it is very toxic, volatile and highly flammable. Moreover, in most cases, to obtain a satisfactory conversion ratio, a highly pressurized syngas is generally required, thereby needing a special equipment to handle pressurized gas. Second, compared with the hydroformylation of alkenes, the hydroformylation of alkynes is more challenging because the regioselectivity is difficult to be controlled and the byproducts such as hydrogenated products of alkynes and saturated aldehydes are hardly suppressed.[9] Thus, considering the importance of hydroformylation of alkynes in both laboratory and industry, it is highly desirable to develop a syngas-free hydroformylation reaction, ideally with a controllable selectivity, albeit it is thought as one of the most challenging tasks in the synthetic chemistry.

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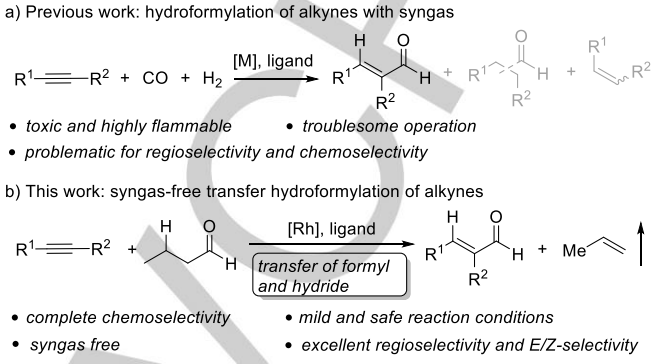
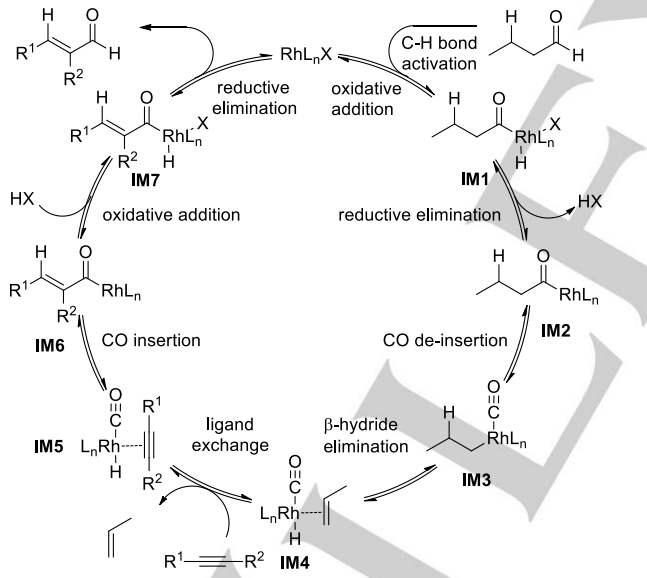


***Scheme* 1.** Hydroformylation of alkynes to *α,β*-unsaturated aldehydes.

In 2015, Dong and coworkers reported an elegant rhodium-catalyzed dehydroformylation of aliphatic aldehydes to generate alkenes under mild conditions.[10] This dehydroformylation protocol employed highly strained norbornadiene as a sacrificial acceptor to drive the reaction running smoothly because of the release of its ring strain. Inspired by this work, we envisaged that a mechanistically relevant transfer of formyl and hydride between simple alkyl aldehyde and alkyne would fulfill the hydroformylation without relying upon syngas (Scheme 1b). We reasoned that the transfer hydroformylation of alkyne with simple alkyl aldehyde would be unlocked through an elaborate rhodium-catalytic pathway illustrated in Scheme 2, involving a sequence of reversible aldehyde C–H bond activation to form acyl-Rh(III)-hydride, reductive elimination, de-insertion of CO, *β*-hydride elimination to forge Rh–hydrido–carbonyl **IM4**, and ligand exchange.[10-12] In this proposed mechanism, the olefin exchange of **IM4** with alkyne to generate **IM5** is the key step to drive the transfer hydroformylation through CO insertion, oxidative addition, and reductive elimination in reverse order. Such a transformation would be particularly powerful because 1) no toxic and highly flammable syngas would be required; 2) no special equipment would be needed to handle pressurized gas; 3) *cis*-insertion of CO would lead to (*E*)-*α,β*-unsaturated aldehyde; and 4) the unwanted saturated aldehydes and hydrogenated products would be mechanistically suppressed (*complete chemoselectivity*). Herein we disclose a syngas-free rhodium-catalyzed transfer hydroformylation of alkynes via shuttle catalysis (Scheme 1b).[13] This protocol uses accessible and inexpensive *n*-butyraldehyde as a donor of formyl and hydride to transform a broad range of alkynes into *α,β*-unsaturated aldehydes with excellent chemo, regio- and *E/Z*-selectivity.

