Homogenous Catalysis

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

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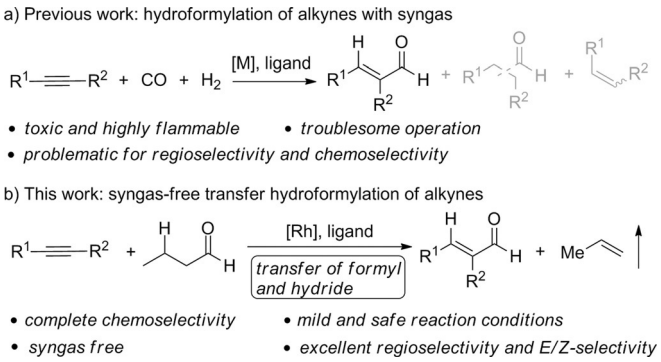
***Abstract:*** *The hydroformylation of alkynes is a fundamental and important reaction in both academic research and industry. Conventional methods focus on the conversion of alkynes, CO, and $H_2$ into α,β-unsaturated aldehydes, but they often suffer from problems associated with operation, regioselectivity,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

As important synthetic intermediates, α,β-unsaturated aldehydes are fundamental 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 the Buchwald,[3] Hidai,[4] Alper,[5] Beller,[6] Breit,[7] and Zhang[8] groups, all of which focus on the conversion of alkynes, CO, and $H_2$ into aldehydes (Scheme 1a). Despite strenuous effort, two fundamental issues remain for 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, highly pressurized syngas is generally required, thereby necessitating special equipment to handle the pressurized gas. Second, compared with the hydroformylation of alkenes, the hydroformylation of alkynes is more challenging because the regioselectivity is difficult to control and the formation of byproducts such as hydrogenated products of alkynes and saturated aldehydes is poorly suppressed.[9] Thus, considering the importance of the hydroformylation of alkynes in both academic research and industry, it is highly desirable to develop a syngas-free hydroformylation reaction, ideally with a controllable selectivity, although this is seen as one of the most challenging tasks in the synthetic chemistry.




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

In 2015, Dong and co-workers reported an elegant rhodium-catalyzed dehydroformylation of aliphatic aldehydes to generate alkenes under mild conditions.[10] This dehydroformylation method employed highly strained norbornadiene as a sacrificial acceptor to drive the reaction through the release of its ring strain. Inspired by this work, we envisaged that a mechanistically relevant transfer of formyl and hydride moieties between simple alkyl aldehyde and alkyne would fulfill the hydroformylation without relying upon syngas (Scheme 1b). We reasoned that the transfer hydroformylation of an alkyne with a simple alkyl aldehyde could be unlocked through the elaborate rhodium-catalyzed pathway illustrated in Scheme 2, which involves a sequence of reversible aldehyde C–H bond activations to form an acyl-$Rh^{III}$-hydride, reductive elimination, de-insertion of CO, β-hydride elimination to form 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 aldehydes; 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 through shuttle catalysis (Scheme 1b).[13] This method uses accessible and inexpensive *n*-butyraldehyde as a formyl and hydride donor to transform a broad range of

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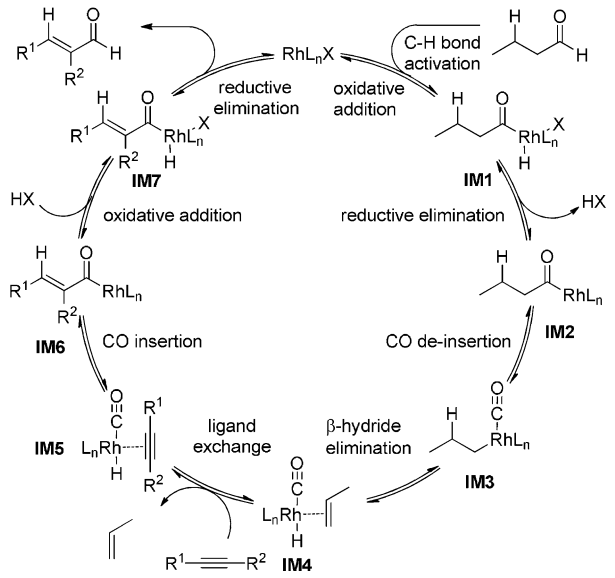
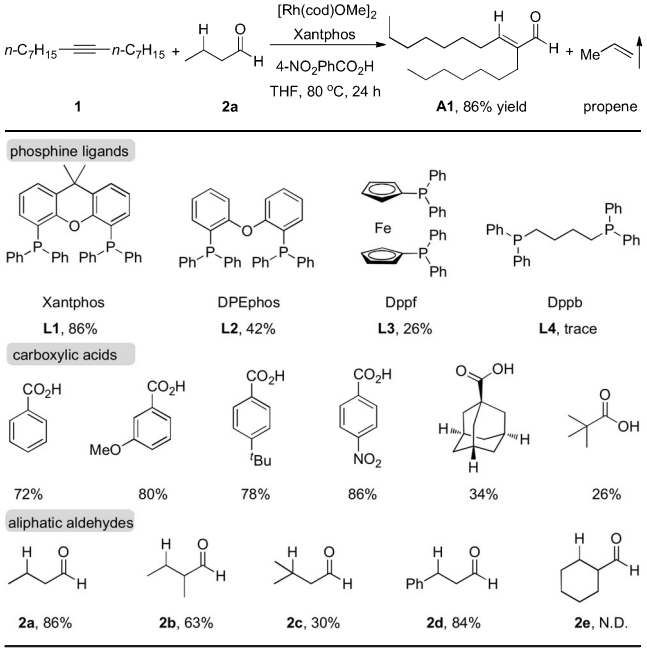



