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Asymmetric Cascade Annulation Based on Enantioselective Oxa-Diels–Alder Cycloaddition of in Situ Generated Isochromenyliums by Cooperative Binary Catalysis of $Pd(OAc)_2$ and (*S*)-Trip

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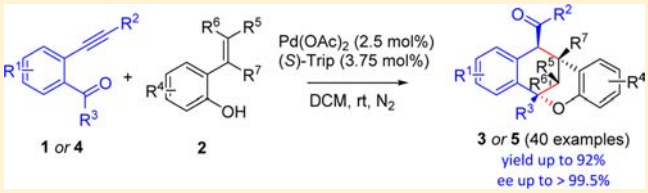
Supporting Information

ABSTRACT: An asymmetric cascade annulation between 2-hydroxystyrenes and 2-alkynylbenaldehyes or 1-(2-alkynylphenyl)ketones has been established with good to excellent enantioselectivities (up to >99.5% ee), on the basis of an enantioselective oxa-Diels–Alder cycloaddition of in situ generated metallo-isochromenylium intermediates, by cooperative binary catalysis of $Pd(OAc)_2$ and (*S*)-Trip. The developed methodology is workable for a broad spectrum of substrates and shows great efficiency in establishing dense multiple chiral centers including quaternary carbons of variable bridged ring systems. The mechanism study suggests that (*S*)-Trip plays multiple roles in assembling the reactants and controlling the stereoselectivity.



INTRODUCTION

Isochromenyliums, a unique type of Hückel aromatic oxonium intermediate, have attracted great attention of organic chemists in recent years.[1−3] These highly reactive intermediates were often generated in situ for various transformations,[4] and a number of air-stable crystalline isochromenylium tetrafluoroborates (ICTBs) were also prepared, characterized and applied by us.[5,6] Rich cationic chemistries of isochromenyliums have been demonstrated in the literature, including various cascade reactions for constructing complex natural and unnatural products.[7] Because of their diverse and high reactivity, enantioselective transformations based on the planar isochromenyliums are still challenging organic chemists. Tanaka group reported the first enantioselective Rh-catalyzed reaction via isochromenylium intermediates between *o*-alkynylbenzaldehydes and *N*-substituted isatin in the presence of a complex ferrocenyl-phosphine ligand,[8] and Slaughter and co-workers developed an enantioselective acetalization of isochromenylium intermediates with a gold(I) acyclic diaminocarbene complex.[9] An asymmetric [3 + 2]-cycloaddition of platinium-containing carbonyl ylide (a 2-oxonium-1,3-diene equivalent similar to isochromenylium) in the presence of chiral phosphine ligand has also been reported by Iwasawa group, providing a series of potentially useful 8-oxabicyclo[3.2.1]-octane derivatives.[10] However, catalytic asymmetric cascade reaction forming multiple C–C and C–X bonds via isochromenyliums remains as a problem yet.

During our recent studies on air-stable isochromenylium salts and their cationic reactions,[5,6] many cascade transformations were found to show high efficiency in constructing complex multiring structures with multiple stereogenic centers. For instance, air-stable ICTB **A** could smoothly react with 2-hydroxylstyrene (**2a**, Figure 1, R^3 = H) in organic media at ambient temperature, providing high yield of *rac*-**3aa** (Figure 1, R^1 = 4,5-$(OCH_3)_2$; R^2 = Ph; R^3 = H)[6a] via cascade intermolecular oxa-Diels–Alder cycloaddition and intramolecular nucleophilic substitution (Figure 1). Such tetrahydronaphthalene framework represents a new type of conformationally constrained analogues of podophyllotoxin (PPT), a famous anticancer natural drug lead.[11] For exploring the biological applications of natural product-like tetrahydronaphthalene derivatives, development of enantioselective cascade transformations via isochromenyliums is thus particularly important and urgent.

