CHEMISTRY

n-Alkanes to n-alcohols: Formal primary C—H bond hydroxymethylation via quadruple relay catalysis

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Nature is able to synergistically combine multiple enzymes to conduct well-ordered biosynthetic transformations. Mimicking nature's multicatalysis in vitro may give rise to new chemical transformations via interplay of numerous molecular catalysts in one pot. The direct and selective conversion of abundant n-alkanes to valuable n-alcohols is a reaction with enormous potential applicability but has remained an unreached goal. Here, we show that a quadruple relay catalysis system involving three discrete transition metal catalysts enables selective synthesis of n-alcohols via n-alkane primary C—H bond hydroxymethylation. This one-pot multicatalysis system is composed of Ir-catalyzed alkane dehydrogenation, Rh-catalyzed olefin isomerization and hydroformylation, and Ru-catalyzed aldehyde hydrogenation. This system is further applied to synthesis of α,ω-diols from simple α-olefins through terminal-selective hydroxymethylation of silyl alkanes.

INTRODUCTION

Alcohol synthesis is critical to the chemical industries. Linear alcohols, n-alcohols, are particularly important chemicals because of their widespread applications as precursors of plasticizers and detergents (1). Current syntheses of n-alcohols rely on α-olefins as the starting materials; a three-step homologation process involving α-olefin hydroformylation (HF), purification of n-aldehyde, and n-aldehyde hydrogenation is a classical route to n-alcohols in industry (Fig. 1A, Eq. 1) (2). Recently, simplified, one-pot procedures without n-aldehyde purification have been developed by Nozaki and co-workers (3, 4). For laboratory-scale synthesis, a hydroboration/oxidation sequence using stoichiometric borane is a reliable approach (5). Dong et al. (6) reported a triple relay catalysis involving three metal catalysts (Pd/Cu/Ru) for synthesis of primary alcohols via formal anti-Markovnikov hydration of aryl-substituted terminal olefins (Fig. 1A, Eq. 2).

In contrast to the synthesis of n-alcohols from α-olefins, synthesis of n-alcohols from n-alkanes has remained elusive (7, 8). As the major constituents of natural gas and petroleum, alkanes are far more readily available and diverse than α-olefins produced primarily by ethylene oligomerization (9). The recent developments of shale gas further stimulate the exploitation of alkanes directly as feedstocks for value-added chemicals (10). Existing methods of n-alkane hydroxylation (n-alkane partial oxidation) mostly occur through hydrogen abstraction from a C—H bond to form an alkyl radical. As a result, the site selectivity of these reactions is controlled primarily by the C—H bond strength, making the selective hydroxylation of terminal, primary C—H bonds versus weaker secondary C—H bonds in the same n-alkane molecule impossible (11). For example, the Fenton reaction offers very low linear selectivity in the n-alkane hydroxylation (Fig. 1B) (12). Likewise, n-alkane hydroxylations catalyzed by high valent porphyrin metal oxides and relevant complexes mainly produce branched alcohols (i-alcohols) (13, 14). CYP153A

enzyme catalyzes terminal-selective hydroxylations of n-alkanes, but the reactions are plagued by overoxidation, particularly for those higher than n-heptane (C7) (15). The Shilov process using Pt catalyst allows for methane oxidation to methanol; unfortunately, the system is not suitable for longer n-alkanes because the resulting alcohols decompose easily under strong acidic reaction conditions (16). Given the vast quantities of underused saturated hydrocarbons and the broad usefulness of n-alcohols, there is a compelling need to develop a catalytic system for conversion of alkanes directly to linear alcohols. Here, we report a new reaction, alkane hydroxymethylation, which enables selective synthesis of n-alcohols from n-alkanes.

RESULTS AND DISCUSSION

Our strategy relies on a quadruple relay catalysis system involving alkane dehydrogenation (AD), olefin HF, and aldehyde hydrogenation (AH) (Fig. 1C). Because the AD cycle inevitably forms internal olefin mixtures as the major products (see below) (17–19), an additional catalytic cycle for internal-to-terminal olefin isomerization (ISO) is required before the HF cycle to achieve high linear selectivity. Hence, the formal hydroxymethylation reaction essentially couples four catalytic cycles, AD-ISO-HF-AH. The AD will be conducted separately because its conditions differ from those for the ISO-HF-AH, which will be performed in a concurrent tandem fashion. This one-pot, AD-ISO-HF-AH quadruple catalysis does not need isolation or purification of any intermediates, thereby to a great extent simplifying the process operation. The success of this strategy depends on the compatibility between the catalysts and the rates of individual catalytic cycles: (i) the HF catalyst (cat-2) and the AH catalyst (cat-3) must tolerate each other, and both should be compatible with the AD catalyst (cat-1) because all these catalysts are present in one pot at the stage of the ISO-HF-AH; (ii) at least one of the three catalysts (cat-x) should be effective for the olefin ISO, and to obtain linear alcohols selectively, the ISO rate (k_1) must be considerably greater than the rates for direct hydrogenation (k_2) and HF (k_3) of internal olefins; (iii) α-olefin anti-Markovnikov HF (k_4) must be faster than its direct hydrogenation (k_5) and Markovnikov HF (k_6), and k_4 should also be greater than k_3 and k_2 because the olefin ISO is reversible; and (iv) the catalyst(s) must strongly favor the hydrogenation of aldehydes versus olefins ($k_7 \gg k_2, k_5$).

