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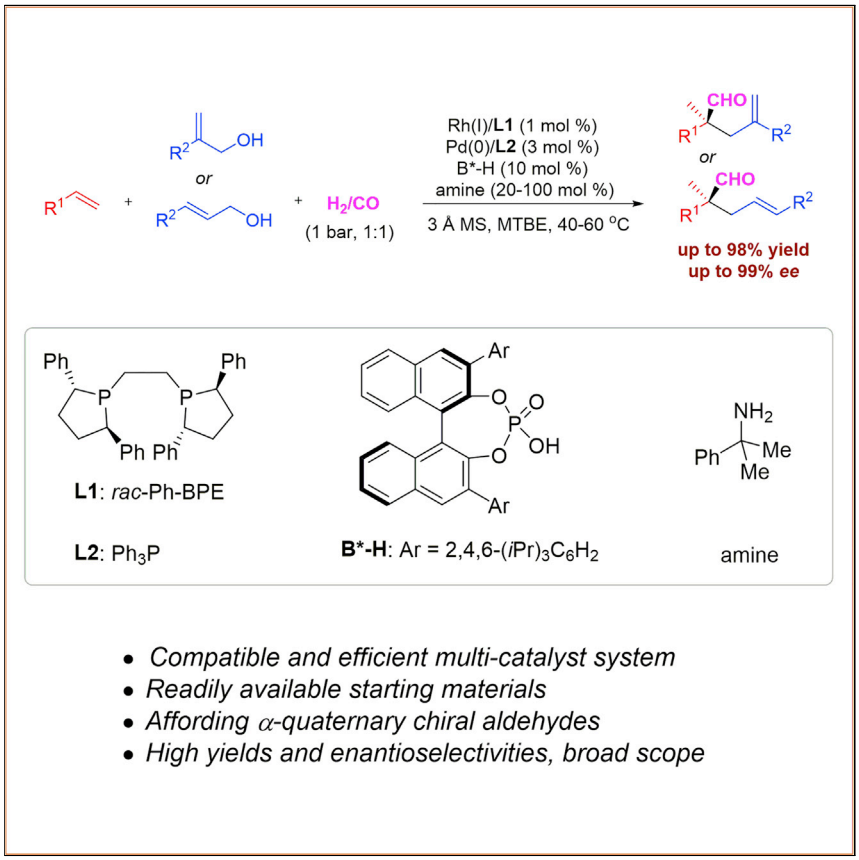
α-Quaternary Chiral Aldehydes from Styrenes, Allylic Alcohols, and Syngas via Multi-catalyst Relay Catalysis



Multi-catalyst relay catalysis (MCRC) has emerged as a promising strategy for achieving ideal synthesis. Here, we show that a multi-catalyst system consisting of a rhodium(I) complex, a palladium(0) complex, a chiral Brønsted acid catalyst, and an achiral amine (20–100 mol %) works ideally to promote a cascade hydroformylation and asymmetric allylation reaction. This method enables the transformation of readily available styrenes, allylic alcohols, and syngas to α-quaternary chiral aldehydes with high yields and enantioselectivities under mild conditions.

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HIGHLIGHTS

α-Quaternary chiral aldehydes synthesized from styrenes, allylic alcohols, and syngas

Highly compatible and efficient multi-catalyst system

High yields and enantioselectivities, mild conditions, and broad scope

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α-Quaternary Chiral Aldehydes from Styrenes, Allylic Alcohols, and Syngas via Multi-catalyst Relay Catalysis

Jing Meng,[1] Lian-Feng Fan,[1] Zhi-Yong Han,[1,3,*] and Liu-Zhu Gong[1,2,*]

SUMMARY

Mimicking the way nature synthesizes organic molecules, multi-catalyst relay catalysis (MCRC), based on the seamless combination of a series of catalytic reactions, has emerged as a promising strategy for achieving ideal synthesis. In such systems, each step takes place orderly and sequentially. Taken as a whole, the entire process appears indistinguishable from a common one-step reaction but provides a means for extraordinary transformations. Here, we report a one-step transformation of styrenes, allylic alcohols, and syngas to α-quaternary chiral aldehydes in a multi-catalyst system consisting of a rhodium(I) complex, a palladium(0) complex, a chiral Brønsted acid catalyst, and an achiral amine (20–100 mol %). The cascade hydroformylation and asymmetric allylation reaction was realized with high yields (up to 98%) and high enantioselectivities (up to 99% ee) under mild conditions (1 bar of syngas).

INTRODUCTION

One extraordinary feature of living organisms is their efficient synthesis of numerous complicated metabolites via a series of enzyme-catalyzed transformations taking place simultaneously and disciplinarily in one reactor (cell).[1] In contrast, multi-step syntheses in the laboratory and the factory generally require each step to be performed separately, both in time and space, and usually with the intermediate products isolated before the next step. In recent years, by mimicking the feature of biosystems, multi-catalyst relay catalysis (MCRC), on the basis of the combined use of two or more distinct catalysts, has emerged as a promising strategy for achieving ideal organic synthesis (Figure 1).[2–7] In such systems, different types of catalysts (i.e., metal catalysts, organocatalysts, or enzyme catalysts) work either cooperatively or independently to fulfill traditional multi-step synthesis in one operation, dramatically reducing waste, solvents, time, labor, etc.