***Scheme 2.*** Proposed mechanism for the transfer hydroformylation reaction of alkynes.

***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.

alkynes into α,β-unsaturated aldehydes with excellent chemo, regio-, and *E*/*Z*-selectivity.

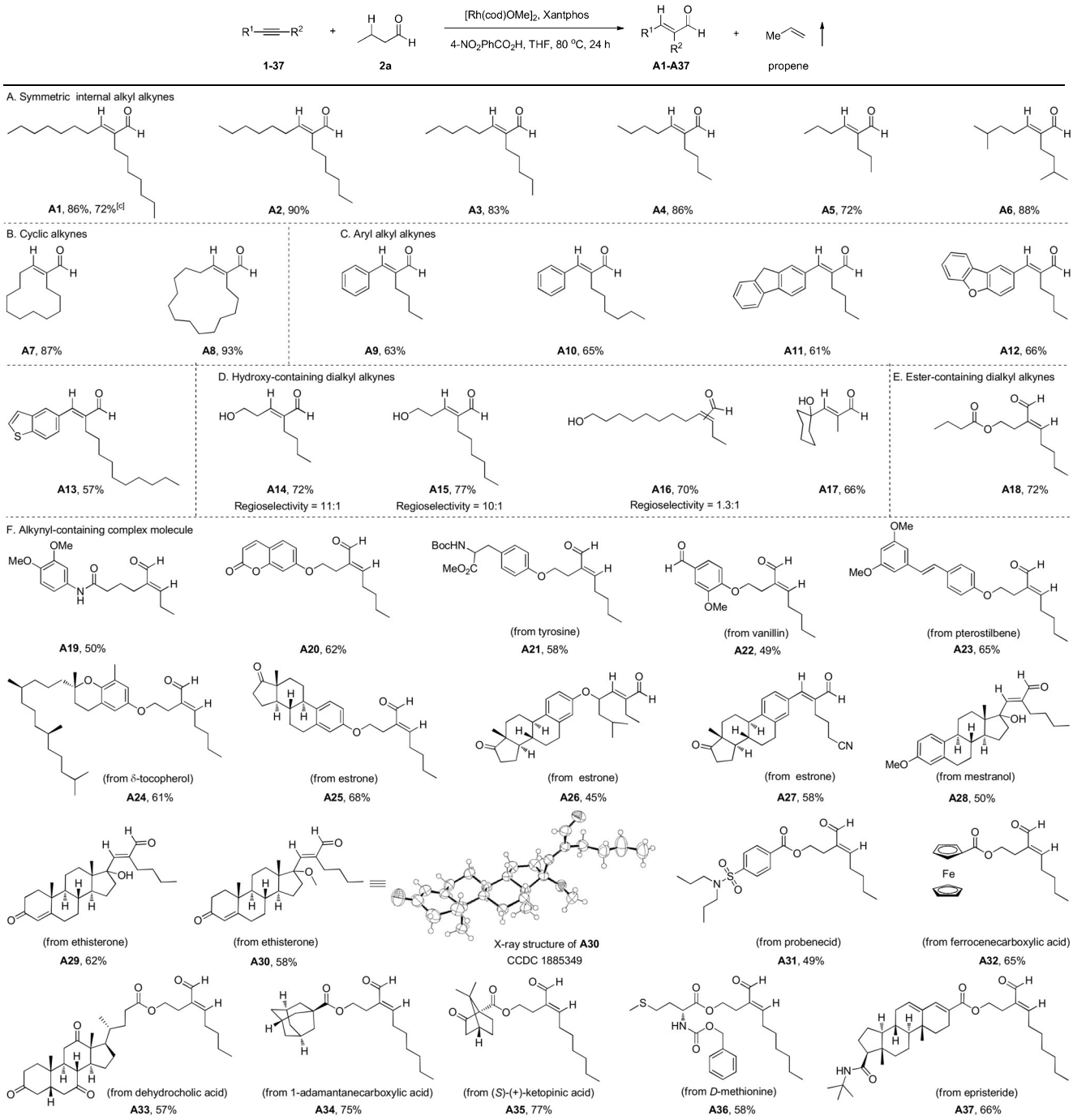
Our investigation commenced with the reaction between hexadec-8-yne (**1**) and *n*-butyraldehyde (**2a**). After a systematic evaluation of the reaction parameters, the best yield for (*E*)-2-heptyldec-2-enal (**A1**) of 86% was reached with a catalytic system composed of [Rh(cod)OMe]$_2$ (2.0 mol%), 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 in the Supporting Information). The choice of the phosphine ligands is critical to this transfer hydroformylation and only bidentate phosphine ligands were 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 $\beta_n$ 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 ligands with a larger natural bite angle might be more efficient. Next, a series of benzoic acids and alkyl carboxylic acids were screened and 4-$NO_2PhCO_2H$ was superior to $PhCO_2H$, 3-$MeOPhCO_2H$, 4-$^tBuPhCO_2H$, 1-$AdCO_2H$, and PivOH. As shown in 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, the aldehyde donor 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).