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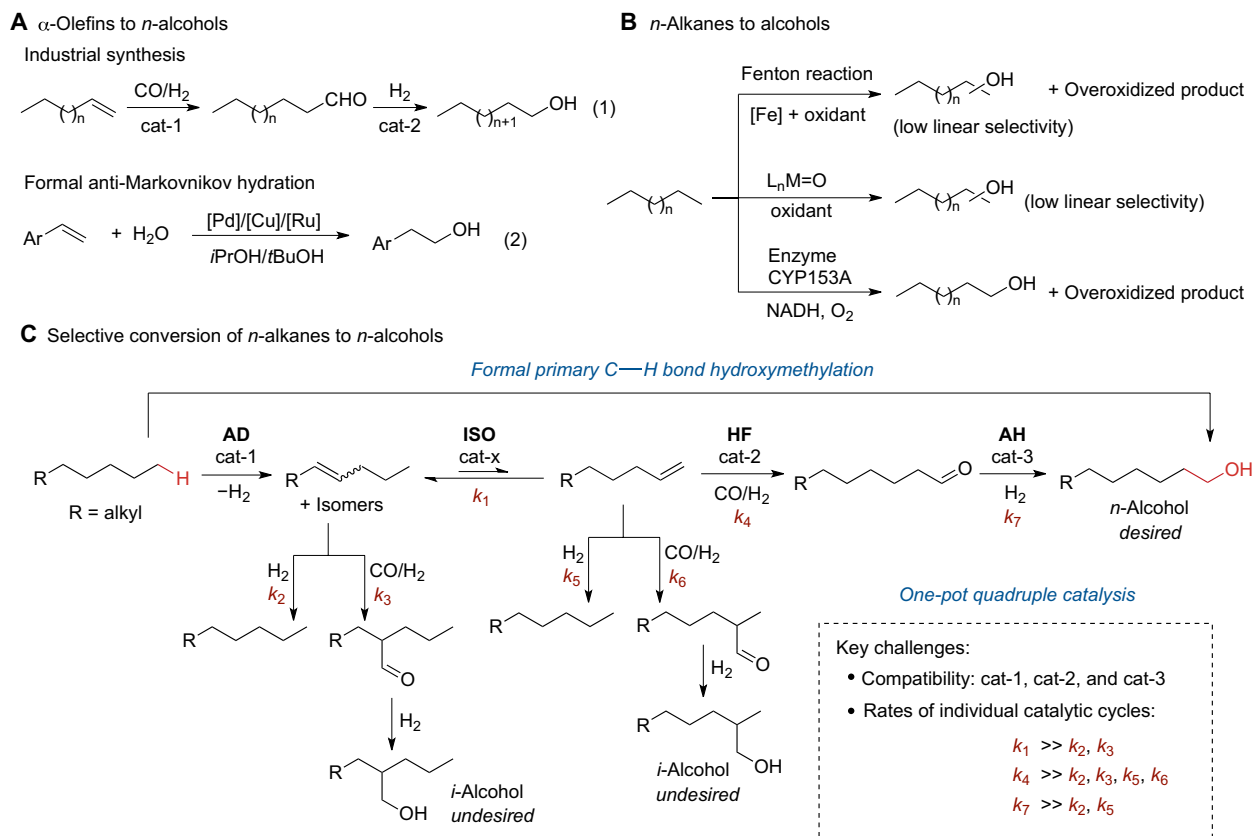*Corresponding author. Email: huangzh@sioc.ac.cn

Fig. 1. A quadruple catalysis strategy for conversion of *n*-alkanes to *n*-alcohols. (**A**) Synthesis of *n*-alcohols from α-olefins. (**B**) Synthesis of alcohols from alkanes via partial oxidation. (**C**) Proposed quadruple relay catalysis for selective synthesis of *n*-alcohols from *n*-alkanes. R, alkyl group; cat-1, cat-2, and cat-3 are three discrete catalysts; cat-x is one of these three catalysts.

We chose molecular pincer Ir complexes as the AD catalysts (cat-1, see Table 1) because this type of catalysts can operate at temperatures much lower than heterogeneous AD catalysts, therefore suitable for the dehydrogenation of various alkanes without C−C bond cleavage (*17*). Early studies of the ISO-HF of internal olefins have shown that Rh(acac)(CO)$_2$ supported by a biphosphinite ligand (biphephos) is selective for the formation of *n*-aldehydes (*20*). Ru-ligand bifunctional catalysts are also known to selectively reduce aldehydes over olefins because of their propensity to mediate the hydrogenation of polar double bonds via an outer sphere mechanism (*21*). Thus, we commenced the study by exploring several Ru-ligand bifunctional catalysts, in combination with the pincer Ir and Rh/ biphephos catalysts, for the hydroxymethylation of *n*-octane (C8).

With the highly active AD precatalyst (PSCOP)IrHCl [cat-1a, 1 mole percent (mol %); PSCOP is a S, O atom–linked tridentate pincer ligand] (*22*) and NaO*t*Bu as the catalyst activator (1.2 mol %), *n*-octane was dehydrogenated at 200°C to octene mixtures using *t*-butylethylene (TBE, 0.25 M) as a hydrogen acceptor. Analysis of the products after 10 min by gas chromatography (GC) revealed that quantitative conversion of TBE to *t*-butylethane (TBA); *trans*-octenes (*E*-octenes), including *E*-4-, *E*-3-, and *E*-2-octene, rather than *cis*-octenes (*Z*-octenes) or 1-octene, were formed as the major dehydrogenation products because of facile ISO to yield olefin mixtures with thermodynamic ratios under the Ir catalysis (*22*). Without purification, cat-2 [0.8 mol % Rh(acac)(CO)$_2$ plus 3.2 mol % biphephos]
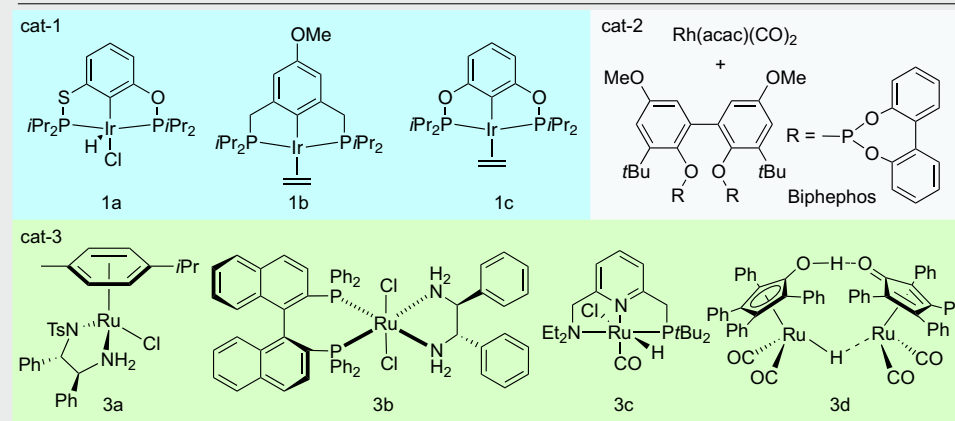
and cat-3 (2.5 mol %) were then added to the solution, which was further charged with syngas (a mixture of CO and H$_2$). Using Noyori-Ikariya's bifunctional catalyst (cat-3a) (*23*), the reaction with 10/10 bar CO/H$_2$ at 120°C afforded 73% nonanals, but only 5.2% nonanols after 28 hours (run 1; yields are relative to TBE). The regioselectivity for *n*-nonanal (n/i: 6.2) is notably lower than that for *n*-nonanol (n/i: 15), suggesting that the hydrogenation of *n*-aldehyde is faster than that of *i*-aldehydes. Small amounts of high boiling-point by-products, mainly esters and aldol adducts, were also detected (3%; see the Supplementary Materials for structures). No octenes remained, indicating the occurrence of olefin direct hydrogenation.

