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Temporal separation of catalytic activities allows anti-Markovnikov reductive functionalization of terminal alkynes

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There is currently great interest in the development of multistep catalytic processes in which one or several catalysts act sequentially to rapidly build complex molecular structures. Many enzymes—often the inspiration for new synthetic transformations—are capable of processing a single substrate through a chain of discrete, mechanistically distinct catalytic steps. Here, we describe an approach to emulate the efficiency of these natural reaction cascades within a synthetic catalyst by the temporal separation of catalytic activities. In this approach, a single catalyst exhibits multiple catalytic activities sequentially, allowing for the efficient processing of a substrate through a cascade pathway. Application of this design strategy has led to the development of a method to effect the anti-Markovnikov (linear-selective) reductive functionalization of terminal alkynes. The strategy of temporal separation may facilitate the development of other efficient synthetic reaction cascades.

Many natural enzymes are capable of processing a substrate through two or more sequential reactions[1]. Chemists have attempted to emulate the power of these natural reaction cascades by developing auto-tandem catalytic reactions[2], wherein a synthetic catalyst transforms a substrate through two or more mechanistically distinct reactions, without the intervening addition of reagents or catalysts, or alteration of the reaction conditions (for selected examples see refs 3–13). However, the development of auto-tandem catalytic processes is challenging. The manifestation of multiple activities concurrently[2] complicates analysis and development, because the rates of each step are interrelated, and the starting material and intermediates need to be selected for a particular activity in the presence of others (Fig. 1a). To address this, one could optimize each step separately, but the observed activities may not accurately reflect the behaviour of the catalyst in the presence of all the reagents. Moreover, the presence of multiple orthogonal activities in a single catalyst structure is not assured.

We envisioned an alternative strategy wherein the activities of the catalyst are separated in the time domain (Fig. 1b). Under these conditions, each intermediate encounters one catalytic activity, thereby diminishing the potential for off-pathway reactions. This approach also decouples the reactions, which facilitates analysis and the optimization of each step. To achieve temporal separation of catalytic activities, we sought to devise a catalyst such that the resting states within each cycle constitute metal–substrate complexes that increase in energy. In this way, the catalyst will be constrained within one cycle until the corresponding substrate is consumed. In addition, because the intermediates accumulate, they may be functionalized by stoichiometric reagents, thereby diverting the pathway in a distinct direction and increasing the scope of products accessible from a single catalyst.

Results

To evaluate the feasibility of this strategy, we investigated the anti-Markovnikov reductive functionalization of terminal alkynes (Fig. 1c). We were motivated by our discovery that two monofunctional ruthenium-based complexes could be used in tandem to effect the reductive hydration (addition of water and dihydrogen) of alkynes to form linear alcohols[14]. This suggested it might be possible to identify a single multifunctional catalyst possessing hydration and hydrogenation activities. We envisioned that the stable (often isolable) metal vinylidene and/or metal–alkyne intermediates[15] involved in the metal-catalysed anti-Markovnikov hydration of alkynes might present a lowest-energy resting state for the catalyst. This would engender temporal separation of the activities, facilitating reaction optimization and allowing for functionalization of the aldehyde intermediate. The realization of catalytic processes for the conversion of unsaturated hydrocarbon feedstocks to functionalized building blocks are longstanding goals in synthetic chemistry[16–23], and the reductive functionalization of alkynes remains underdeveloped.

Catalyst design and development. Our initial studies focused on developing an anti-Markovnikov reductive hydration reaction using a single multifunctional catalyst. Owing to the unrivaled efficiencies of piano-stool ruthenium complexes as catalysts for alkyne hydration[24–28], we began with precursors incorporating this metal–ligand framework. After an extensive evaluation of metal–ligand complexes, solvents and reducing agents, we identified tris(acetonitrile) (η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**2**) in combination with various nitrogen-based ligands, water and formic acid (as reductant) as effective for the reductive hydration of (2-fluorophenyl)acetylene (**1a**). Selected ligands we evaluated are shown in Fig. 2a. To find the optimal balance in activity for both steps simultaneously, we collected two data points for each ligand evaluation: hydration activity (left-hand *y*-axis, blue bars, Fig. 2a) was measured as the time required to achieve >95% of **1a**; hydrogenation activity (right-hand *y*-axis, purple bars, Fig. 2a) was assessed as the yield of 2-(2-fluorophenyl)ethanol (**5a**) after 24 h by catalysts possessing hydration activity. When viewed in this way, the optimum catalysts have the smallest value along the time axis and the highest value along the yield axis. These studies demonstrated that transfer hydrogenation