To achieve the above-mentioned purpose, controlling the stereoselectivity of oxa-Diels–Alder reaction between isochromenylium diene and styrene-type dienophile is a crucial work. Since isochromenylium intermediate could be generated in situ by treatment of *o*-alkynylbenzaldehyde with a variety of metal catalysts,[4] we deduced that certain proper combination of a metal catalyst and a chiral Brønsted acid might efficiently organize both the reactants into one unified transition state, delivering satisfactory enantioselectivity to the final product. In the past decade, chiral Brønsted acids have emerged as the versatile enantioselective catalysts in various enantioselective procedures.[12] Among them, BINOL-derived phosphoric acids are commonly applied as superior bifunctional catalysts of strong Brønsted acid (P–OH) and hydrogen-bond acceptor (P=O).[13] According to our proposal (Figure 1), a cooperative binary catalysis mode[14,15] was expected to execute multiple tasks, including converting *o*-alkynylbenzaldehyde **1** into the

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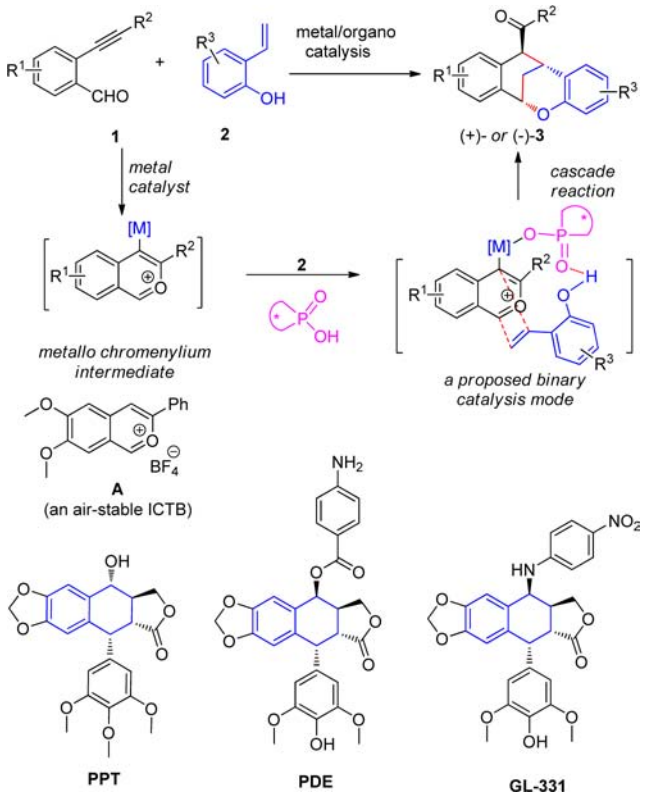


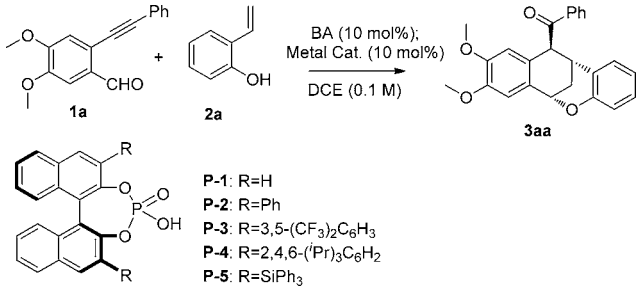
Figure 1. Rational design of asymmetric cascade annulation of *o*-alkynylbenzaldehyde with 2-hydroxylstyrene; anticancer tetrahydronaphthalene natural product podophyllotoxin (PPT) and its bioactive analogues PDE and GL-331.

corresponding metallo-isochromenylium intermediate, exchanging encounter anion with the chiral Brønsted acid, assembling olefin **2** through hydrogen bond, and delivering the enantio-differentiative environment to the key [4 + 2]-cyclization.