Using Noyori's diphosphine-diamine catalyst (cat-3b) (*24*), the yield of nonanols grew to 12% (run 2). Although the total yield of aldehydes and alcohols (70%) was lower than that with cat-3a (78%), the overall regioselectivity was somewhat improved (overall n/i: 8.4). Milstein's pincer Ru catalyst (cat-3c) (*25, 26*) is similar to cat-3a in terms of productivity and selectivity, furnishing a low yield of nonanols (3.8%) (run 3). Note that substantial amounts of branched products (*i*-nonanals and *i*-nonanols) were observed in the runs with cat-3a and cat-3c (~10%). In contrast, Shvo's catalyst (cat-3d) (*27–29*) was found to be highly effective for the AH, producing 74% nonanols with an alcohol n/i value of 9.3. Nonanals (1.7%) and high boiling-point by-products (3%) were also observed, but in minimal amounts (run 4).

With Shvo's catalyst as the AH catalyst, another two AD catalysts ligated by PCP and POCOP ligands were tested (PCP and POCOP

Table 1. [Ir]/[Rh]/[Ru]-catalyzed hydroxymethylation of *n*-octane to *n*-nonanol. Conditions for AD: *n*-octane (2 ml), *t*-butylethylene (TBE) (0.5 mmol), cat-1 (1.0% relative to TBE), NaO*t*Bu (1.2%) (not needed for cat-1b and cat-1c), 200°C, 10 min; conditions for ISO-HF-AH: cat-2 [Rh(acac)(CO)$_2$ (0.8% relative to TBE) and biphephos (3.2%)], cat-3 (2.5%; 1.25% for cat3-d); yields of alcohols and aldehydes were determined by gas chromatography (GC) with mesitylene as an internal standard; yields are relative to TBE; n/i, linear/branched ratio.

n-Octane	cat-1 (1.0%) TBE (0.5 mmol) 200°C, 10 min		cat-2 (0.8%); cat-3 (2.5%) CO/H$_2$ 120°C, 28 hours			Nonanals + nonanols		
Run	cat-1	cat-3	CO/H$_2$ (bar)	Aldehyde (%) [n/i]	Alcohol (%) [n/i]	Linear* (%)	Overall n/i	By-product[†] (%)
1[‡]	1a	3a	10/10	73 [6.2]	5.2 [15]	68	7.0	3
2[§]	1a	3b	10/10	58 [7.5]	12 [19]	62	8.4	3
3[§]	1a	3c	10/10	74 [7.5]	3.8 [8.2]	68	7.5	4
4	1a	3d	10/10	1.7	74 [9.3]	68	9.1	3
5	1b	3d	10/10	1.0	81 [9.6]	73	9.6	4
6	1c	3d	10/10	1.5	82 [12]	76	12	6
7	1a	3d	2.5/10	<1	69 [25]	66	25	4
8	1a	3d	5/10	<1	79 [18]	75	18	<2
9	1a	3d	7.5/10	<1	81 [12]	76	12	3
10[‖]	1a	3d	5/10	<1	81 [19]	77	19	4
11[¶]	1a	3d	5/10	<1	79 [16]	74	16	3

cat-1: 1a, 1b, 1c; cat-2: Rh(acac)(CO)$_2$ + Biphephos; cat-3: 3a, 3b, 3c, 3d

*Combined yields of *n*-aldehyde and *n*-alcohol. †High boiling-point by-products are esters and aldol adducts. ‡KOH (2.5%) was added as the catalyst activator. §2.5% KO*t*Bu was added as the catalyst activator. ‖110°C for ISO-HF-AH. ¶130°C for ISO-HF-AH.

are pincer ligands with C and O atoms as the linkers, respectively.). To simplify the operation by eliminating the use of NaO*t*Bu as the catalyst activator, the ethylene-bound Ir complexes (PCP)Ir(C$_2$H$_4$) (cat-1b) and (POCOP)Ir(C$_2$H$_4$) (cat-1c) were prepared (see the Supplementary Materials). The reaction with cat-1b afforded 81% nonanols (n/i: 9.6) (run 5), and that with cat-1c gave 82% nonanols (n/i: 12) (run 6). Although these reactions offered higher yields than the run using cat-1a/NaO*t*Bu, more by-products were generated with cat-1b (4%) and cat-1c (6%).