MCRC has achieved successes in important transformations in recent years. For example, combining olefin hydrogenation and dehydrogenation with olefin metathesis has led to successful hydrocarbon upgrading reactions, including an alkane metathesis process.[8,9] Huff and Sanford[10] reported the reduction of CO_2 to methanol by combining three different metal-catalyzed processes. The Marks group achieved etheric C–O hydrogenolysis using coupled tandem catalytic cycles.[11] Using the Rh/Ru dual catalyst system, Nozaki and co-workers realized an efficient transformation from alkenes to linear alcohols,[12] and the Shell hydroformylation process has used cobalt or phosphine catalyst to convert higher olefins to linear alcohols for years. The Lautens group combined a Rh-catalyzed alkyne arylation process and palladium (Pd)-catalyzed C–X (X = O, N) bond coupling process to obtain

The Bigger Picture

The contradiction between the growing demands for chemicals and decreasing fossil resources has prompted chemists to search for ideal synthetic strategies. Living cells produce complicated molecules with an extreme efficiency that organic chemists have long tried to imitate. In recent years, mimicking the way that nature synthesizes organic molecules has emerged as a promising strategy for achieving ideal synthesis. A prominent example of such an approach is multi-catalyst relay catalysis (MCRC), which requires the seamless combination of a series of catalytic reactions. In this paper, using a highly compatible and efficient multi-catalyst system, we have developed a cascade hydroformylation and asymmetric allylation reaction that transforms styrenes, allylic alcohols, and syngas to α-quaternary chiral aldehydes in one step. The current work offers the potential for multi-catalytic approaches and new types of relay processes.

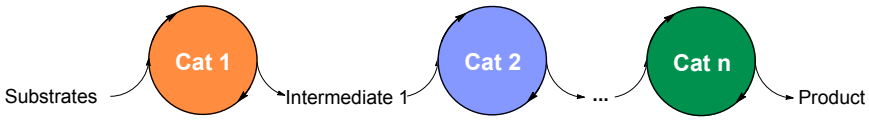

Figure 1. The Concept of Multi-catalyst Relay Catalysis (MCRC)

pharmacologically relevant heterocycles.[13] Catalytic asymmetric reactions have also been coupled with other catalytic processes. Within this subfield, the combination of a metal catalyst (either chiral or achiral) and a chiral organocatalyst has led to a large number of successful cascade reactions.[14–18] As examples, Eilbracht[19] and Breit[20] and co-workers independently reported Rh/chiral-amine-catalyzed hydroformylation and asymmetric aldol reactions. Che and co-workers[21] and our group[22] independently developed the Au/chiral-Brønsted-acid-catalyzed hydroamination and asymmetric reduction process. Through the combination of Rh/chiral Brønsted acid, the asymmetric hydroaminomethylation of alkenes was reported by Xiao and coworkers[23] and our group.[24]

Although this area has witnessed continuous success, problems and formidable challenges still exist: (1) multi-catalyst systems involving more than three distinct catalysts, which provide opportunities to fulfill more sophisticated transformations and at the same time may obviously cause much more compatibility issues between catalysts and intermediates, are rarely seen; (2) the number of successful multi-catalyst systems, especially those providing general and versatile transformations, are still limited; and (3) most of the multi-catalyst-system-catalyzed asymmetric cascade transformations use carefully designed substrates, which require multi-step synthesis of themselves. With understanding of the state of the art and the challenges in mind, here, using three (or four) different types of catalysts, we establish a transformation of readily available styrenes, allylic alcohols, and syngas into chiral α-quaternary functionalized aldehydes through the combination of Rh-catalyzed hydroformylation and asymmetric allylation catalyzed cooperatively by Pd and organocatalysts.

Transition-metal-catalyzed hydroformylation is one of the largest homogeneous catalytic processes in the world (Figure 2A).[25–30] Transition-metal-catalyzed allylation (known as the Tsuji-Trost reaction for the Pd-catalyzed process) is one of the most versatile transformations to form C–C bonds in organic synthesis (Figure 2B).[31,32] The combination of these two important processes, which means performing the two reactions simultaneously in one reactor, may provide great opportunities to develop efficient transformations from simple starting materials. In our hypothesis (Figure 2C), the alkenes undergo rhodium (Rh)-catalyzed branch-selective hydroformylation, followed by a synergistically Pd- and amine-catalyzed asymmetric α-allylation of the aldehydes generated *in situ* to produce α-quaternary functionalized chiral aldehydes, a class of highly valuable compounds.[33–47] However, such a combined process poses a number of formidable challenges, some of which even appear to be intrinsic issues and virtually impossible to overcome. For examples, a careful selection of catalysts and reaction conditions is needed to inhibit the hydroformylation of the allylating reagent and the product, which also possess C–C double bonds. The presence of CO gas will almost definitely deactivate the Pd catalyst and make the whole reaction sluggish. The π-allyl Pd complex could be reduced by H_2 gas or the intermediary Rh hydride[48,49] or undergo a carbonylation reaction in the presence of CO.[50] List and co-workers reported the direct α-allylation of aldehydes and ketones cooperatively catalyzed