RESULTS AND DISCUSSION

Reaction between *o*-alkynylbenzaldehyde **1a** and 2-hydroxylstyrene **2a** was chosen as the examination platform for the above hypothesis (Table 1). No reaction was observed with only 10 mol % of phosphoric acid P-1 at room temperature, while heating the mixture to reflux resulted in the production of **3aa** (88% yield) with low enantioselectivity (10% ee) (entry 1) (the absolute structure of **3aa** was assigned later according to the X-ray single crystal structures of its analogues **3ac**, **3aj**, **3ak**, **5ca**, and **5fa**). Further attempts to improve the enantioselectivity all failed including increasing the loading of phosphoric acid catalyst and using other phosphoric acids. Requirement of high temperature to promote this reaction is owing to the weak activating ability of phosphoric acid to the alkyne group of **1a**, and it is harmful for the stereochemical control. In order to reduce the reaction temperature and examine the proposed binary catalysis mode, a number of metal catalysts (10 mol %) were further screened together with P-1. Most of the reactions gave the racemic product **3aa** in satisfactory yields except two with $Cu(OTf)_2$ and $Pd(OAc)_2$. Combination of $Pd(OAc)_2$ and P-1 afforded **3aa** in 96% yield and 26% ee at rt (entry 7). Delightedly, varying the 3,3′-subsitituents of phosphoric acid P-1 (P-2−P-5) was proven to be effective to improve the enantioselectivity (entries 8−11), and (*S*)-Trip (P-4) was

Table 1. Screening of Binary-Catalyst Combinations[a]



entry	BA	metal catal	temp	yield (ee)[b] (%)
1	P-1	–	reflux	88 (10)
2	P-1	AgOTf	rt	97 (0)
3	P-1	$AuCl_3$	rt	63 (0)
4	P-1	$PtCl_2$	rt	96 (0)
5	P-1	$Cu(OTf)_2$	rt	20 (20)
6	P-1	$Zn(OTf)_2$	rt	12 (0)
7	P-1	$Pd(OAc)_2$	rt	96 (26)
8	P-2	$Pd(OAc)_2$	rt	85 (43)
9	P-3	$Pd(OAc)_2$	rt	73 (15)
10	P-4	$Pd(OAc)_2$	rt	75 (79)
11	P-5	$Pd(OAc)_2$	rt	37 (10)

[a]Reaction conditions: **1a** (0.5 mmol) and **2a** (0.75 mmol), metal catalyst (10 mol %) and Brønsted acid (10 mol %) in 1,2-dichloroethane (5 mL) under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC.

identified to be the best acid catalyst for this cascade annulation (entry 10, 75% yield, 79% ee).

With the catalyst combination of $Pd(OAc)_2$ and (*S*)-Trip (P-4), other reaction parameters were investigated (Table 2). The reaction could be completed in many solvents, and DCM was identified to be the best one (entry 7). Incomplete conversion was observed in CH_3CN, though the reaction afforded a higher enantioselectivity (entry 4). Lowering the catalyst loadings did not cause any detriment on the enantioselectivity of product (entries 7 and 8). A slightly better result was observed when the reaction was performed at 0 °C with a longer reaction time (21 h, entry 9). An improved enantioselectivity was achieved when increasing the loading of (*S*)-Trip over that of $Pd(OAc)_2$, and 50% excess (0.5 equiv more than $Pd(OAc)_2$) was found to be sufficient (entries 8, 10−11). Further reducing the catalyst loadings did not significantly affect the enantioselectivity of product but slowed down the reaction (entry 12). Though use of as low as 1 mol % $Pd(OAc)_2$ could provide similar enantioselectivity (95% ee), a much longer reaction time was required (30 h, entry 13). Water was found to be detrimental but not fatal to this reaction (entries 14−15). Therefore, anhydrous solvent is preferred for the reaction. The optimal catalyst combination was finally determined as $Pd(OAc)_2$ (2.5 mol %) and (*S*)-Trip (3.75 mol %), giving **3aa** (in DCM, rt, 13 h) in 71% yield and 95% ee (entry 12).