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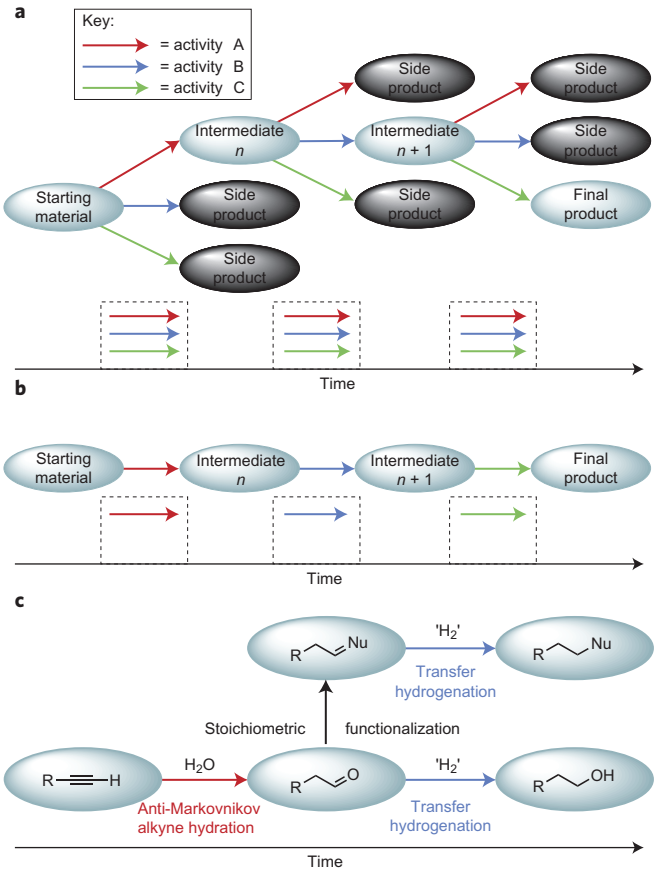


Figure 1 | Comparison of previous auto-tandem catalytic reactions and tandem reactions exhibiting temporal separation of catalytic activities. **a**, Previous auto-tandem catalysts display two or more activities simultaneously. This complicates reaction optimization because the rates of product formation for each step are co-dependent, and can lead to undesired side reactions, decreasing efficiency. Coloured arrows represent discrete catalytic activities (A, B and C). **b**, Temporal separation of these activities reduces the number of pathways presented to each intermediate, facilitating reaction optimization and creating higher overall efficiency by minimizing the production of side products. **c**, Anti-Markovnikov reductive functionalization of terminal alkynes by a catalyst exhibiting temporal separation of activities.

activity is sensitive to the electron density of the ligand, while responses in the hydration domain were less pronounced. For example, complexes derived from the electron-rich ligand 4,4′-dimethoxy-2,2′-bipyridine (**3a**) displayed reasonable hydration activity (5.5 h for full conversion of **1a**) but low hydrogenation activity (34% yield of **5a** after 24 h). Conversely, complexes derived from the electron-deficient ligands 4,4′-dicarbomethoxy-2,2′-bipyridine (**3c**) and 6-bromo-2,2′-bipyridine (**3f**) displayed high hydration activity (complete hydration within 4 h), but were ineffective promoters of the reduction step (34% and 18% yield of **5a** after 24 h for **3c** and **3f**, respectively). Ultimately, the inexpensive, air-stable ligand 2,2′-bipyridine (**3b**) emerged as optimal. Using this ligand, the hydration was complete within 2.5 h, and a 92% yield of 2-(2-fluorophenyl)ethanol (**5a**) was obtained after only 17 h. The commercially available, air- and moisture-stable precursor (η^5-cyclopentadienyl)(η^6-naphthalene)ruthenium hexafluorophosphate (**6**)[29] could be used in place of the air-sensitive complex **2**. In this case, 2 equiv. of 2,2′-bipyridine (**3b**, with respect to ruthenium) led to improved yields, presumably because displacement of the η^6-naphthalene ligand from **6** is slow. This precursor was employed in subsequent studies.