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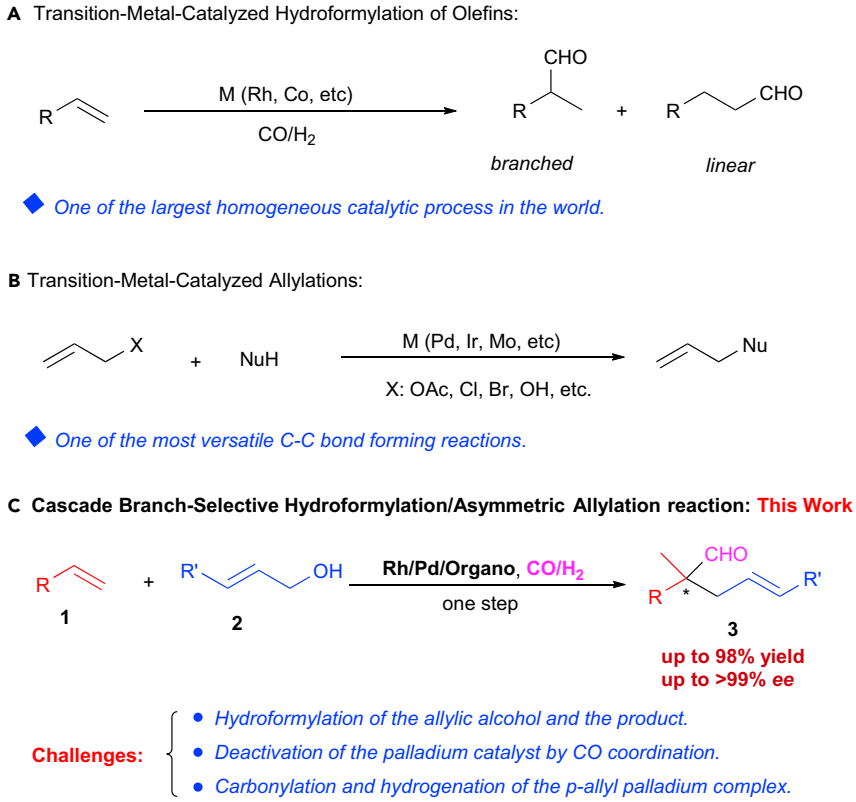


Figure 2. Transition-Metal-Catalyzed Hydroformylation of Olefins, Transition-Metal-Catalyzed Allylation, and Cascade Hydroformylation and Asymmetric Allylation Reaction

by Pd and organocatalysts.[51–53] We previously reported Rh/chiral-Brønsted-acid-catalyzed hydroaminomethylation of alkenes.[24] Encouraged by these and other studies on asymmetric α-allylation of aldehydes,[54–59] we initiated the hypothesized reaction. Allylic alcohols were chosen as the allylating agent because of their easy accessibility.[60] A catalyst system combining Pd and organocatalysts[17,52] was selected to promote the asymmetric α-allylation of the aldehyde generated *in situ*. As shown in a detailed mechanism (Figure 3), in the presence of an achiral Pd(0) catalyst and the BINOL-derived chiral phosphoric acid,[61,62] the allylic alcohol transforms into a π-allyl Pd complex bearing a chiral counter anion[63–66] (the chiral phosphate). The achiral amine (catalytic or stoichiometric amount) forms the enamine intermediate with the α-branched aldehyde generated from the alkene hydroformylation process.[67,68] The enamine **II** reacts with the π-allyl Pd complex **IV** to form a chiral imine **VI**, which yields the α-quaternary chiral aldehyde **3** and releases the amine after *in situ* hydrolysis. In this proposed catalytic system, asymmetric hydroformylation is not necessary because of the racemization caused by the enamine formation process. The chiral phosphoric acid works as the sole chiral element to control the stereoselectivity in the whole reaction.

RESULTS AND DISCUSSION

We initiated our study by investigating the model reaction of styrene **1a** and cinnamyl alcohol **2a** in a syngas atmosphere by using a multi-catalyst system consisting of a Rh complex, $Pd(Ph_3P)_4$, a chiral phosphoric acid (*R*)-TRIP (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate), and an achiral

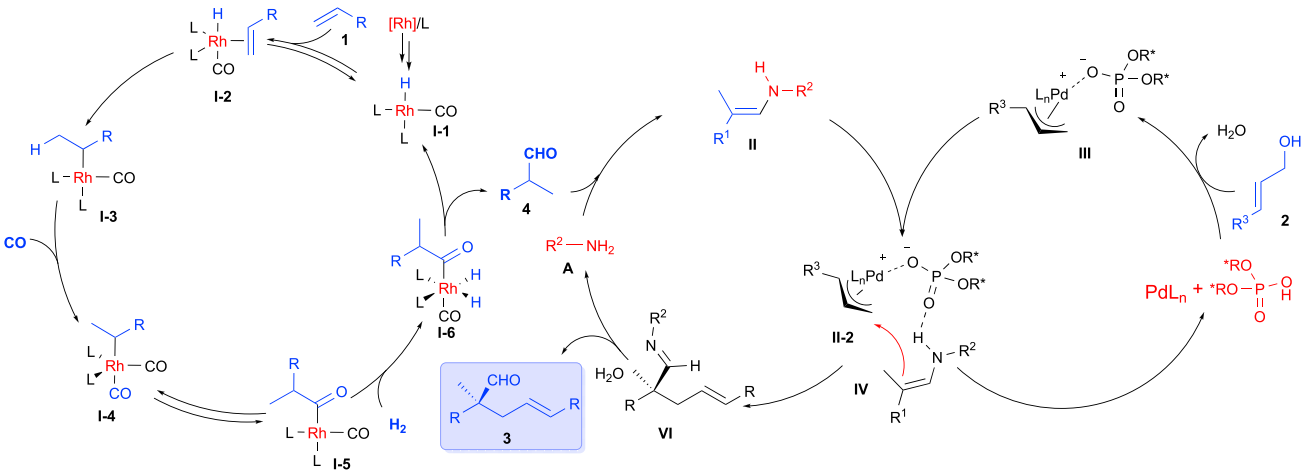
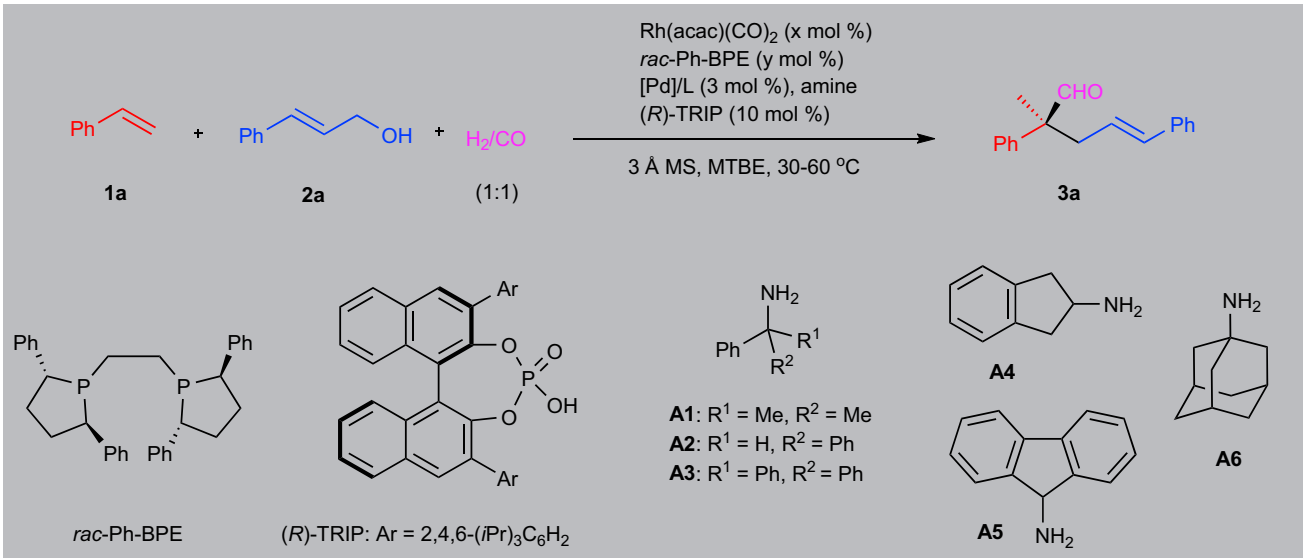