Under the optimized conditions, generality of the reaction was then explored (Tables 3−5). Significant electronic effect was observed through the substituent(s) R^1 of **1** (Table 3). When the electron density of the phenyl ring of **1** decreased, the enantioselectivity of products turned poor (entries 1−5, **3aa**−**3ea**). The electron-donating substituent(s) R^1 is believed to stabilize the resulting palladium-containing isochromenylium intermediate, an electron-deficient 2-oxonium-1,3-diene, and thus favors the following cycloaddition. This well agrees with

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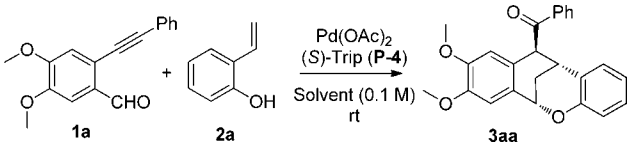
Table 2. Optimization of the Reaction Conditions[a]



entry	$Pd(OAc)_2$ (mol %)	(S)-Trip (mol %)	solvent	time (h)	yield (ee)[b] (%)
1	10	10	DCE	4	75 (79)
2	10	10	THF	6	38 (78)
3	10	10	Toulene	4	68 (79)
4	10	10	CH_3CN	19	43 (87)
5	10	10	DMF	19	trace
6	10	10	Dioxane	6	41 (77)
7	10	10	DCM	6	71 (85)
8	5	5	DCM	7	65 (88)
9[c]	5	5	DCM	21	79 (90)
10	5	10	DCM	7	69 (93)
11	5	7.5	DCM	7	67 (93)
12	2.5	3.75	DCM	13	71 (95)
13	1	1.5	DCM	30	69 (95)
14[d]	2.5	3.75	DCM	13	68 (89)
15[e]	2.5	3.75	DCM	13	69 (83)

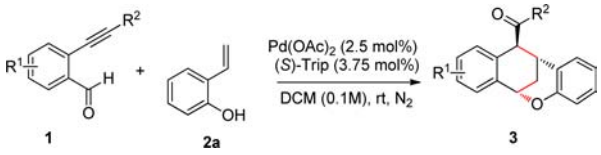
[a]Unless otherwise noted, the reaction was conducted between **1a** (0.5 mmol) and **2a** (0.75 mmol) with indicated catalysts in 5 mL of solvent at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC. [c]The reaction was performed at 0 °C. [d]The reaction was performed without N_2 protection. [e]The reaction was conducted with the addition of water (1 equiv).

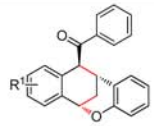
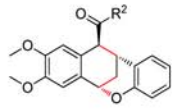
our previous observation on the air-stable ICTBs.[5] Little effect was observed when the alkyne substituent R^2 of **1** was a phenyl ring bearing various functionalities (such as OMe, CO_2Me, CN, CHO, *t*-Bu, NO_2 etc.). All these reactions could be carried out smoothly and gave the desired tricyclic products in good yields and excellent enantioselectivities (**3fa**−**3pa**). Compared to the weak electronic effect of R^2, the hindrance effect seemed to be more sensitive (**3fa**−**3ha**). Poor ees were observed in those having a heteroaromatic subsitituent (**3qa** and **3ra**). This might be caused by unclear heteroatom-poisoning effects on $Pd(OAc)_2$. Unsatisfactory results also happened to the reactions of substrates **1** having an aliphatic or alicyclic substituent at R^2 (**3sa**−**3va**). We guess that insufficient interactions between substrate **1** and the phenyl ring of catalyst P-4 might be a reason for the low ees of these reactions (for more discussion on the mechanism, see below text).