Spectroscopic studies establish temporal separation. In our optimization experiments, we did not observe production of **5a** until **1a** was almost consumed, suggesting temporal separation of the steps. To probe this, the reductive hydration of **1a** was monitored continuously by ^{19}F NMR spectroscopy (Fig. 2b). Complete conversion of **1a** occurred within 16 h, and the reduction product **5a** did not form until nearly all **1a** was consumed, which is consistent with stepwise catalytic processing. In a separate experiment, the reductive hydration of **1a** was allowed to proceed until the mixture consisted of (2-fluorophenyl)acetaldehyde (**4a**, 44%) and **5a** (53%, Fig. 2c). An equimolar amount of 3-fluorophenylacetylene (**1b**, based on **1a**) was added. The second alkyne substrate **1b** arrested the hydrogenation activity, and reduction of **4a** did not resume until all of **1b** had been converted to (3-fluorophenyl)acetaldehyde (**4b**). Additionally, an ion corresponding to an (η^5-cyclopentadienyl) ruthenium cation coordinated to the ligand **3b** and the substrate (presumably, a metal alkyne or vinylidene complex) was observed by high-resolution electrospray mass spectrometry immediately after mixing, suggesting the resting state of the catalyst consists of an intermediate in the hydration cycle. These experiments demonstrate that the catalyst is sequestered within the hydration cycle and that hydrogenation activity does not manifest until the alkyne is almost consumed. The experiment in Fig. 2c also establishes that the oscillation between catalytic activities is reversible.

Influence of reaction parameters and substrate scope (reductive hydration). The experiments shown in Table 1 were conducted to interrogate the influence of catalyst loading, temperature and scale. Decreasing the catalyst loading to as little as 1 mol% **6** resulted in only a small diminution in yield (entries 1–3). On increasing the reaction temperature to 80 °C, the reductive hydration was complete within 2 h using 4.5 mol% of **6** (entry 4). Finally, the reaction was readily-scaled; using the conditions of entry 1, the reductive hydration proceeded in 90% yield on a 10 mmol scale (entry 5).

The scopes of alkynes that undergo reductive hydration are shown in Table 2. Electron-neutral, electron-deficient, and electron-rich aryl acetylenes (**1a–1j**) and the hindered substrates (2-methylphenyl)acetylene (**1c**) and (2,4,6-trimethylphenyl)acetyl ene (**1j**) undergo efficient reductive hydration (81–97%). Silyl (**1k**, 95%) and aliphatic alkynes (**1l–1u**) were also competent substrates. Alkyl chlorides, phthalimides, alcohols, carboxylic acids, secondary amides and amines are accommodated by this system (80–90%). Several other substrates that are not compatible with the dual catalytic approach we reported[14] were suitable with this single catalyst. For example, the ynone **1q** is efficiently converted to the hydroxyketone **5q** (87%), without detectable ketone reduction. Alkyl esters such as **1s**, which underwent transesterification using our dual catalytic system[14], are viable substrates (90%). The enyne **1x**, which bears a terminal alkene, underwent extensive isomerization during the reductive hydration using our dual catalyst system[14]. Using this single catalyst, no alkene isomerization was detectable (by proton NMR analysis), and the substrate was efficiently converted to product **5x** (90%). Finally, the propargylic sulfonamide **1y** and alcohol **1z** underwent high-yielding reductive hydration (83 and 72%, respectively).