Figure 3. Proposed Mechanism for the Cascade Hydroformylation and Asymmetric Allylation Reaction Catalyzed by Rh, Pd, and Organocatalysts
The multi-catalyst system enables the direct transformation of alkenes, allylic alcohols, and syngas to α-quaternary chiral aldehydes.

amine **A1** (Table 1). To diminish the side reactions caused by syngas and suppress the inactivation effect on the Pd catalyst by CO coordination, we used 1 bar of syngas (CO/H_2 = 1:1), which later proved to be a key factor for the reaction.[69] Given that low syngas pressure can also result in a sluggish hydroformylation process, a Rh complex prepared *in situ* from $Rh(acac)(CO)_2$ and commercially available *rac*-Ph-BPE (1,2-bis(2,5-diphenylphospholano)ethane), which has proven to be highly active and highly branch-selective for the alkene hydroformylation reaction, was used. Encouragingly, the expected product **3a** was observed in 20% NMR yield and with 89% ee (entry 1). Surprisingly, lowering the catalyst loading of Rh complex to 1 mol % greatly increased the yield to 78%, albeit with a slightly lower enantioselectivity (entry 2). This could have resulted from the ligand exchange between the Rh complex and the Pd complex. The coordination of the excess bidentate ligand Ph-BPE to the Pd probably led to poor conversion of the allylation step, which was supported by a control experiment shown later. Further lowering the Rh complex loading led to decreased yields, albeit with slightly enhanced enantioselectivities (entries 3 and 4). Then, a detailed evaluation of different achiral amines was performed. It turned out that the structure of the amines had a great impact on both the yield and the stereoselectivity of the reaction (entries 5–9). However, the initial amine **A1** still proved optimal for the transformation. Further investigation revealed that the ligand of the Pd complex was also crucial for the reaction. Using $Pd(dppe)_2$ or $Pd[P(o\text{-}tol)_3]_2$ instead of $Pd(Ph_3P)_4$ resulted in unproductive reactions (entries 10 and 11). Increasing the amount of the achiral amine **A1**, which is readily available and inexpensive, was found to be beneficial to the reaction in terms of the yield and enantioselectivity (entries 12 and 13). In the presence of 1 equiv of **A1**, the product **3a** could be isolated in 87% yield and with 92% ee (entry 13). At this stage, we investigated the effect of the pressure of the syngas. As expected, probably as a result of the deactivation effect caused by CO coordination to the Pd catalyst, increasing the syngas pressure to 2 bar led to a sluggish reaction (entry 14). Syngas at 4 bar rendered the reaction completely unproductive (entry 15). Finally, a slightly higher yield and maintained enantioselectivity were obtained by reducing the reaction time to 48 hr (entry 16). At 60°C, similar levels of yield and enantioselectivity were observed (entry 17).

Having established the optimized reaction conditions, we first investigated the scope of allylic alcohols for the reaction with styrene **1a** (Scheme 1; see also

Table 1. Optimization of Catalysts and Reaction Conditions



Entry	x/y	[Pd]/L	Amine (mol %)	H_2/CO (bar)	Yield (%)[a]	ee (%)[b]
1	2/2.4	$Pd(PPh_3)_4$	**A1** (40)	1	20	89
2	1/1.2	$Pd(PPh_3)_4$	**A1** (40)	1	78	75
3	0.5/0.6	$Pd(PPh_3)_4$	**A1** (40)	1	45	90
4	0.25/0.3	$Pd(PPh_3)_4$	**A1** (40)	1	27	91
5	1/1.2	$Pd(PPh_3)_4$	**A2** (40)	1	50	11
6	1/1.2	$Pd(PPh_3)_4$	**A3** (40)	1	51	5
7	1/1.2	$Pd(PPh_3)_4$	**A4** (40)	1	72	31
8	1/1.2	$Pd(PPh_3)_4$	**A5** (40)	1	43	60
9	1/1.2	$Pd(PPh_3)_4$	**A6** (40)	1	83	49
10	1/1.2	$Pd(dppe)_2$	**A1** (40)	1	trace	–
11	1/1.2	$Pd[P(o\text{-}tol)_3]_2$	**A1** (40)	1	NR	–
12	1/1.2	$Pd(PPh_3)_4$	**A1** (80)	1	78	91
13	1/1.2	$Pd(PPh_3)_4$	**A1** (100)	1	87[c]	92
14	1/1.2	$Pd(PPh_3)_4$	**A1** (100)	2	47[c]	91
15	1/1.2	$Pd(PPh_3)_4$	**A1** (100)	4	trace	–
16[d]	1/1.2	$Pd(PPh_3)_4$	**A1** (100)	1	93[c]	92
17[e]	1/1.2	$Pd(PPh_3)_4$	**A1** (100)	1	91[c]	92