To our delight, this binary catalytic system worked well for the reactions with *o*-alkynylketones **4** (Table 4). The desired products **5aa**−**5ca** containing a newly formed quaternary carbon were obtained in good yields and satisfactory enantioselectivities under standard conditions (entries 1−3). As for the aryl ketones, these transformations also could be smoothly carried out and delivered the products with good enantioselectivities using a higher catalyst loading (5 mol % $Pd(OAc)_2$ and 7.5 mol % (*S*)-Trip) (**5da**−**5fa**, entries 4−6).

Effect of the substituents of *o*-hydroxystyrene **2** was also investigated (Table 5). Variation of the 5-substituent (R^4) was insensitive to the reaction (**3ab**−**3ae**, entries 1−4), while a 4-CH_3 at R^4 brought significant decrease in both chemical yield and enantioselectivity (**3af**, entry 5). No desired reaction happened when the *o*-hydroxystyrene substrate had a 3-CH_3 group (not shown in Table 5). A number of multisubstituted

Table 3. Examination of the Reaction Scope of 1[a]



Entry	1 (R^1/R^2)	Time	3 (yield, ee)[b]
	1a-1e (R^2=Ph)		
1	**1a** (R^1=4,5-di-OCH_3)	15h	**3aa** (71%, 95%)[c]
2	**1b** (R^1=4-OCH_3)	45h	**3ba** (61%, 76%)
3	**1c** (R^1=5-OCH_3)	13h	**3ca** (66%, 75%)
4	**1d** (R^1=H)	30h	**3da** (68%, 71%)
5	**1e** (R^1=4,5-OCH_2O)	16h	**3ea** (71%, 92%)[d]
	1f-1v (R^1=4,5-di-OCH_3)		
6	**1f** (R^2= 4-$NO_2C_6H_4$)	18h	**3fa** (73%, 94 %)
7	**1g** (R^2= 3-$NO_2C_6H_4$)	8h	**3ga** (67%, 88%)
8	**1h** (R^2= 2-$NO_2C_6H_4$)	44h	**3ha** (80%, 63%)
9	**1i** (R^2= 4-$CH_3C_6H_4$)	23h	**3ia** (75%, >99.5%)
10	**1j** (R^2= 4-$CH_3OC_6H_4$)	25h	**3ja** (75%, >99.5%)
11	**1k** (R^2= 4-BrC_6H_4)	18h	**3ka** (80%, >99.5%)
12	**1l** (R^2= 4-CNC_6H_4)	31h	**3la** (64%, 97%)
13	**1m**(R^2= 4-$CHOC_6H_4$)	43h	**3ma** (65%, 99%)
14	**1n** (R^2= 4-(MeO_2C)C_6H_4)	26h	**3na** (78%, >99.5%)
15	**1o** (R^2= 4-*t*-BuC_6H_4)	39h	**3oa** (73%, 90%)
16	**1p** (R^2= 2-naphthyl)	38h	**3pa** (70%, 91%)
17	**1q** (R^2= 2-furfuryl)	33h	**3qa** (37%, 76%)
18	**1r** (R^2= 2-thienyl)	26h	**3ra** (40%, 86%)
19	**1s** (R^2= *n*-C_5H_{11})	16h	**3sa** (78%, 33%)
20	**1t** (R^2= *n*-C_6H_{13})	14h	**3ta** (74%, 27%)
21	**1u** (R^2= *c*-C_6H_{11})	20h	**3ua** (61%, 19%)
22	**1v** (R^2= *c*-C_3H_5	15h	**3va** (46%, 37%)

[a]Unless otherwise noted, the reaction was conducted with **1** (0.5 mmol) and **2a** (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %), (*S*)-Trip (3.75 mol %) in anhydrous DCM (5 mL) at rt under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC. [c]When the reaction was conducted with $Pd(OAc)_2$ (2.5 mol %) and (*R*)-Trip (3.75 mol %), the desired compound **3aa** was obtained with 75% yield and −96% ee. [d]The yields of two diastereomers (dr = 3:1), and the shown ee value is for the major isomer.