Reductive alkylation: development and scope. As outlined, the temporal separation of catalytic activities provides the opportunity to divert the reaction cascade by stoichiometric functionalization of the intermediates, thereby increasing the diversity of products produced from a single substrate and catalyst. In the present study,

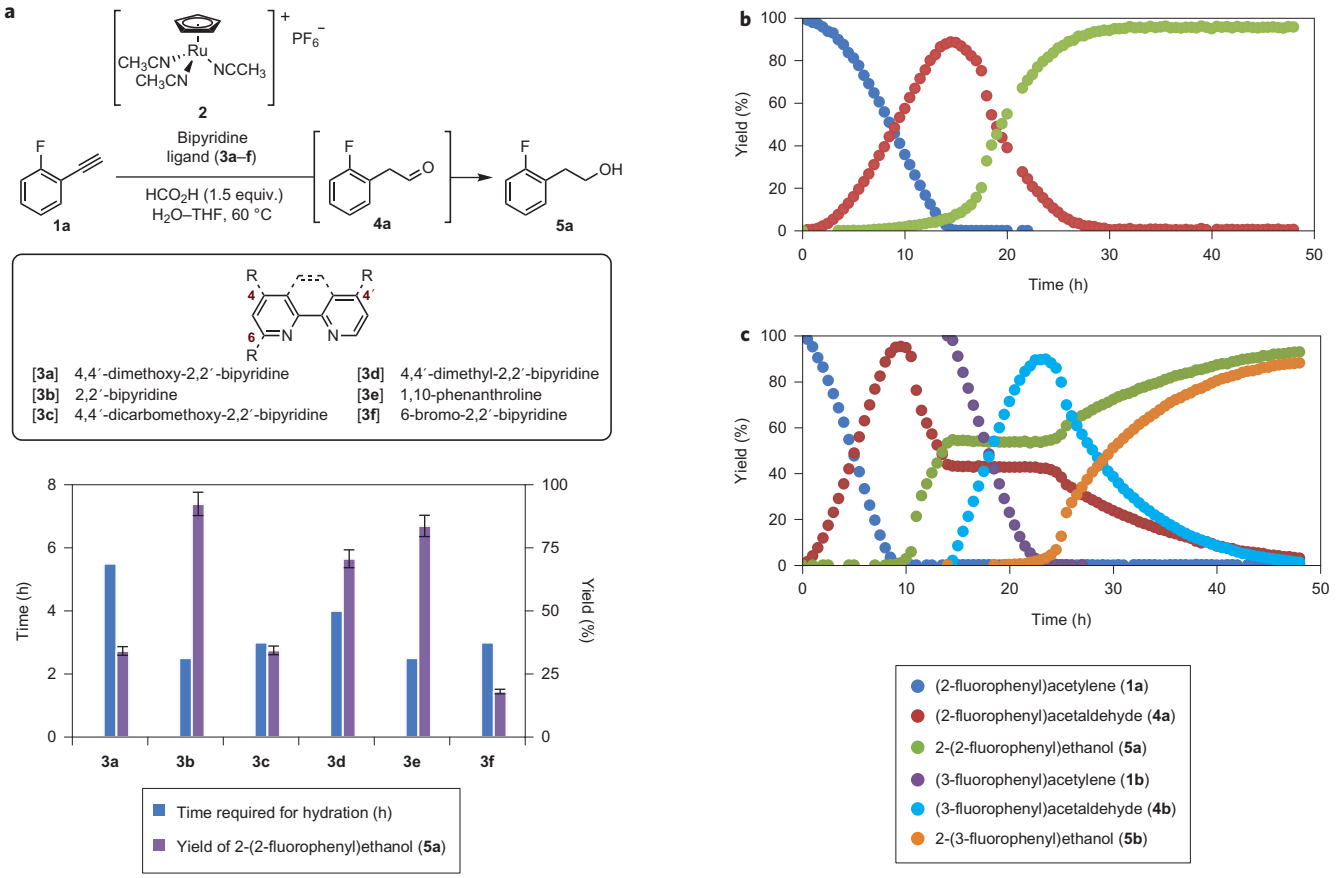
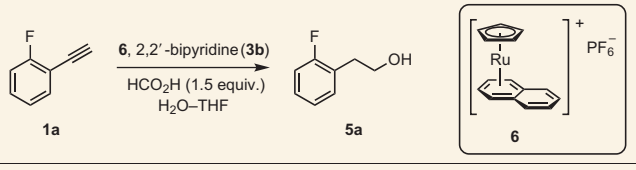