Unless indicated otherwise, the reaction was carried out under a CO/H_2 (1:1, 1–4 bar) atmosphere in the scale of **1a** (0.2 mmol), **2a** (0.4 mmol), $Rh(acac)(CO)_2$ (0.25–2 mol %), ligand (0.3–2.4 mol %), (*R*)-TRIP (10 mol %), and 3 Å molecular sieve (150 mg) in *tert*-butyl methyl ether (2.0 mL). NR, no reaction.

[a]NMR yield with trimethyl benzene-1,3,5-tricarboxylate as the internal standard.

[b]Determined by chiral high-performance liquid chromatography.

[c]Isolation yield.

[d]The reaction was carried out for 48 hr.

[e]The reaction was carried out at 60°C.

Figures S1–S36 and S71–S106). A series of cinnamyl alcohols with either electron-withdrawing or electron-donating substituents at the *para*, *ortho*, or *meta* position of the arene moiety underwent the reactions smoothly to give the corresponding α-quaternary aldehydes in moderate to excellent yields (57%–97%) and high to excellent enantioselectivities (86%–99% ee, **3b–3i**). An apparent trend was that allylic alcohols bearing electron-withdrawing groups provided higher yields than

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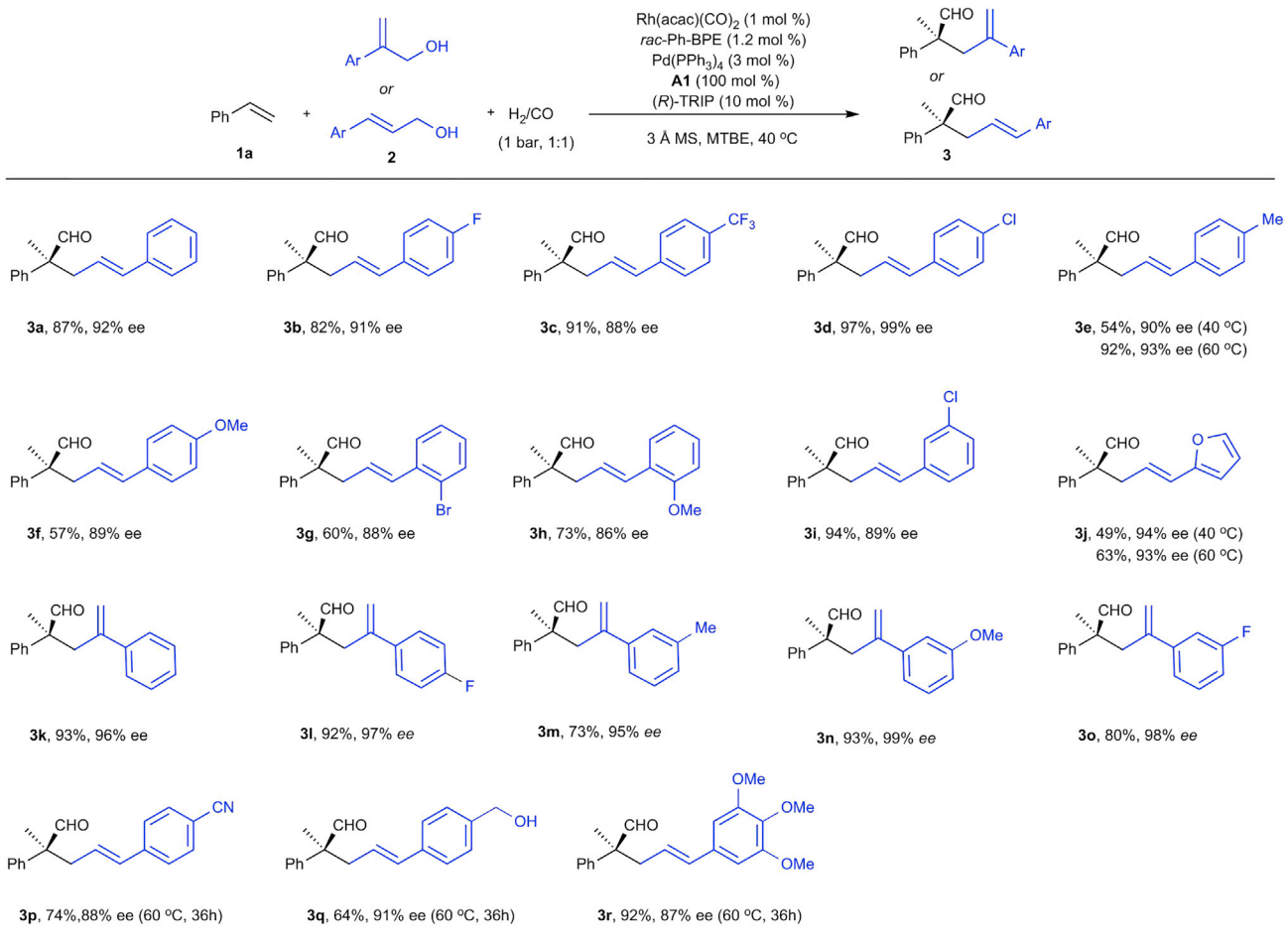
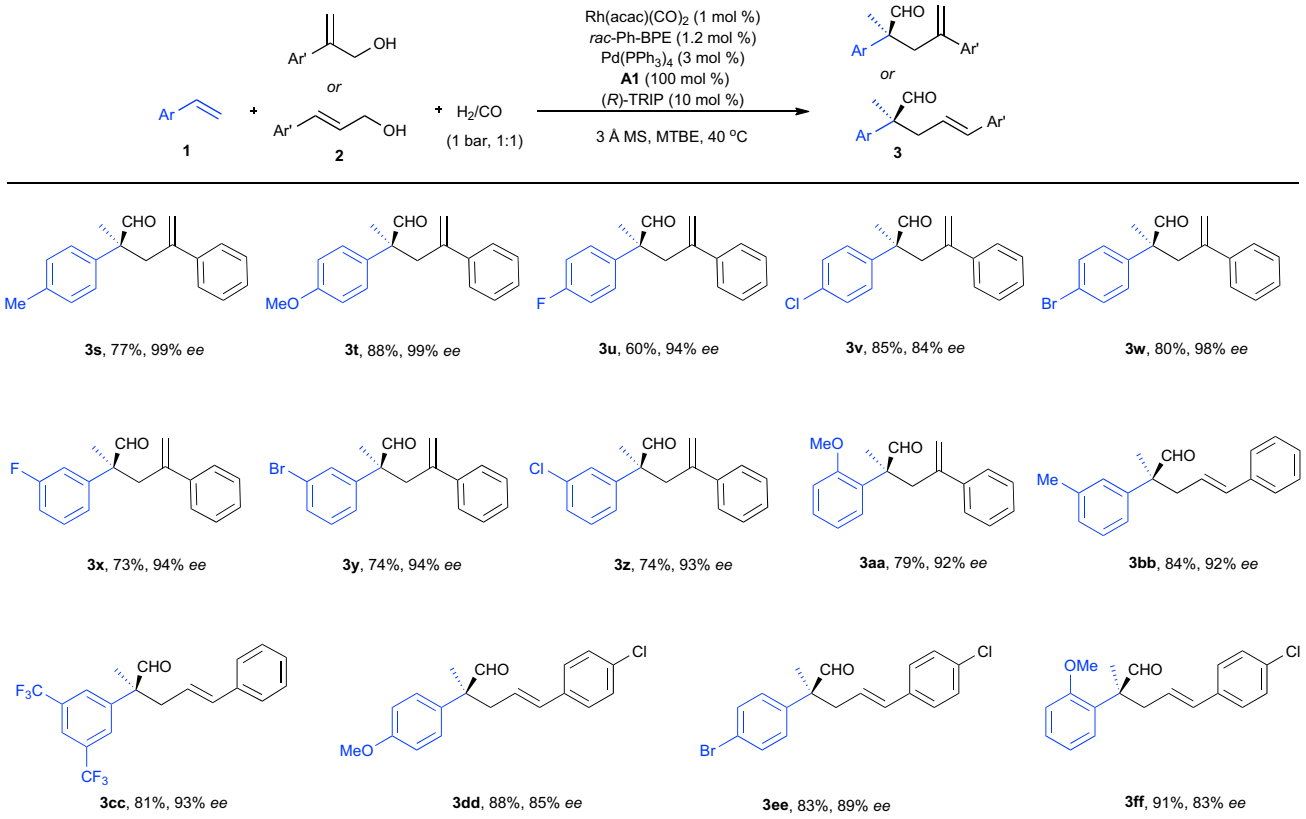


Scheme 1. Substrate Scope for Allylic Alcohols

Unless indicated otherwise, the reaction was carried out under a CO/H_2 (1:1, 1 bar) atmosphere in the scale of **1a** (0.2 mmol), **2a** (0.4 mmol), $Rh(acac)(CO)_2$ (1 mol %), ligand (1.2 mol %), (*R*)-TRIP (10 mol %) and 3 Å molecular sieve (150 mg) in *tert*-butyl methyl ether (2.0 mL) at 40°C for 48 hr.