Our investigation commenced with the reaction between hexadec-8-yne (**1**) and *n*-butyraldehyde (**2a**). After a systematic evaluation of the reaction parameters, the best yield for (*E*)-2-heptyldec-2-enal (**A1**) reached 86% under the catalytic system composed of $[Rh(cod)OMe]_2$ (2.0 mol %), Xantphos (4.0 mol %), and 4-NO_2PhCO_2H (4.0 mol %) in tetrahydrofuran (THF) at 80 °C for 24 h (Table 1) (For detailed optimization, see Table S1). The

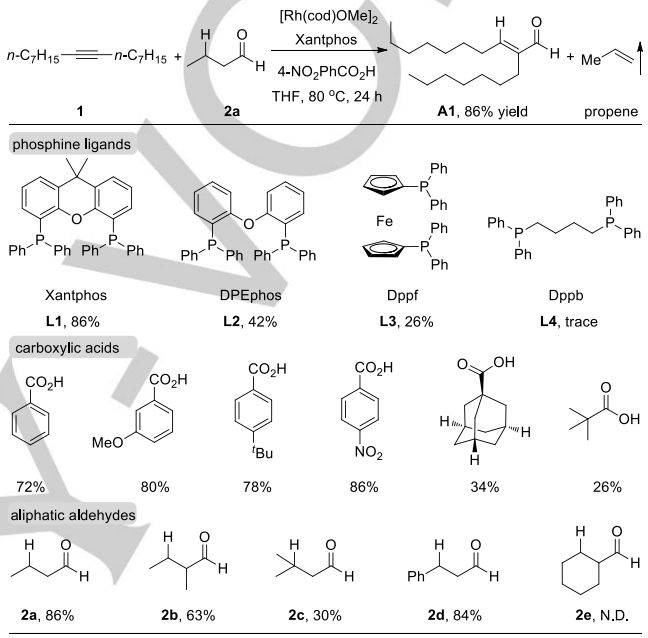
choice of the phosphine ligands is critical to this transfer hydroformylation and only bidentate phosphine ligands were proven to be effective. As shown in Table 1, Xantphos (**L1**) is obviously superior to other bidentate ligands such as DPEphos (**L2**), Dppf (**L3**), and Dppb (**L4**). The natural bite angles β_n of Xantphos, DPEphos, Dppf and Dppb are around 107°, 102°, 96°, and 98°, respectively.[14] Thus, it seems that the reaction efficacy is correlated to the bite-angle of the bidentate ligand and the ligand with a larger natural bite-angle might be more efficient. Next, a series of benzoic acids and alkyl carboxylic acids were screened and 4-NO_2PhCO_2H proved to be superior to $PhCO_2H$, 3-$MeOPhCO_2H$, 4-$^tBuPhCO_2H$, 1-$AdCO_2H$, and PivOH. From Scheme 2, the acid additive could play the important role in three steps of this catalytic cycle. At the beginning of the reaction, 4-NO_2PhCO_2H could react with $[Rh(cod)OMe]_2$ and Xantphos to generate the catalytic active rhodium benzoate complex RhL_nX (L = Xantphos; X = 4-$NO_2PhCO_2^-$). The benzoate counterion could also participate in the deprotonation (reductive elimination process between intermediates **IM1** and **IM2**) and the protonation (oxidative addition process between intermediates **IM6** and **IM7**) steps.[12] Moreover, aldehyde donors significantly influenced the transfer hydroformylation. Replacing *n*-butyraldehyde with 2-methylbutanal, 3-methylbutanal, or 3-phenylpropanal led to a diminished yield of **A1** and the reaction was shut down completely when using cyclohexanecarbaldehyde as the donor. Notably, **A1** could also be obtained in 75% yield by using paraformaldehyde as aldehyde donor (Table S1, entry 23).