Figure 2 | Optimization and spectroscopic studies of the reductive hydration reaction. a, Bipyridine ligands **3a–f** were evaluated for their ability to promote the reductive hydration of (2-fluorophenyl)acetylene (**1a**) using catalyst precursor **2**. Two data points are reported for each experiment: blue bars denote the time required to achieve >95% conversion of **1a** to (2-fluorophenyl)acetaldehyde (**4a**), and purple bars denote the yield of 2-(2-fluorophenyl)ethanol (**5a**) after 24 h (except for ligand **3b**, yield after 17 h). General conditions: **1a** (250 μmol), **2** (4.5 mol%), **3a–f** (4.5 mol%), HCO_2H (2.50 equiv.), THF–H_2O (4:1 vol/vol; [**1a**] = 0.4 M), 60 °C. Error bars represent 5% uncertainty in NMR integration. **b**, Reductive hydration of **1a**, monitored every 30 min by ^{19}F NMR spectroscopy. Conditions: **1a** (250 μmol), **6** (4.5 mol %), **3b** (9.0 mol%), HCO_2H (1.50 equiv.), THF–H_2O (4:1 vol/vol; [**1a**] = 0.2 M), 60 °C, 47.5 h. **c**, Partial reductive hydration of **1a**, followed by addition of (3-fluorophenyl)acetylene (**1b**), monitored every 30 min by ^{19}F NMR spectroscopy. Conditions: **1a** (125 μmol), **6** (9.0 mol%), **3b** (18 mol%), HCO_2H (1.50 equiv.), THF–H_2O (4:1 vol/vol; [**1a**] = 0.1 M), 60 °C, 14 h, then add **1b** (125 μmol), HCO_2H (1.50 equiv., 188 μmol), 60 °C, 47.5 h total reaction time. Yields were determined using (trifluoromethyl)benzene as an internal standard.

Table 1 | Influence of reaction parameters on the reductive hydration of (2-fluorophenyl)acetylene.



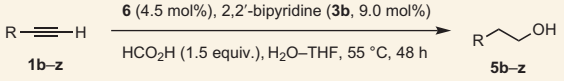
Entry	Scale (mmol)	6 (mol%)	3b (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	0.250	4.5	9.0	55	48	97
2	0.500	**2.0**	**4.0**	70	72	88
3	0.500	**1.0**	**2.0**	70	96	80
4	0.250	4.5	9.0	**80**	**2**	85
5*	**10**	4.5	9.0	55	48	90

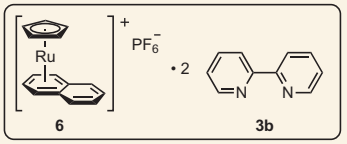
Conditions: alkyne, **6**, **3b**, HCO_2H (1.50–2.50 equiv.), THF–H_2O (4:1 vol/vol; [alkyne] = 0.2–0.4 M). All yields are of spectroscopically homogeneous material, after purification by flash-column chromatography. *Using phenylacetylene (**1f**) as substrate.

we envisioned that the reactive aldehyde intermediate could serve as a precursor to a wide array of products by 1,2-nucleophilic addition, followed by reduction. To illustrate this, we developed a triple-cascade reductive alkylation reaction comprising anti-Markovnikov hydration, olefination of the intermediate aldehyde[4] and 1,4-reduction of the resulting α,β-unsaturated ketone (Fig. 3).

We investigated the reductive alkylation of octylacetylene (**1l**) and decanal (**4l**) under the conditions of the reductive hydration (Fig. 3b). Reductive alkylation of octylacetylene (**1l**) provided a 7:1 ratio of the triple-cascade product **7a** and the primary alcohol **5l**. Under identical conditions but starting from decanal (**4l**), the reaction proceeded with lower selectivity (**7a**:**5l** = 2:1). These

Table 2 | Scope of the single catalyst reductive hydration.