The internal-to-terminal olefin ISO rate (k_1) is key to the regioselectivity. We envisioned that reducing the CO partial pressure, while keeping the H$_2$ partial pressure unchanged, might favor the formation of metal hydride complex, the proposed catalytically active species for the ISO (*30*). In line with this supposition, conducting the reaction at 2.5/10 bar CO/H$_2$ using cat-1a/cat-2/cat-3d gave 69% nonanols with a 25 n/i selectivity, accompanied by trace amounts of nonanals (<1%) (run 7). Thus, reducing the CO partial pressure improved not only the linear selectivity but also the chemoselectivity [the alcohol/aldehyde (alc/ald) value]. This can be rationalized by the increased concentration of Ru hydride, the species responsible for the catalytic AH (*30*), with greater relative pressure of H$_2$ versus CO. The total yield of alcohols and aldehydes (69%), however, is

lower than that using 10/10 bar CO/H_2 (76%), which can be attributed to the declined HF rate as a result of reduced CO pressure. Attempts to balance the selectivity and productivity led to the finding that the run at 5/10 bar CO/H_2 gave 79% nonanols with an 18 n/i selectivity (run 8). Increasing the CO partial pressure further (7.5/10 bar CO/H_2) enhanced the yield to 81%, but with reduced linear selectivity (n/i: 12) (run 9). Both runs gave neglectable amounts of aldehydes (<1%). The yield of the by-products was minimal (<2%) in the case of run 8. Further optimization by changing the reaction temperatures showed little impact on the alcohol productivity and the selectivity but led to more by-products (runs 9 and 10). Thus, the reaction parameters shown in run 8 were used to explore the substrate scope.

A range of n-alkanes were investigated for the hydroxymethylation (Fig. 2A). In all cases, a hydroxymethyl group could be added to the terminal positions with satisfactory yields (63 to 85%). Alkanes shorter than n-nonane (C5-C8) offered excellent chemoselectivity (alc/ald: >50) (see **5a** to **5d**). In particular, the runs with C5 and C6 almost exclusively yielded alcohols. C9 and C12 gave a 47 and 17 alc/ald selectivity, respectively (see **5e** and **5f**). Alcohols derived from short alkanes also showed greater n/i values than those from long alkanes. For example, while C12 gave an 11 n/i selectivity, C5 furnished a >50 n/i selectivity. The double bonds resulting from the dehydrogenation of long alkanes (e.g., C12) are remote from the

terminal position, thus adversely affecting the linear selectivity because the generation of the corresponding α-olefin becomes more difficult compared to that with shorter alkanes. The reduced regioselectivity is accompanied by the reduced chemoselectivity since i-aldehydes are less reactive than n-aldehyde (see above), accounting for the fact that both the regio- and chemoselectivity decline as the chain length increases.

As a cheaper alternative to TBE (*31*), ethylene proved to be a suitable hydrogen acceptor for the hydroxymethylation. For example, the reaction of n-nonane with ethylene (two atmospheres) smoothly yielded n-decanol (alc/ald: 11; n/i: 12), producing 82/204/130 turnover numbers relative to Ir/Rh/Ru, respectively (see the Supplementary Materials for details).

In addition to n-alkanes, the alkyl chains of aryl-substituted alkanes with dimethyl substitution at the benzyl position underwent the terminal-selective hydroxymethylation (**5g** to **5i**). Substitution of the benzyl H atoms is essential because it prevents the formation of styrene derivatives, which are reluctant toward the ISO because of thermodynamic reason (*32*). Consistent with the observed selectivity in the reactions with n-alkanes, the shorter alkyl chain (**5g**, >50 n/i) afforded a higher linear selectivity than the longer chains (**5h**, n/i: 26; **5i**, n/i: 16). The yield of **5g** is relatively low (51%), which can be ascribed to its low reactivity toward the dehydrogenation because of steric hindrance.
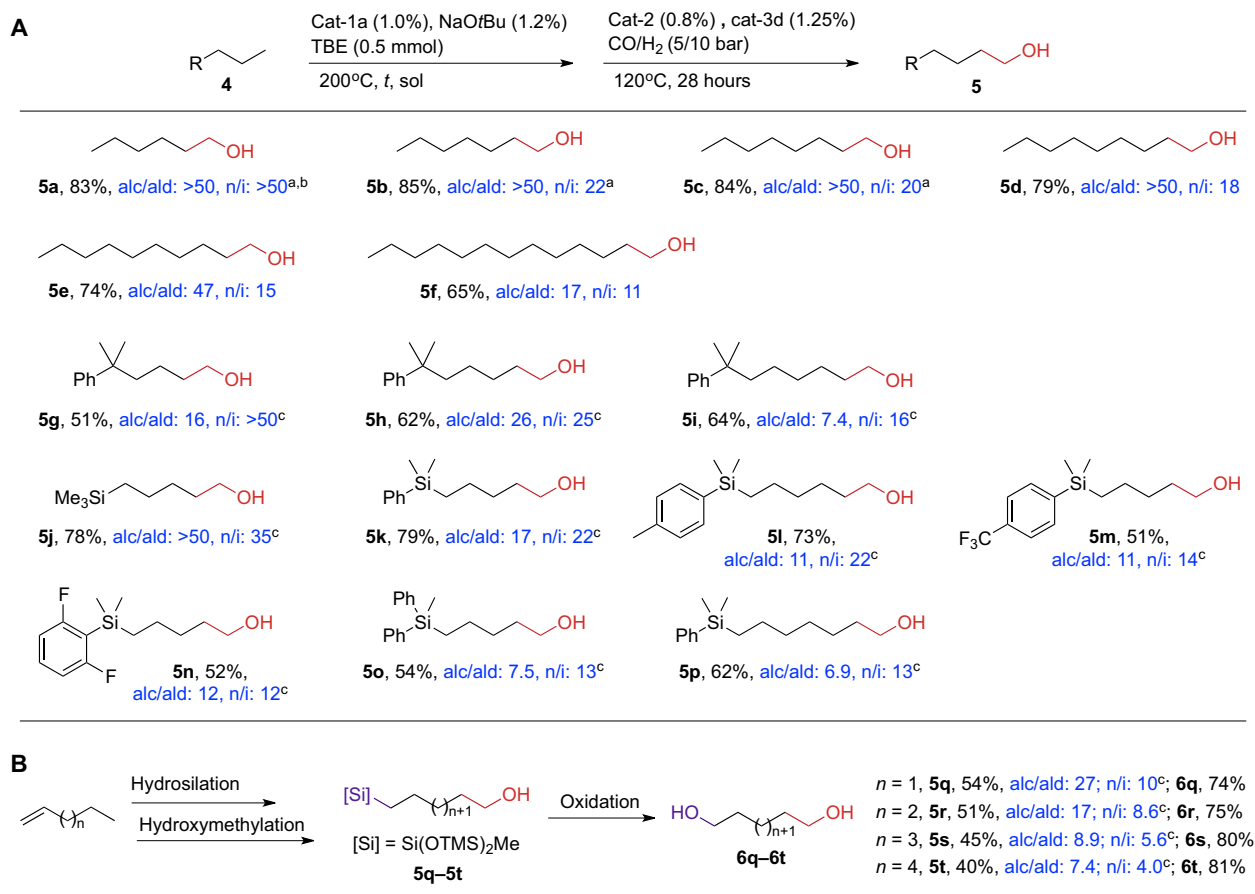
Fig. 2. Substrate scope and synthetic application of primary C—H bond hydroxymethylation. (**A**) Conversion of n-alkanes to n-alcohols. Conditions described in run 8 in Table 1 were used otherwise noted; t, time for the AD; yields of **5** are relative to TBE; alc/ald, alcohol/aldehyde; alc/ald and n/i ratios were determined by GC; high boiling by-products: <2%. [a] t = 30 min. [b] 190°C for the AD. [c] TBE (0.5 mmol), alkane (1.5 mmol), p-xylene (1.5 ml). (**B**) Synthesis of α,ω-diols from α-olefins via hydroxymethylation of silyl alkane. Conditions for hydrosilylation and oxidation were described in the Supplementary Materials; yields of **6** are relative to **5**.