those with electron-donating substituents (entries **3b–3d** versus **3e** and **3f**). Cinnamyl alcohol incorporating a heteroarene (i.e., entry **3j**) was also tolerated and converted to the expected product in moderate yield and excellent enantioselectivity. For some substrates (i.e., **3e** and **3j**), elevating the reaction temperature from 40°C to 60°C led to higher yields and similar levels of enantioselectivity. Allylic alcohols with a terminal double bond, e.g., 1-arylallyl alcohol, were not tolerated for the reaction, probably because of their high activity to undergo hydroformylation under the reaction conditions. However, 2-aryl allylic alcohols bearing a disubstituted terminal olefin moiety, because of their lower tendency to participate in the hydroformylation process, were well tolerated for the reaction (**3k–3n**). Compared with those of the linear cinnamyl alcohol substrates, generally higher enantioselectivities (95%–99% ee) were observed. To improve the functional group diversity of the reaction, 4-CN, 4-CH_2OH, and 3,4,5-trimethoxyl-substituted cinnamyl alcohols were also tested and were all well tolerated for the reaction (**3p** and **3r**).

Next, the generality of styrenes was investigated with 2-phenylprop-2-en-1-ol and cinnamyl alcohols as the counterparts (Scheme 2; see also Figures S37–S64 and



Scheme 2. Substrate Scope for Styrenes

Unless indicated otherwise, the reaction was carried out under a CO/H_2 (1:1, 1 bar) atmosphere in the scale of **1a** (0.2 mmol), **2a** (0.4 mmol), $Rh(acac)(CO)_2$ (1 mol %), ligand (1.2 mol %), (*R*)-TRIP (10 mol %), and 3 Å molecular sieve (150 mg) in *tert*-butyl methyl ether (2.0 mL) at 40°C for 48 hr.