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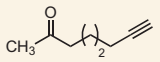
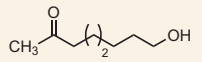
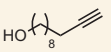
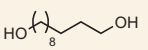
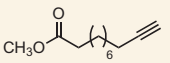
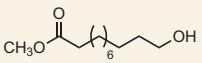
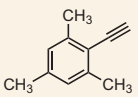
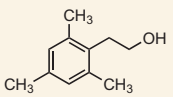
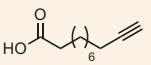
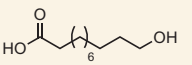
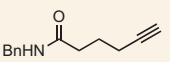
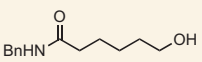
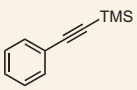
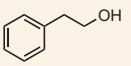
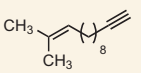
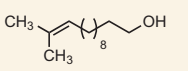
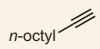
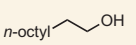
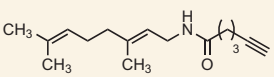
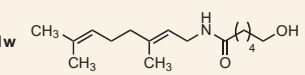
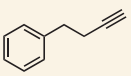
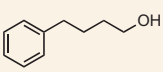
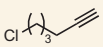
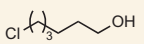
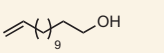
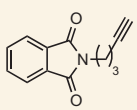
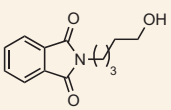
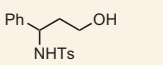
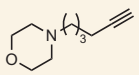
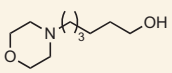
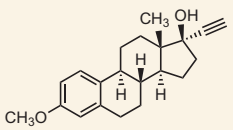
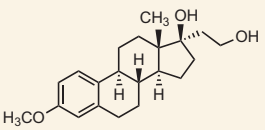
Catalog # L511692

Entry	Substrate	Product, yield	Entry	Substrate	Product, yield
1	**1b** R′ = *m*-F	**5b**, 96%	16		**1q**  **5q**, 87%
2	**1c** R′ = *o*-CH_3	**5c**, 86%			
3	**1d** R′ = *m*-CH_3	**5d**, 95%			
4	**1e** R′ = *m*-Cl	**5e**, 95%	17		**1r**  **5r**, 80%
5	**1f** R′ = H	**5f**, 97%			
6	**1g** R′ = *p*-OCH_3	**5g**, 91%	18**		**1s**  **5s**, 90%
7	**1h** R′ = *p*-F	**5h**, 93%			
8	**1i** R′ = *p*-CH_3	**5i**, 85%			
9*	 **1j**	 **5j**, 81%	19‡		**1t**  **5t**, 80%
			20**		**1u**  **5u**, 90%
10	 **1k**	 **5k**, 95%	21**		**1v**  **5v**, 84%
11**	 **1l**	 **5l**, 85%	22‡		**1w**  **5w**, 89%
12	 **1m**	 **5m**, 88%			
13	 **1n**	 **5n**, 80%	23§		**1x**  **5x**, 90%
14	 **1o**	 **5o**, 93%	24¶		**1y**  **5y**, 83%
15†	 **1p**	 **5p**, 81%	25¶		**1z**  **5z**, 72%

Conditions: alkyne (250 μmol), **6** (4.5 mol%), **3b** (9.0 mol%), HCO_2H (1.50 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.2 M), 55 °C, 48 h. All yields are of spectroscopically homogeneous material, after purification by flash-column chromatography. *Conditions: alkyne (250 μmol), **2** (4.5 mol%), **3b** (9.0 mol%), HCO_2H (2.50 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.2 M), 80 °C, 48 h. **Conditions: alkyne (250 μmol), **2** (4.5 mol%), **3b** (9.0 mol%), HCO_2H (2.50 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 70 °C, 48 h. ‡Conditions: alkyne (250 μmol), **6** (4.5 mol%), **3b** (9.0 mol%), HCO_2H (2.50 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.2 M), 55 °C, 48 h. ‡Conditions: alkyne (250 μmol), **2** (4.5 mol%), **3b** (9.0 mol%), HCO_2H (2.50 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 80 °C, 48 h. §Conditions: alkyne (250 μmol), **2** (9.0 mol%), **3b** (18.0 mol%), HCO_2H (5.00 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 80 °C, 48 h. ¶Conditions: alkyne (250 μmol), **2** (9.0 mol%), **3b** (18.0 mol%), HCO_2H (5.00 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.2 M), 80 °C, 48 h.