The alkyl chains of quaternary silanes have proven to be reactive for the dehydrogenation (*33, 34*). Moreover, the silyl group with suitable substituents on Si can undergo further transformation. Thus, we explored the hydroxymethylation of silyl-substituted alkanes (Fig. 2A). The *n*-butyl chain of trimethylsilane was converted to the linear alcohol (**5j**) with high yield and high chemo- and regioselectivity. Various monoaryl-substituted silanes underwent the hydroxymethylation at the terminal position of *n*-butyl chains, although the yields for those with electron-withdrawing substituents (CF₃ and F) on the aryl rings were moderate (**5m** and **5n**). Bulky silane with two Ph groups (**5o**) on Si is suitable for the hydroxymethylation, albeit with relatively low chemoselectivity. The *n*-hexyl chain was converted to the corresponding linear alcohol (**5p**); comparison with its *n*-butyl analog (**5k**) revealed the chain length effect on the selectivity.

Diols that bear two hydroxyl groups at both terminal positions of linear carbon chains (α,ω-diols) are valuable monomers for polymer synthesis (*35, 36*). The terminal-selective hydroxymethylation of silyl alkanes provides an approach to α,ω-diols from simple α-olefins. The protocol consists of a three-step procedure: (i) anti-Markovnikov hydrosilylation of α-olefins, (ii) hydroxymethylation of silyl alkanes, and (iii) Tamao oxidation (Fig. 2B). Because the oxidation reaction occurs readily with silanes containing siloxy substituents on Si (*37*), bis(trimethylsiloxy)methylsilane [(TMSO)₂MeSiH] was selected as the hydrosilylation reagent. The alkyl chains of the resulting silyl alkanes smoothly underwent the hydroxymethylation (**5q** to **5t**), and the siloxy-terminated linear alcohols were easily oxidized to form α,ω-diols with the chain length ranging from six to nine carbons (**6q** to **6t**). The shorter α-olefins afforded higher chemo- and regioselectivity than the longer α-olefins, which is again consistent with the chain length effect as observed in the reactions with *n*-alkanes (see **5a** to **5f**).

To gain a better understanding of the role of the three transition metal catalysts in this quadruple catalysis, we conducted experiments that used only two of these three catalysts. A comparative experiment using *E*-2-octene as the starting material was conducted with cat-2 and cat-3d, but without cat-1a. The reaction with 10/10 bar CO/H₂ at 120°C gave 10% nonanols and 79% nonanals after 18 hours; extending the reaction time to 28 hours furnished 94% nonanols (n/i: 13) and <1% nonanals (Fig. 3A, Eq. 3). Taking into account the fact that the ISO of *E*-2-octene to 1-octene is faster than *E*-3- and *E*-4-octene [which are the other two major dehydrogenation products in addition to *E*-2-octene (*22*)], the product yield and selectivity obtained in this comparative experiment is comparable to those observed in run 4 using *n*-octane as the starting material (see Table 1). This suggests that cat-1a is probably not involved in the ISO-HF-AH process. Under the conditions otherwise identical to those used for run 4, the control experiment without cat-3 gave a full conversion of octenes, furnishing 69% nonanals (9.0 n/i), but neglectable amounts of nonanols (<1%) (Fig. 3A, Eq. 4). The combined yield (62%) of linear products (*n*-nonanal and *n*-nonanol) in this reaction is lower than that (68%) obtained in the reaction with cat-3d (see run 4, Table 1).

On the basis of these results, a quadruple relay catalysis system with the role of each individual catalyst defined is proposed for the alkane hydroxymethylation (Fig. 3B). Pincer Ir complexes are catalytically active for olefin ISO and hydrogenation (*38, 39*), but in this quadruple catalysis system, cat-1a merely acts as the AD catalyst according to the comparative experiment. ³¹P nuclear magnetic resonance experiments revealed that the addition of 2/2 bar CO/H₂ to
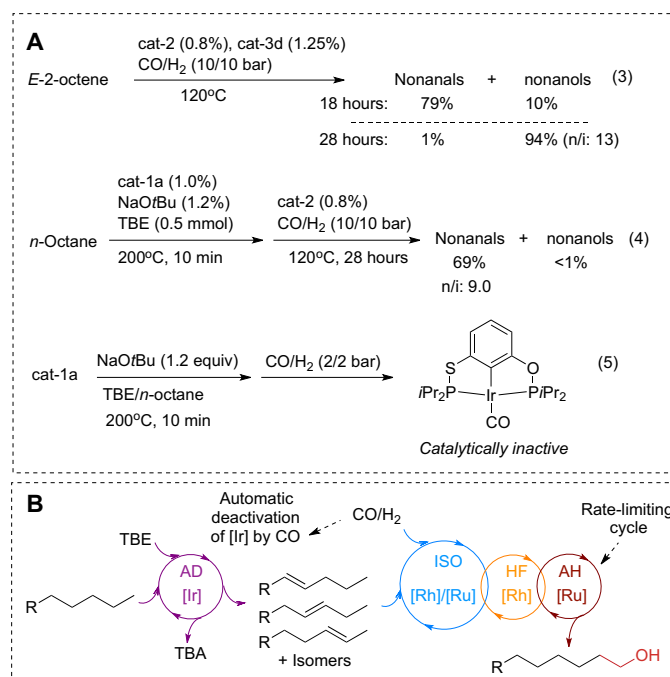