***Scheme* 2.** Proposed mechanism involved in the transfer hydroformylation reaction of alkynes.

With the optimized conditions in hand, we investigated the scope of this transfer hydroformylation using internal alkynes with *n*-butyraldehyde (**2a**) (Table 2). First, various symmetric alkyl alkynes smoothly underwent the transfer hydroformylation reaction, producing the desired *α,β*-unsaturated aldehydes with almost complete *E*-selectivity in good to excellent yields (**A1**-**A6**). Satisfactorily, when the amount of $[Rh(cod)OMe]_2$ was reduced to 0.5 mol %, **A1** could still be obtained in 72% yield (Table 2; Table S1, entry 22). The transfer hydroformylation can be extended to cyclic alkynes, giving the corresponding products in excellent yields (**A7**-**A8**). A series of asymmetric aryl alkyl alkynes gave remarkably high regioselectivity at the distal position relative to the aryl group (**A9**-**A13**). To our delight, the free hydroxyl-containing asymmetric dialkyl alkynes smoothly reacted with **2a**, delivering the corresponding unsaturated aldehydes in good yields with a relatively high regioselectivity probably because of the chelation of hydroxyl group (**A14**-**A17**). Similarly, the ester-containing asymmetric dialkyl alkyne also gave the desired product with almost complete regioselectivity (**A18**).

***Table 1*:** Evaluation of the reaction parameters.[a,b]



[a] Standard conditions: alkyne (0.4 mmol), aldehyde (0.2 mmol), $[Rh(cod)OMe]_2$ (2.0 mol %), phosphine ligand (4.0 mol %), and carboxylic acid (4.0 mol %) in THF (100 μL) at 80 °C under N_2 for 24 h. [b] Isolated yields.

To further test the compatibility of the protocol in more structurally intricate contexts, a variety of asymmetric internal alkynes embedded in pharmaceutical agents and biologically relevant molecules were tested (**A19**-**A37**), including those derived from tyrosine (**A21**), vanillin (**A22**), pterostilbene (**A23**), *δ*-tocopherol (**A24**), estrone (**A25**-**A27**), mestranol (**A28**), ethisterone (**A29**-**A30**), probenecid (**A31**), ferrocenecarboxylic acid (**A32**), dehydrocholic acid (**A33**), (*S*)-(+)ketopinic acid (**A35**), *D*-methionine (**A36**), and epristeride (**A37**). Satisfactorily, the above alkynyl-containing complex molecules were compatible well with this protocol to provide *α,β*-unsaturated aldehydes in mediate to good yields and with almost complete regioselectivities because of steric encumbrance and/or chelation. The structure of **A30** was confirmed by X-ray crystallography.[15] These examples highlight the synthetic utility of this transfer hydroformylation and its compatibility with complex molecules. Finally, we tried to couple butyraldehyde with internal alkyne bearing the more sterically hindered group at both sides, such as 2,5-dimethylhex-3-yne-2,5-diol and 2,5-dimethoxy-2,5-dimethylhex-3-yne, but none of these could work.

To obtain a clearer perception of the reaction, a set of control experiments were performed. First, the transfer hydroformylation of terminal alkyne (**38**) with **2a** did not afford any hydroformylated product **A38** (Scheme 3a, (i)). In order to address this limitation,