experiments demonstrate an enhancement in selectivity starting from the alkyne, which we attribute to the delayed onset of hydrogenation activity by the catalyst. By decreasing the reaction temperature to 55 °C, a higher selectivity for the homologation product **7a** was obtained (75% isolated yield of **7a**, **7a**:**5l** = 11:1, Table 3, entry 1). Under these conditions, both aromatic (entry 1) and aliphatic (entries 2–5) alkynes undergo efficient reductive homologation (70–76%). Although the substrate scope was not intensively investigated, phthalimide (entry 4) and ester (entry 5) substituents were shown to be compatible. Importantly, hydrogenation of the ketone functional group was not observed in any of the products.

Discussion

The cyclopentadienylruthenium–bipyridine system we have developed constitutes a useful catalyst for the reductive functionalization of terminal alkynes. Both the ligand and metal precursor are air-stable, and a mixture of **6** and **3b** is now commercially available (Aldrich, catalog # L511692). The catalytic transformation proceeds at convenient concentrations (0.2–0.4 M), and the system displays broad substrate scope. Longer reaction times were used to ensure full conversion of all substrates, but the data in Table 1 reveal that the reductive hydration of **1a** is complete within 2 h at 80 °C. Additionally, the reaction proceeds with as little as 1 mol% of the ruthenium precursor (Table 1, entry 3), and comparable yields are obtained on a 10 mmol scale (Table 1, entry 5).

More broadly, the temporal separation of catalytic activities provides a strategy to identify the optimum catalyst structure, increase the overall efficiency, and modulate the pathways of multistep sequences mediated by a single catalyst. In the current system, we hypothesize that the formation of a stable ruthenium–alkyne or ruthenium–vinylidene complex impedes reduction of the intermediate aldehyde, thereby blocking the hydrogenation activity of the catalyst. The generality of this concept remains to be defined, but as noted by Fogg, auto-tandem catalytic processes are 'normally

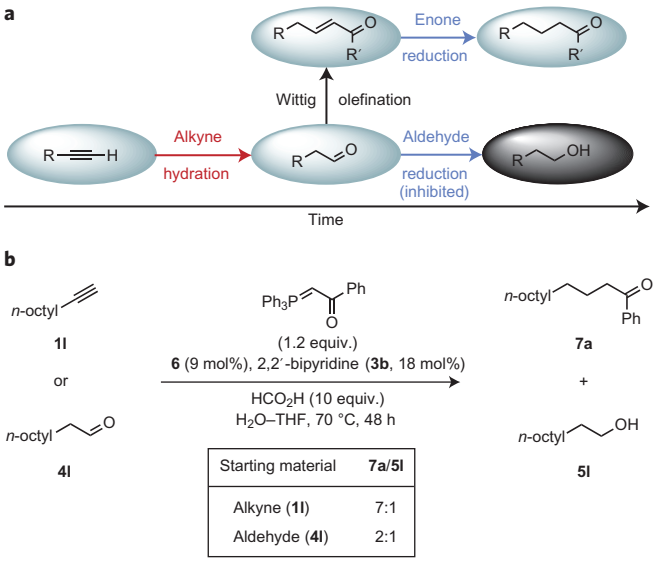
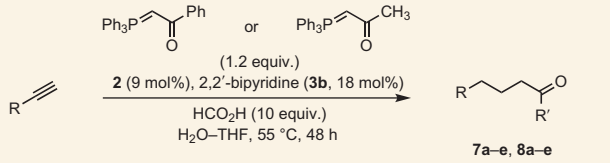
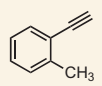
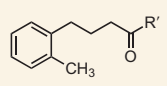
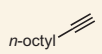
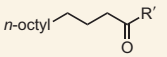
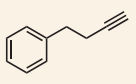
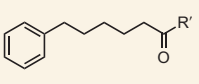
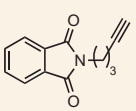
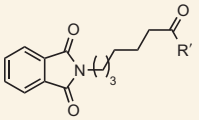
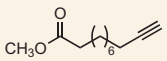
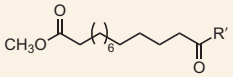