Fig. 3. Mechanistic insights into the role of each catalyst in the hydroxymethylation reaction. (**A**) Comparative and control experiments, and deactivation of cat-1a by syngas. (**B**) Proposed quadruple relay catalysis effected by three transition metal catalysts.

the solution resulting from the AD led to the formation of a catalytically inactive species, carbonyl adduct (PSCOP)Ir(CO) (Fig. 3A, Eq. 5) (*40*). The automatic deactivation of cat-1a by exposure to syngas alleviates the concerns of compatibility between the catalysts and eliminates potential side reactions caused by the Ir catalyst, such as olefin direct hydrogenation (*41*). The control experiment (Eq. 4) indicates that the Rh catalyst (cat-2) is the catalyst mainly responsible for the ISO-HF, but the presence of the Ru catalyst (cat-3d) can enhance the total yields of alcohols and aldehydes, as well as the linear selectivity by promoting the internal-to-terminal olefin ISO [earlier studies have shown that Shvo's catalyst is active for olefin ISO but has a minimal effect on the HF (*28*)]. The AH, however, proceeds only under the effect of Shvo's catalyst. The aldehyde reduction is slow at the early stage of the reaction as demonstrated by the low yield of nonanols after 18 hours, but the rate is markedly accelerated when the HF is nearly complete (see Eq. 3). These results suggest that the AH is the rate-limiting cycle in the tandem catalysis of ISO-HF-AH, and the Ru catalyst is subject to inhibition by the reactants. The inhibition of Shvo's catalyst by CO is evident (see above). Precedents also exist for the inhibition of the AH by olefins, particularly by sterically less hindered α-olefin and *Z*-olefins (*28*). In this regard, the turnover of the AH cycle benefits from the product distribution of Ir-catalyzed AD with *E*-olefins as the major products.

The terminal-selective hydroxymethylation provides an efficient approach to *n*-alcohols from abundant and diverse *n*-alkane feedstocks. Although this protocol is still far from ideal with relatively high catalyst loadings and the use of an acceptor olefin, we are encouraged by the excellent selectivity with short and medium-long *n*-alkanes and the substitution of the hydrogen acceptor from TBE to inexpensive ethylene. This relay catalysis operating in one-pot circumvents the problems associated with the isolation and

purification of olefin mixtures produced from the dehydrogenation of n-alkanes higher than C3, which would be very difficult, if not entirely unmanageable. We expect that the future development of more efficient and recyclable heterogeneous catalysts, coupled with a continuous-flow system designed for relay catalysis, may make this multicatalysis system attractive for industrial synthesis of linear alcohols.

MATERIALS AND METHODS
Hydroxymethylation of n-alkanes
A thick-wall Kontes flask (5 ml) was charged with cat-1a (1.0 mol %), NaOtBu (1.2 mol %), n-alkane (2.0 ml), and TBE (0.5 mmol) in an argon-filled glove box. The flask was sealed with a Teflon plug under an argon atmosphere, and the solution was stirred in a 200°C oil bath for allotted time. After that, the flask was cooled to room temperature. Another 5-ml vial with a magnetic stirring bar was charged with Rh(acac)(CO)$_2$ (0.8 mol %, 20 mM in toluene) and biphephos ligand (3.2 mol %) in the glove box. The mixture stirred at room temperature for 5 min. Then, cat-3d (1.25 mol %) and the solution derived from the AD were added to the 5-ml vial under an argon atmosphere. The vial was placed in a 50-ml autoclave, which was further purged with H$_2$, and then charged with CO (5 bar) and H$_2$ (10 bar). The autoclave was heated at 120°C for 28 hours and then cooled by an icy bath. The gases were carefully released in a well-ventilated hood. After adding mesitylene (20 µl) as an internal standard, the reaction mixture was analyzed by GC and GC–mass spectrometry. The product was isolated by flash column chromatography on silica gel using petroleum ether: ethyl acetate = 10:1 as eluent.