styrene-type olefins were also examined (entries 6−12). All of them were found to undergo the cascade reactions smoothly under the optimal catalytic conditions, except the one with a CH_3 group at R^7 (entry 12, **3am**). The hindrance of R^7 might interfere with the formation of hydrogen-bond in the transition

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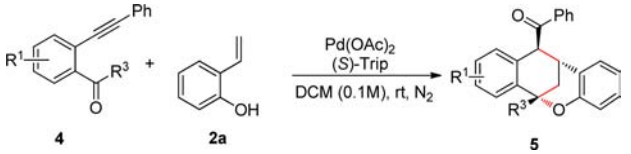
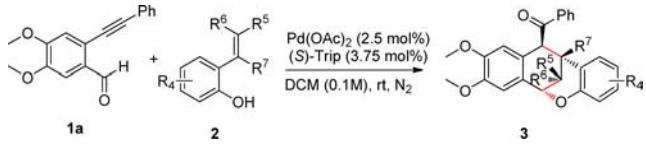
Table 4. Examination of the Reactions of *o*-Alkynylketones 4[a]

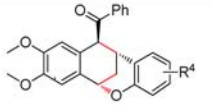
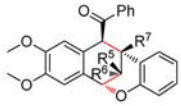


entry	4 (R^1/R^3)	time (h)	5 (yield, ee)[b] (%)
1	**4a** (R^1 = 4,5-di-OCH_3; R^3 = CH_3)	6	**5aa** (80, 93)
2	**4b** (R^1 = 4,5-di-OCH_3; R_3 = *i*-Pr)	46	**5ba** (80, 85)
3[c]	**4c** (R^1 = 4,5-di-OCH_3; R^3 = *c*-C_6H_{11})	54	**5ca** (86, 93)
4[d]	**4d** (R^1 = 4,5-di-OCH_3; R^3 = 4-$CH_3C_6H_4$)	46	**5da** (78, 83)
5[d]	**4e** (R^1 = 4,5-di-OCH_3; R^3 = 4-$CH_3OC_6H_4$)	96	**5ea** (87, 85)
6[c,e]	**4f** (R^1 = 4,5-OCH_2O; R_3 = 3,4,5-$(CH_3O)_3C_6H_2$)	54	**5fa** (77, −92)

[a]Unless otherwise noted, the reaction was conducted with **4** (0.5 mmol) and **2a** (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %), (*S*)-Trip (3.75 mol %) in anhydrous DCM (5 mL) at rt under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC. [c]Its absolute structure was confirmed by X-ray crystal analysis; see Figure 2. [d]$Pd(OAc)_2$ (5 mol %) and (*S*)-Trip (7.5 mol %) were used. [e]$Pd(OAc)_2$ (5 mol %) and (*R*)-Trip (7.5 mol %) were used.

Table 5. Examination of the Scope of Substrate 2[a]



Entry	2 (R^4/R^5/ R^6/R^7)	Time (h)	3 (yield, ee)[b]
	2b-2f (R^5= R^6=R^7=H)		
1	**2b** (R^4=5-NO_2)	12	**3ab** (89%, >99.5%)
2	**2c** (R^4=5-Br)	17	**3ac** (86%, 98%)[c,d]
3	**2d** (R^4=5-CH_3)	14	**3ad** (60%, 90%)
4	**2e** (R^4=5-OCH_3)	14	**3ae** (73%, 97%)
5	**2f** (R^4=4-CH_3)	72	**3af** (50%, 55%)
	2g-2m (R^4=H)		
6	**2g** (R^5=CH_3; R^6=R^7= H)	25	**3ag** (73%, 84%)
7	**2h** (R^5=C_2H_5; R^6=R^7= H)	17	**3ah** (87%, 92%)
8	**2i** (R^5=*n*-C_4H_9; R^6= R^7= H)	14	**3ai** (90%, >99.5%)
9	**2j** ((R^5=*c*-C_6H_{11}; R^6=R^7=H)	14	**3aj** (92%, >99.5%)[c]
10	**2k** (R^5,R^6=*c*-C_6H_{10}; R^7=H)	15	**3ak** (80%, 97%)[c,e]
11	**2l** (R^5=R^6=CH_3; R^7=H)	18	**3al** (64%, 89%)
12	**2m** (R^5= R^7=CH_3; R^6=H)	16	**3am** (48%, 33%)