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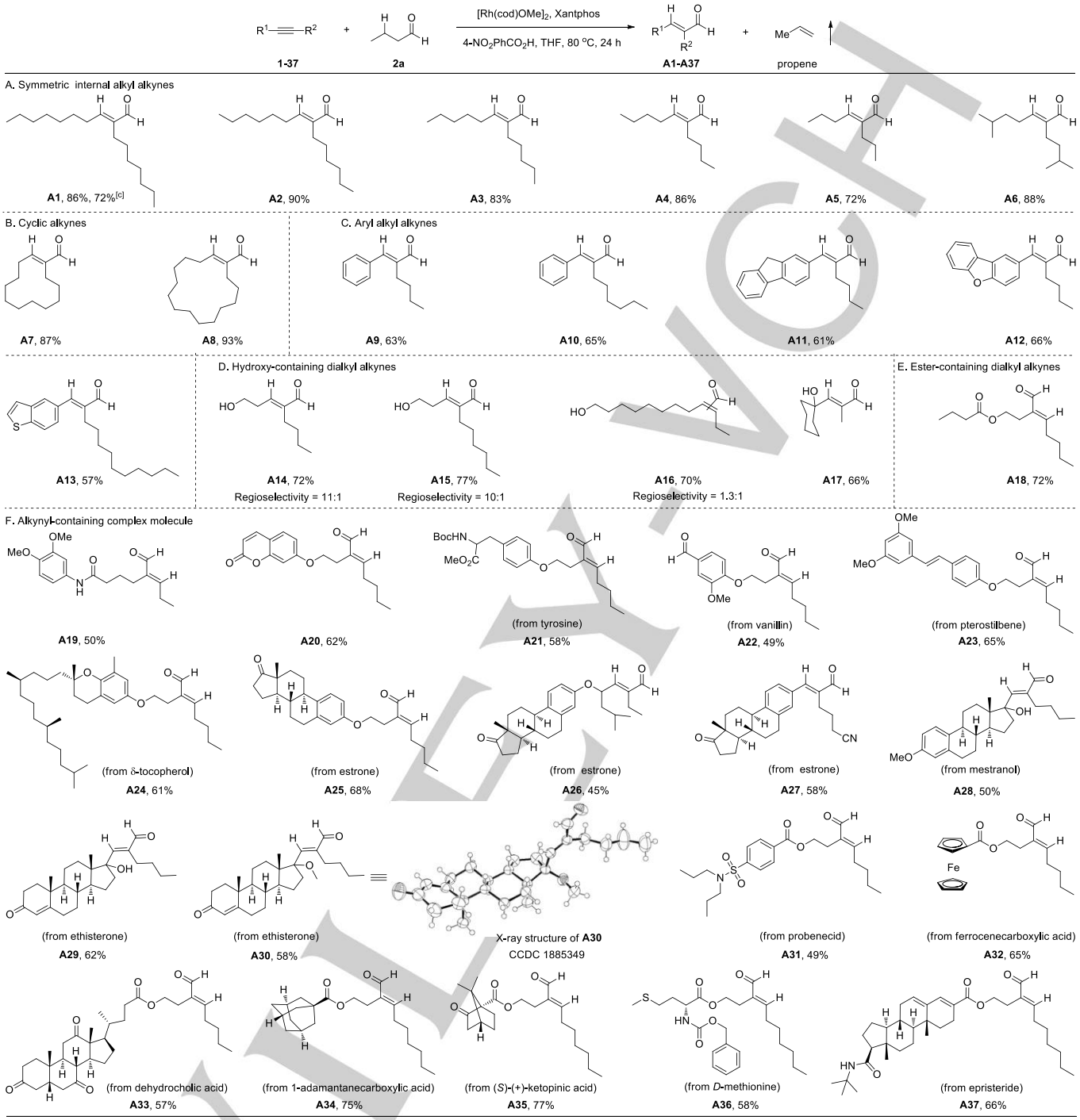
Table 2: Scope of rhodium-catalyzed transfer hydroformylation of internal alkynes with *n*-butyraldehyde to *α,β*-unsaturated aldehydes.[a,b]



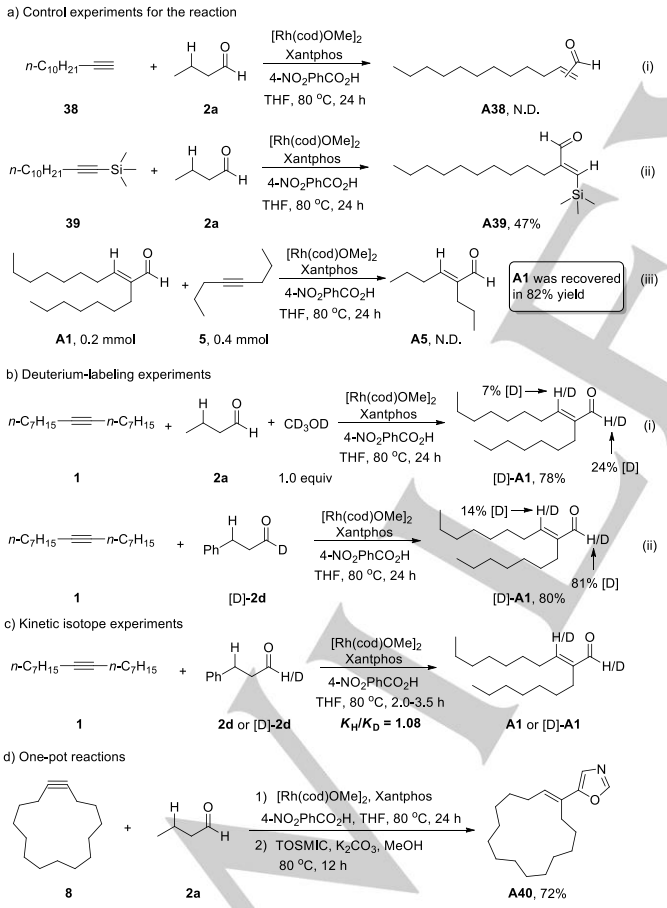
[a] Reaction conditions: **1-37** (0.4 mmol), **2a** (0.2 mmol), $[Rh(cod)OMe]_2$ (2.0 mol %), Xantphos (4.0 mol %), and 4-NO_2PhCO_2H (4.0 mol %) in THF (100 μL) at 80 °C under N_2 for 24 h. [b] Isolated yields. [c] The reaction was performed with $[Rh(cod)OMe]_2$ (0.5 mol %), Xantphos (1.0 mol %), and 4-NO_2PhCO_2H (1.0 mol %) in THF (100 μL) at 80 °C under N_2 for 24 h.