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/47/eabc6688/DC1

REFERENCES AND NOTES
1. J. Falbe, H. Bahrmann, W. Lipps, D. Mayer, G. D. Frey, *Alcohols, Aliphatic in Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH, 2013).
2. G. M. Torres, R. Frauenlob, R. Franke, A. Börner, Production of alcohols via hydroformylation. *Catal. Sci. Technol.* **5**, 34–54 (2015).
3. K. Takahashi, M. Yamashita, T. Ichihara, K. Nakano, K. Nozaki, High-yielding tandem hydroformylation/hydrogenation of a terminal olefin to produce a linear alcohol using a Rh/Ru dual catalyst system. *Angew. Chem. Int. Ed.* **49**, 4488–4490 (2010).
4. K. Takahashi, M. Yamashita, M. K. Nozaki, Tandem hydroformylation/hydrogenation of alkenes to normal alcohols using Rh/Ru dual catalyst or Ru single component catalyst. *J. Am. Chem. Soc.* **134**, 18746–18757 (2012).
5. M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (John Wiley & Sons Inc., ed. 6, 2007).
6. G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, Primary alcohols from terminal olefins: Formal anti-markovnikov hydration via triple relay catalysis. *Science* **333**, 1609–1612 (2011).
7. J. A. Labinger, J. E. Bercaw, Understanding and exploiting C-H bond activation. *Nature* **417**, 507–514 (2002).
8. J. F. Hartwig, M. A. Larsen, Undirected, homogeneous C–H bond functionalization: Challenges and opportunities. *ACS Cent. Sci.* **2**, 281–292 (2016).
9. W. Keim, Oligomerization of ethylene to α-olefins: Discovery and development of the shell higher olefin process (SHOP). *Angew. Chem. Int. Ed.* **52**, 12492–12496 (2013).
10. 2013 Annual Energy Outlook with projections to 2040 (U.S. Energy Information Administration), U.S. Department of Energy, April, 2013; www.eia.gov/forecasts/aeo.
11. A. Company, J. Lloret, L. Gómez, M. Costas, in *Alkane C-H Activation by Single-Site Metal Catalysis*, P. J. Pérez, Ed. (Springer,2012), pp. 143–228.
12. V. B. Romakh, B. Therrien, G. Süss-Fink, G. B. Shul'pin, Synthesis, molecular structure, and catalytic potential of the tetrairon complex [Fe$_4$(N$_3$O$_2$-L)$_4$(µ-O)$_2$]$^{4+}$ (L = 1-carboxymethyl-4,7-dimethyl-1,4,7-triazacyclononane). *Inorg. Chem.* **46**, 3166–3175 (2007).
13. B. R. Cook, T. J. Reinert, K. S. Suslick, Shape-selective alkane hydroxylation by metalloporphyrin catalysts. *J. Am. Chem. Soc.* **108**, 7281–7286 (1986).
14. C.-W. Tse, T. W.-S. Chow, Z. Guo, H. K. Lee, J.-S. Huang, C.-M. Che, Nonheme iron mediated oxidation of light alkanes with oxone: Characterization of reactive oxoiron(IV) ligand cation radical intermediates by spectroscopic studies and DFT calculations. *Angew. Chem. Int. Ed. Engl.* **53**, 798–803 (2014).
15. D. Scheps, S. Honda Malca, H. Hoffmann, B. M. Nestl, B. Hauer, Regioselective ω-hydroxylation of medium-chain n-alkanes and primary alcohols by CYP153 enzymes from *Mycobacterium marinum* and *Polaromonas* sp. strain JS666. *Org. Biomol. Chem.* **9**, 6727–6733 (2011).
16. R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, Platinum catalysts for the high-yield oxidation of methane to a methanol derivative. *Science* **280**, 560–564 (1998).
17. J. Choi, A. H. R. MacArthur, M. Brookhart, A. S. Goldman, Dehydrogenation and related reactions catalyzed by iridium pincer complexes. *Chem. Rev.* **111**, 1761–1779 (2011).
18. A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, Catalytic alkane metathesis by tandem alkane dehydrogenation-olefin metathesis. *Science* **312**, 257–261 (2006).
19. X. Jia, C. Qin, T. Friedberger, Z. Guan, Z. Huang, Efficient and selective degradation of polyethylenes into liquid fuels and waxes under mild conditions. *Sci. Adv.* **2**, e1501591 (2016).
20. A. Behr, D. Obst, C. Schulte, T. Schosser, Highly selective tandem isomerization–hydroformylation reaction of *trans*-4-octene to n-nonanal with rhodium-biphephos catalysis. *J. Mol. Cat. A: Chem.* **206**, 179–184 (2003).
21. P. A. Dub, J. C. Gordon, Metal–ligand bifunctional catalysis: The "accepted" mechanism, the issue of concertedness, and the function of the ligand in catalytic cycles involving hydrogen atoms. *ACS Catal.* **7**, 6635–6655 (2017).
22. W. Yao, Y. Zhang, X. Jia, Z. Huang, Selective catalytic transfer dehydrogenation of alkanes and heterocycles by an iridium pincer complex. *Angew. Chem. Int. Ed.* **53**, 1390–1394 (2014).
23. T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, Preferential hydrogenation of aldehydes and ketones. *J. Am. Chem. Soc.* **117**, 10417–10418 (1995).
24. T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *trans*-RuH(η^1-BH$_4$)(binap)(1,2-diamine): A catalyst for asymmetric hydrogenation of simple ketones under base-free conditions. *J. Am. Chem. Soc.* **124**, 6508–6509 (2002).
25. J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, Facile conversion of alcohols into esters and dihydrogen catalyzed by new ruthenium complexes. *J. Am. Chem. Soc.* **127**, 10840–10841 (2005).
26. C. Gunanathan, D. Milstein, Metal–ligand cooperation by aromatization–dearomatization: A new paradigm in bond activation and "Green" catalysis. *Acc. Chem. Res.* **44**, 588–602 (2011).
27. Y. Blum, D. Czarkie, Y. Rahamim, Y. Shvo, (Cyclopentadienone)ruthenium carbonyl complexes - a new class of homogeneous hydrogenation catalysts. *Organometallics* **4**, 1459–1461 (1985).
28. Y. Yuki, K. Takahashi, Y. Tanaka, K. Nozaki, Tandem isomerization/hydroformylation/hydrogenation of internal alkenes to n-alcohols using Rh/Ru dual- or ternary-catalyst systems. *J. Am. Chem. Soc.* **135**, 17393–17400 (2013).
29. F. M. S. Rodrigues, P. K. Kucmierczyk, M. Pineiro, R. Jackstell, R. Franke, M. M. Pereira, M. Beller, Dual Rh–Ru catalysts for reductive hydroformylation of olefins to alcohols. *ChemSusChem* **11**, 2310–2314 (2018).
30. Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, A new group of ruthenium complexes: Structure and catalysis. *J. Am. Chem. Soc.* **108**, 7400–7402 (1986).
31. A. Kumar, T. Zhou, T. J. Emge, O. Mironov, R. J. Saxton, K. Krogh-Jespersen, A. S. Goldman, Dehydrogenation of n-alkanes by solid-phase molecular pincer-iridium catalysts. High yields of α-olefin product. *J. Am. Chem. Soc.* **137**, 9894–9911 (2015).
32. X. Tang, X. Jia, Z. Huang, Thermal, catalytic conversion of alkanes to linear aldehydes and linear amines. *J. Am. Chem. Soc.* **140**, 4157–4163 (2018).
33. G. E. Dobereiner, J. Yuan, R. R. Schrock, A. S. Goldman, J. D. Hackenberg, Catalytic synthesis of n-alkyl arenes through alkyl group cross-metathesis. *J. Am. Chem. Soc.* **135**, 12572–12575 (2013).
34. X. Jia, Z. Huang, Conversion of alkanes to linear alkylsilanes using an iridium–iron-catalysed tandem dehydrogenation–isomerization–hydrosilylation. *Nat. Chem.* **8**, 157–161 (2016).
35. H. Gräfje, W. Körnig, H.-M. Weitz, W. Reiß, G. Steffan, H. Diehl, H. Bosche, K. Schneider, H. Kieczka, R. Pinkos, *Butanediols, Butenediol, and Butynediol in Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH, 2020).
36. J. Yang, J. Liu, H. Neumann, R. Franke, R. Jackstell, M. Beller, Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes. *Science* **366**, 1514–1517 (2019).
37. K. Tamao, N. Ishida, Silafunctional compounds in organic synthesis: XXVI. Silyl groups synthetically equivalent to the hydroxy group. *J. Organomet. Chem.* **269**, c37–c39 (1984).
38. S. Biswas, Z. Huang, Y. Choliy, D. Y. Wang, M. Brookhart, K. Krogh-Jespersen, A. S. Goldman, Olefin isomerization by iridium pincer catalysts. Experimental evidence for an η^3-allyl pathway and an unconventional mechanism predicted by DFT calculations. *J. Am. Chem. Soc.* **134**, 13276–13295 (2012).