[a]All the reaction was conducted with **1a** (0.5 mmol) and **2** (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %) and (*S*)-Trip (3.75 mol %) in anhydrous DCM (5 mL) at rt under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC. [c]Its absolute structure was determined by X-ray crystal analysis; see Figure 2. [d]A scale-up reaction was performed with **1a** (1.33 g, 5 mmol) and **2c** (0.90 g, 7.5 mmol), giving the desired product **3ac** (2.04 g, 88%, 95% ee). [e]When the reaction was conducted with $Pd(OAc)_2$ (2.5 mol %) and (*R*)-Trip (3.75 mol %), the desired compound **3ak** was obtained with 78% yield and −96% ee.

state (see below text). Furthermore, reaction with the *Z*-isomer of olefin **2g** was surprisingly slow and gave **3ag** (the same product from the reaction with *E*-**2g**, entry 6) in a much lower yield after 6 days. The Z-olefin seems to be unfavorable for formation of the transition state (see below text for mechanism discussion), and slow conversion of *Z*-isomer into *E*-isomer took place prior to its reaction with **1a**. More attractively, this type of reaction showed great efficiency in generating four densely continuous stereogenic centers, including two examples giving a newly born all-carbon quaternary stereocenter (entries 10−11, **3ak** and **3al**).

In order to understand the reaction mechanism, several control experiments were performed (Table 6). Failure of the cascade transformation at rt in the absence of either $Pd(OAc)_2$ or (*S*)-Trip reveals that both metal catalyst and organocatalyst are needed for the reaction (entries 1 and 2), and it more likely adopts a cooperative metal/organo binary catalysis mode. Only a trace amount of product was detected after 3 days by replacing $Pd(OAc)_2$ with $PdCl_2$ (entry 4). This suggests that the suitable encounter anion of Pd(II) (AcO^- vs Cl^-) is also very important for the reaction, and a weaker acid anion (AcO^- in this work) favors the anionic exchange with (*S*)-Trip upon Pd(II) before the assembly of both reactants for the oxa-Diels−Alder cycloaddition.

Furthermore, masking the hydroxyl group of styrene **2a** with methoxyl group seriously affected the progress of this reaction, giving the corresponding adduct in only 10% yield after 5 days (Scheme 1). Shifting the *ortho*-phenolic hydroxyl group of **2a** to the *meta*- or *para*- position resulted in no reaction or much lower yield of the corresponding adduct. Therefore, the *ortho*-phenolic hydroxyl group in the styrene substrate is conservatively essential to achieve this type of highly enantioselective cascade transformation.

On the basis of the results from the cascade reactions and control experiments, a possible mechanism was proposed (Figure 3). First, the alkyne bond of *o*-alkynylbenzaldehyde **1** (or *o*-alkynylketone **4**) is coordinated and activated by $Pd(OAc)_2$ to initiate a cycloisomerization by attack of the oxygen of the internal C═O group, affording an Pd(II)-isochromenylium intermediate **A**. After anionic exchange with (*S*)-trip and release of a molecule of HOAc, the resulting intermediate **B** grasps *o*-hydroxyl styrene **2** through hydrogen-bond between the phenolic OH of styrene and the P═O of Trip.[16] Such highly ordered supramolecular assembly of two substrates and two catalysts perfectly devises a transition state for an "intramolecular" oxa-Diels−Alder reaction[17] under asymmetric environment. After the asymmetric [4 + 2]-cyclization, the resulting carbocation **C** (stabilized by the oxygen atom of the internal carbonyl group) is quickly trapped by the internal phenol hydroxyl to provide **D**. Finally, the C−Pd bond of **D** is broken down by protonation with HOAc to