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**). To our satisfaction, 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 hydroxy-containing asymmetric dialkyl alkynes smoothly reacted with **2a**, delivering the corresponding unsaturated aldehydes in good yields with a relatively high regioselectivity, probably because of chelation of hydroxy group (**A14**–**A17**). Similarly, the ester-containing asymmetric dialkyl alkyne also gave the desired product with almost complete regioselectivity (**A18**).

To further test the compatibility of the method in more structurally complex 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**),

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



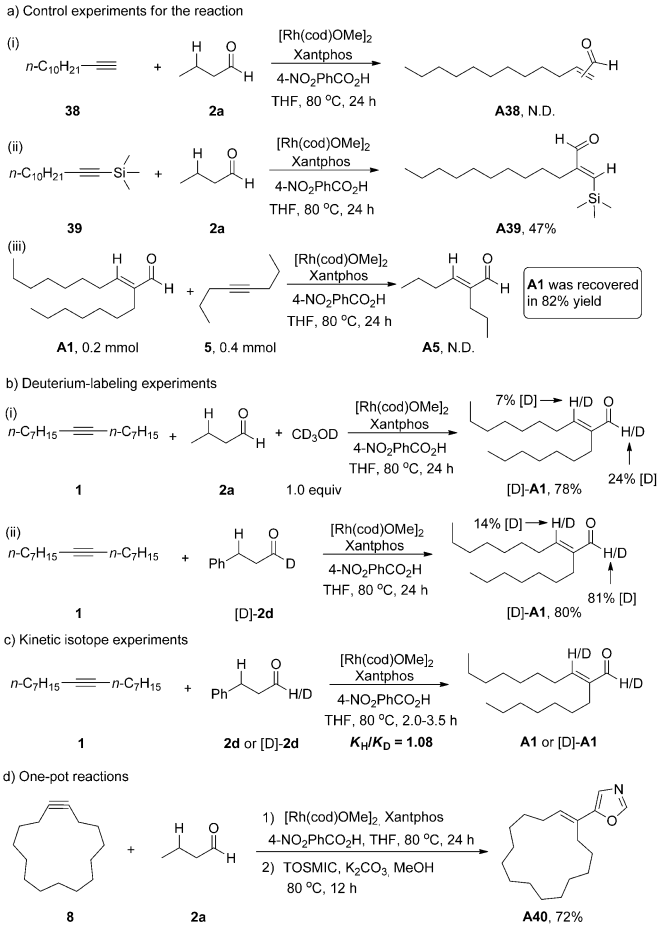

[a] Reaction conditions: **1**–**37** (0.4 mmol), **2a** (0.2 mmol), $[Rh(cod)OMe]_2$ (2.0 mol%), Xantphos (4.0 mol%), and 4-$NO_2PhCO_2H$ (4.0 mol%) in THF (100 μL) at 80 °C under $N_2$ for 24 h. [b] Yields of isolated product. [c] The reaction was performed with $[Rh(cod)OMe]_2$ (0.5 mol%), Xantphos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

ferrocenecarboxylic acid (**A32**), dehydrocholic acid (**A33**), (*S*)-(+)ketopinic acid (**A35**), D-methionine (**A36**), and epristeride (**A37**). To our satisfaction, the above alkynyl-containing complex molecules were compatible with the reaction and provided the corresponding α,β-unsaturated aldehydes in moderate to good yields and with almost complete regioselectivity because of steric hinderance 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 worked.

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, TMS-protected dodec-1-yne (**39**) was employed as a reactant, and 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 of 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 β-H elimination of the alkenyl group to give an alkyne is generally thermodynamically uphill.




***Scheme 3.*** a) Control experiments. b) Deuterium-labeling experiments. c) Kinetic isotope effect (KIE) experiments. d) One-pot reactions. TOSMIC = tosylmethyl isocyanide.

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, thus 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). Following 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, thus implying that the aldehyde proton of **A1** mainly came from the aldehyde of **2d** rather than the β-hydrogen (Scheme 3b, ii). These results provide 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), thus suggesting that the C–H bond cleavage of alkyl aldehyde might not be related with the rate-determining step. In 2016, Lan and co-workers presented 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]

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

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** C–C bond cleavage · homogenous catalysis · rhodium · transfer hydroformylation · α,β-unsaturated aldehyde

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