S107–S134). Generally, the reactions of 2-phenylprop-2-en-1-ol with various styrene derivatives took place smoothly, giving the corresponding α-quaternary chiral aldehydes in moderate to high yields with high to excellent enantioselectivities (84%–99% ee, **3s**–**3aa**). Surprisingly, bromo-substituted styrenes were also well tolerated for the cascade reaction involving Pd(0), giving bromo-containing products with excellent enantioselectivities (**3w** and **3y**). This was probably because the oxidative addition of Pd(0) to the bromoarene was suppressed in the CO atmosphere. 4-Iodo-substituted styrene was also examined but failed to provide the product. A number of substituted styrenes were also tested in the reactions with cinnamyl alcohol and *p*-chlorocinnamyl alcohol and showed satisfying results (**3bb**–**3ff**). An arylalkene bearing two strong electron-withdrawing substituents was also applicable to the reaction (**3cc**). Notably, in the presence of a catalytic amount of amine **A1** (40 or 20 mol %), the model reaction of **1a** and **2a** could proceed completely at a higher temperature and prolonged reaction time, and provided the product **3a** with satisfying yields and enantioselectivities (Scheme 3).

As mentioned previously, one unusual observation was that a higher loading of Rh catalyst (2/2.4 mol % Rh precursor and ligand) resulted in a much slower reaction. To verify our hypothesis that the presence of the excess bidentate phosphine ligand might prohibit the Pd-catalyzed allylation process, we performed a control experiment starting from the aldehyde **4** with *rac*-Ph-BPE instead of Ph_3P as the ligand (Figure 4A). In accordance with our hypothesis, the reaction turned out to be

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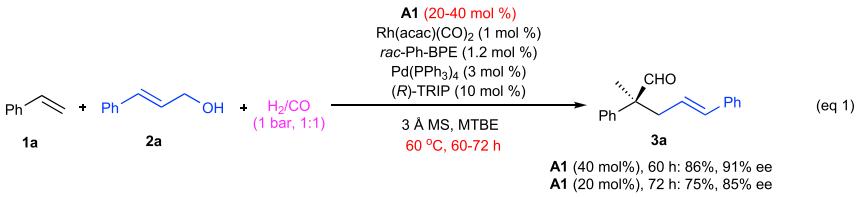


Scheme 3. Cascade Reaction Using a Catalytic Amount of Amine

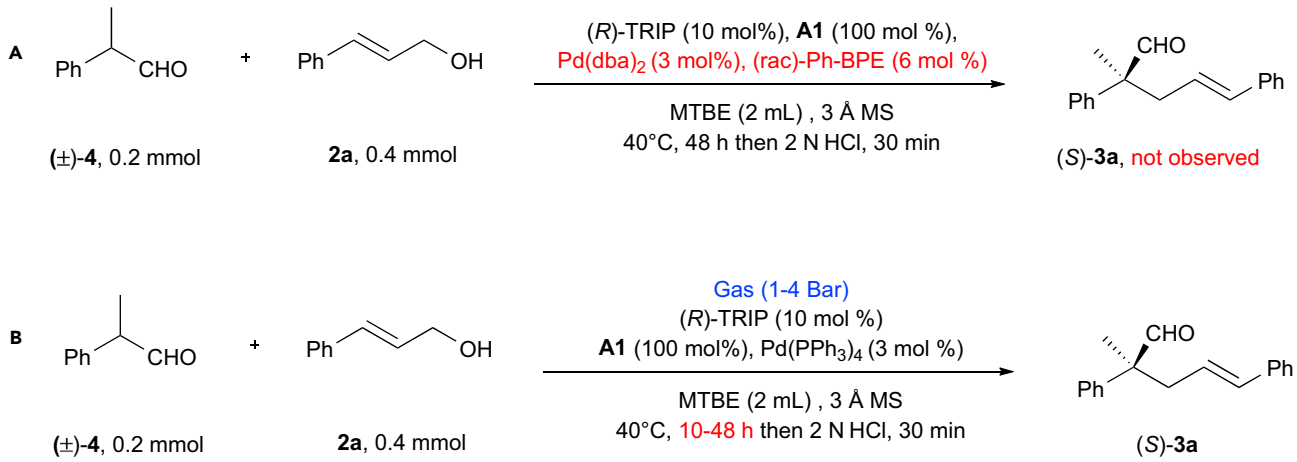
completely unproductive. To gain insight into the pathway of the reaction and also to clarify the impact of CO and H_2 on the asymmetric allylation process, we performed a serial of control experiments with racemic 2-phenylpropanal **4** as the reactant in the absence of Rh catalyst under various gas atmospheres (Figure 4B). In the nitrogen atmosphere, the reaction of **4** and **2a** provided (*S*)-**3a** in 84% yield and with 93% ee after a 10-hr reaction time (entry 1). The results strongly supported that the cascade reaction of alkene and allylic alcohol proceeded through a hydroformylation and asymmetric allylation pathway. In the same reaction time, replacement of the nitrogen gas with CO (1, 2, or 4 bar) severely suppressed the reaction and slightly eroded the enantioselectivity (entries 2–4). Hydrogen gas (1 bar) also led to a diminished yield, although the impact was much milder in comparison with CO gas (entry 5). Switching to a syngas atmosphere (1 bar, 1:1), a serious inhibition effect was observed as well (entry 6). However, 86% yield and 90% ee could also be achieved in a prolonged reaction time (entry 7). In contrast, performing the reaction with 2 bar of syngas (1:1) for 48 hr provided the product only in 41% yield (entry 8), also indicating that low syngas pressure was a key factor for the cascade reaction.