Figure 3 | Triple-cascade anti-Markovnikov hydration, olefination and enone reduction. a, Temporal separation of the hydration and hydrogenation activities was anticipated to allow for stoichiometric functionalization of the aldehyde intermediate *in situ*. In this instance, we investigated *in situ* Wittig olefination of the aldehyde. 1,4-Hydrogenation of the resulting enone would provide the reductive alkylation product. **b**, Control experiments to probe for an enhancement in selectivity starting from an alkyne. Reductive alkylation of the alkyne **1l** provided higher selectivity for the ketone **7a** than that beginning with aldehyde **4l**. We attribute this increase in selectivity to the delayed onset of hydrogenation activity by the catalyst, which allows for progression of the Witting olefination.

Table 3 | Hydration-olefination-1,4-reduction triple cascade.



Entry	Substrate		Product	Yield R′ = Ph	Yield R′ = CH_3
1		**1c**		**7a**, 75%	**8a****, 71%
2		**1l**		**7b***, 72%	**8b**, 70%
3		**1m**		**7c**†, 75%	**8c**, 70%
4		**1o**		**7d**†, 81%	**8d****, 76%
5		**1s**		**7e**, 72%	**8e**, 76%

Conditions: alkyne (250 μmol), **2** (9.0 mol%), **3b** (18 mol%), HCO_2H (10.0 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 55 °C, 48 h. All yields are of spectroscopically homogeneous material, after purification by flash-column chromatography. *Conditions: alkyne (250 μmol), **2** (9.0 mol%), **3b** (18 mol%), HCO_2H (10.0 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 55 °C, 72 h. **Conditions: alkyne (125 μmol), **2** (9.0 mol%), **3b** (18 mol%), HCO_2H (15.0 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 55 °C, 72 h. †Conditions: alkyne (250 μmol), **2** (9.0 mol%), **3b** (18 mol%), HCO_2H (5.0 equiv.), THF-H_2O (4:1 vol/vol; [alkyne] = 0.4 M), 55 °C, 48 h.

concurrent in the *macroscopic* sense'[2]. A survey of the literature would seem to support this, as in instances where the reaction composition is monitored as a function of time, simultaneous processing of the substrate and intermediates is reported (for examples see refs 3, 8, 9, 12 and 13). Conceptually, approaches to metal-catalysed, temporally separated systems might begin by identifying pairs of reactions that are conducted by transition-metal complexes with similar coordination environments. These initial candidates could be further prioritized by the presence or absence of isolable (stable) substrate–catalyst intermediates in the first catalytic cycle. Monitoring the composition of multistep reactions as a function of time can provide evidence for temporal separation. This was demonstrated herein using NMR spectroscopy, although other common analytical methods (infrared and ultraviolet/visible spectroscopy, and tandem liquid chromatography–mass spectrometry) are likely to be suitable. The experiment outlined in Fig. 2c provides an unequivocal test for temporal separation. By adding a second substrate to the reaction mixture after processing of the first substrate is under way, one can determine if the activity of the subsequent step is arrested. In this work we have used this design strategy to develop a useful catalyst for the anti-Markovnikov reductive functionalization of alkynes. The discovery that catalyst activity can be modulated as a function of time may create new opportunities for the development of tandem reaction processes.

Methods

Full experimental details and characterization data for all new compounds are provided in the Supplementary Information.

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Author contributions

L.L. and S.B.H. designed the research, analysed the data and wrote the manuscript. L.L. performed the experiments.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to S.B.H.

Competing financial interests

The authors declare no competing financial interests.