39. I. Göttker-Schnetmann, M. Brookhart, Mechanistic studies of the transfer dehydrogenation of cyclooctane catalyzed by iridium bis(phosphinite) *p*-XPCP pincer complexes. *J. Am. Chem. Soc.* **126**, 9330–9338 (2004).

40. X. Zhang, S.-B. Wu, X. Leng, L. W. Chung, G. Liu, Z. Huang, *N*-Bridged pincer iridium complexes for highly efficient alkane dehydrogenation and the relevant linker effects. *ACS Catal.* **10**, 6475–6487 (2020).

41. Y. Wang, Z. Huang, X. Leng, H. Zhu, G. Liu, Z. Huang, Transfer hydrogenation of alkenes using ethanol catalyzed by a NCP pincer iridium complex: Scope and mechanism. *J. Am. Chem. Soc.* **140**, 4417–4429 (2018).

42. C. P. Prasanth, E. Joseph, A. Abhijith, D. S. Nair, I. Ibnusaud, J. Raskatov, B. Singaram, Stabilization of NaBH$_4$ in methanol using a catalytic amount of NaOMe. Reduction of esters and lactones at room temperature without solvent-induced loss of hydride. *J. Org. Chem.* **83**, 1431–1440 (2018).

43. M. Szostak, M. Spain, D. J. Procter, Electron transfer reduction of unactivated esters using SmI$_2$–H$_2$O. *Chem. Commun.* **47**, 10254–10256 (2011).

44. I. Fleischer, K. M. Dyballa, R. Jennerjahn, R. Jackstell, R. Franke, A. Spannenberg, M. Beller, From olefins to alcohols: Efficient and regioselective ruthenium-catalyzed domino hydroformylation/reduction sequence. *Angew. Chem. Int. Ed.* **52**, 2949–2953 (2013).

45. T. Pei, R. A. Widenhoefer, Use of pentamethyldisiloxane in the palladium-catalyzed cyclization/hydrosilylation of functionalized dienes. *Org. Lett.* **2**, 1469–1471 (2000).

46. D. Fuchs, G. Rousseau, L. Diab, U. Gellrich, B. Breit, Tandem rhodium-catalyzed hydroformylation-hydrogenation of alkenes by employing a cooperative ligand system. *Angew. Chem. Int. Ed.* **51**, 2178–2182 (2012).

47. M. Zeng, L. Li, S. B. Herzon, A highly active and air-stable ruthenium complex for the ambient temperature anti-Markovnikov reductive hydration of terminal alkynes. *J. Am. Chem. Soc.* **136**, 7058–7067 (2014).

48. Y. Shi, P. C. J. Kamer, D. J. Cole-Hamilton, A new route to α,ω-diamines from hydrogenation of dicarboxylic acids and their derivatives in the presence of amines. *Green Chem.* **19**, 5460–5466 (2017).

49. A. Kistenmacher, M. Baumgarten, V. Enkelmann, J. Pawlik, K. Muellen, Novel donor 1,4-Benzothiazino[2,3-b]phenothiazine. *J. Org. Chem.* **59**, 2743–2747 (1994).

50. C. Eaborn, K. L. Jones, P. D. Lickiss, Preparation of the iodides (Me$_3$Si)$_2$C(SiMe$_2$C$_6$H$_4$Y)(SiMe$_2$I) and some related compounds. *J. Organomet. Chem.* **466**, 35–42 (1994).

51. J. W. Wilt, W. K. Chwang, C. F. Dockus, N. M. Tomiuk, Aryl shifts from silicon to carbon via .gamma.- and .delta.-silyl radicals. *J. Am. Chem. Soc.* **100**, 5534–5540 (1978).

52. K. Murakami, K. Hirano, H. Yorimitsu, K. Oshima, Silver-catalyzed transmetalation between chlorosilanes and aryl and alkenyl Grignard reagents for the synthesis of tetraorganosilanes. *Angew. Chem. Int. Ed.* **47**, 5833–5835 (2008).

53. B. Marciniec, H. Maciejewski, K. Szubert, M. Kurdykowska, Modification of (poly)siloxanes via hydrosilylation catalyzed by rhodium complex in ionic liquids. *Monatsh. Chem.* **137**, 605–611 (2006).

54. D. Noda, A. Tahara, Y. Sunada, H. Nagashima, Non-precious-metal catalytic systems involving iron or cobalt carboxylates and alkyl isocyanides for hydrosilylation of alkenes with hydrosiloxanes. *J. Am. Chem. Soc.* **138**, 2480–2483 (2016).

Citation: X. Tang, L. Gan, X. Zhang, Z. Huang, *n*-Alkanes to *n*-alcohols: Formal primary C—H bond hydroxymethylation via quadruple relay catalysis. *Sci. Adv.* **6**, eabc6688 (2020).

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