To illustrate the synthetic utility of the reaction, we performed a series of transformations of the α-quaternary chiral aldehyde **3k** (Figure 5; see also Figures S65–S70 and S135–S140). The aldehyde **3k** could also be applied to the Wittig reaction to give chiral compound **5** bearing two C=C double bonds. The treatment of **3k** with hydroxylamine hydrochloride followed by heating at 70°C in the presence of carbonyldiimidazole afforded chiral nitrile **6** with the conservation of the stereochemical information. A one-pot sequential reductive amination of **3k** with 4-methoxylbenzyl amine furnished chiral amine **7** with excellent stereochemical fidelity.

In summary, we have successfully developed a cascade transformation of styrenes, allylic alcohols, and syngas to α-quaternary chiral aldehydes in a multi-catalyst system consisting of a Rh(I) complex, a Pd(0) complex, a chiral Brønsted acid, and an achiral amine (20–100 mol %). The reaction proceeds through an alkene hydroformation and asymmetric allylation sequence. Under a 1 bar syngas atmosphere, which was demonstrated to be crucial for the reaction, Rh-catalyzed branched-selective hydroformylation and Pd- and organo-catalyzed asymmetric allylation occur simultaneously and orderly, allowing for the generation of α-quaternary chiral aldehydes in high yields (up to 98%) and enantioselectivities (up to 99% ee).

EXPERIMENTAL PROCEDURES

To a flame-dried, nitrogen-filled Schlenk tube equipped with a stir bar were added alkene **1** (20.8 mg, 0.2 mmol), allylic alcohol **2** (0.4 mmol, 2.0 equiv), 2-phenylpropan-2-amine (5.4–27.0 mg, 0.2–1.0 equiv), $Rh(acac)(CO)_2$ (0.52 mg, 0.002 mmol, 0.01 equiv), $Pd(Ph_3P)_4$ (6.9 mg, 0.006 mmol, 0.03 equiv), (*R*)-TRIP (15.1 mg, 0.02 mmol, 0.1 equiv), a 3 Å molecular sieve (150 mg). Then, *rac*-Ph-BPE



Entry	Gas	Yield (%)	*ee* (%)
1	N_2 (1 bar), 10 h	84	93
2	CO (1 bar), 10 h	7	89
3	CO (2 bar), 10 h	7	87
4	CO (4 bar), 10 h	6	87
5	H_2 (1 bar), 10 h	57	90
6	H_2/CO (1 bar), 10 h	12	90
7	H_2/CO (1 bar), 48 h	86	90
8	H_2/CO (2 bar), 48 h	41	90

Figure 4. Control Experiments Using *rac*-2-Phenylpropanal as Substrate

(A) The inhibition effect of Ph-BPE ligand to asymmetric allylation catalyzed by Pd and organocatalysts.

(B) Influence of CO and H_2 on the allylation reaction.

(0.0024 mmol, 0.012 equiv) in 0.25 mL of toluene and 2.0 mL of *tert*-butyl methyl ether were added under nitrogen. After that, oxygen was removed by a freeze-pump-thaw process three times. The Schlenk tube was refilled with 1 bar of syngas ($CO:H_2$ = 1:1). After being stirred at 40°C for 48 hr, the vial was cooled down to room temperature, and the reaction mixture was acidified with 2 N HCl (2 mL) at room temperature for 30 min and extracted with ethyl ether (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated *in vacuo*. The residue was purified through flash column chromatography (SiO_2, hexanes/acetonitrile = 8/1) to provide product **3**. See the Supplemental Information for more detailed experimental procedures and characterization data for all products.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and 140 figures and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.03.010.

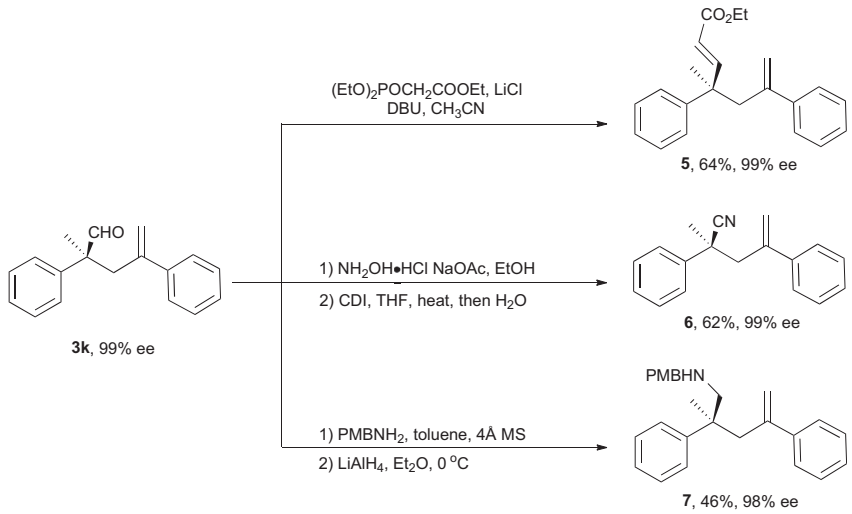


Figure 5. Transformations of α-Quaternary Chiral Aldehyde Products

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AUTHOR CONTRIBUTIONS

J.M. carried out the experimental and data-analysis work. L.-F.F. performed the derivation reactions of the product. Z.-Y.H. and L.-Z.G. designed the reaction and directed the project. Z.-Y.H. and L.-Z.G. wrote the paper with the assistance of J.M. and L.-F.F.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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