employing TMS-protected dodec-1-yne (**39**) as a reactant, the desired hydroformylated product **A39** was obtained in 47% yield (Scheme 3a, (ii)). Treatment of **A1** with **5** under the standard reaction conditions for 24 h did not lead to any transfer hydroformylated product **A5** except for the recovery of **A1** in 82% yield (Scheme 3a, (iii)). This is likely due to the poor reactivity of **A1**, because after CO de-insertion the beta-H elimination of the alkenyl group to give an alkyne is generally thermodynamically uphill.

Next, two deuteration experiments were conducted to study the transfer process (Scheme 3b). Under the standard conditions, the reaction of **1** with **2a** in the presence of 1 equiv of CD_3OD led to 7% and 24% deuterations of alkenyl hydrogen and aldehyde hydrogen of [D]-**A1**, respectively, suggesting that the aldehyde

proton of **2a** could be transferred to the product through the benzoate counterion as a proton shuttle, in which 4-NO_2PhCO_2H could undergo proton exchange with CD_3OD (Scheme 3b, (i)). Treatment of **1** with deuterated [D]-**2d**, the deuterated ratios of the corresponding alkenyl hydrogen and aldehyde hydrogen of [D]-**A1** were approximately 14% and 81%, respectively, implying that the aldehyde proton of **A1** mainly came from the aldehyde of **2d** rather than the *β*-hydrogen (Scheme 3b, (ii)). These results provided a powerful support for the proposed mechanism illustrated in Scheme 2. In addition, two parallel competition reactions between **1** with **2d** or [D]-**2d** gave a kinetic isotope effect (KIE) value of 1.08 (Scheme 3c), suggesting that the C−H bond cleavage of alkyl aldehyde might not be related with the rate-determining step. In 2016, Lan and coworkers demonstrated a computational study of the rhodium-catalyzed dehydroformylation of aliphatic aldehydes and indicated that the *β*-hydride elimination might be the rate-determining step of the catalytic cycle.[12] As a mechanistically relevant transfer hydroformylation, we reasoned that the *β*-hydride elimination might also be the rate-determining step of this reaction.

To further highlight the synthetic utility of our strategy, a one-pot reaction was performed to produce (*E*)-5-(cyclopentadec-1-en-1-yl)oxazole (**A40**, 72% yield) (Scheme 3d).[16]



***Scheme* 3.** Control experiments and one-pot reactions. TOSMIC = tosylmethyl isocyanide.

In summary, we have demonstrated a syngas-free rhodium-catalyzed highly chemo-, regio- and *E/Z*-selective transfer hydroformylation of alkynes under safe and mild conditions. This protocol uses inexpensive and easy-to-handle *n*-butyraldehyde as a donor of formyl and hydride to overcome the challenge posed by the use of syngas in traditional approaches. We believe that this method would offer an operationally simple, effective and practical route to *α,β*-unsaturated aldehydes in both laboratory and industry.

Acknowledgements

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Keywords: transfer hydroformylation • rhodium catalysis • C–C bond cleavage • *α,β*-unsaturated aldehyde • syngas free

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[15] CCDC 1885349 (**A30**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data request/cif.

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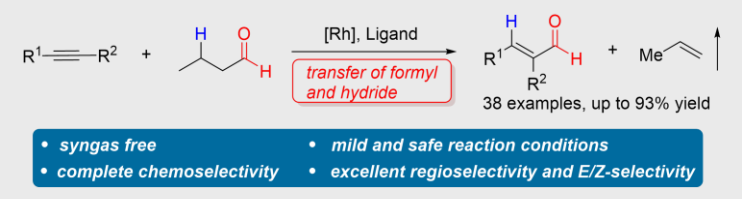

Overcoming the challenge posed by the use of syngas: A syngas-free highly chemo-, regio- and *E/Z*-selective transfer hydroformylation of internal alkynes with simple alkyl aldehydes under safe and mild conditions has been developed to provide a broad range of stereodefined *α,β*-unsaturated aldehydes.

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