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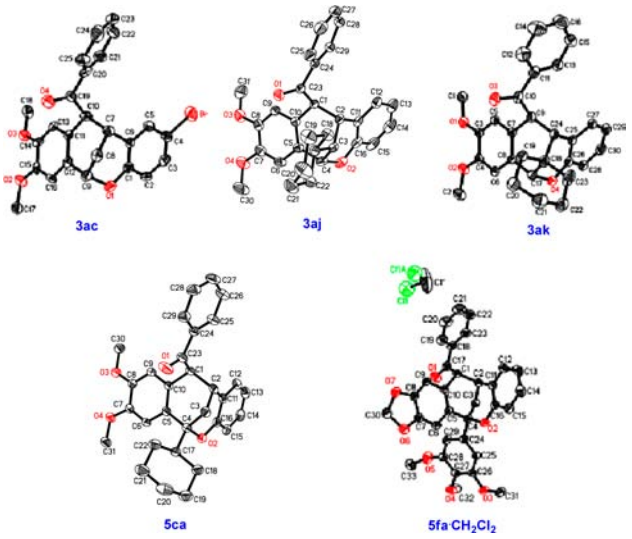
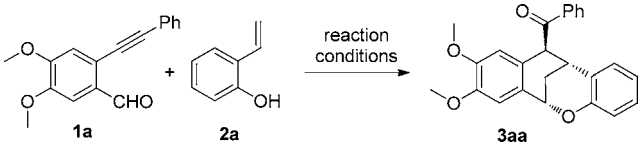


Figure 2. X-ray structures of representative compounds **3ac**, **3aj**, **3ak**, **5ca**, and **5fa**.

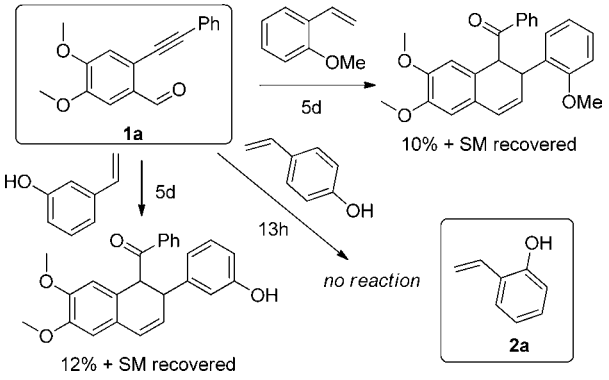
Table 6. Control Experiments of the Cooperative Catalysis[a]



entry	Pd(II) (2.5 mol %)	(*S*)-Trip (3.75 mol %)	temp (°C)	time	yield (ee)[b] (%)
1	$Pd(OAc)_2$	–	23	3 d	trace
2	–	(*S*)-Trip	23	3 d	NR
3	$Pd(OAc)_2$	(*S*)-Trip	23	16 h	71 (95)
4	$PdCl_2$	(*S*)-Trip	23	3 d	trace
5	$PdCl_2$	(*S*)-Trip	30	4 d	60 (32)

[a]All the reactions were carried out beween **1a** (0.5 mmol) and **2a** (0.75 mmol) with the indicated catalysts in 5 mL of DCM under nitrogen atmosphere. [b]Isolated yields, and ee values were determined by chiral HPLC.

Scheme 1. Examination of the Role of *ortho*-Phenolic Hydroxyl Functionality of Styrene 2a



deliver product **3** (or **5**), and the metal catalyst $Pd(OAc)_2$ is regenerated in the meanwhile. The high enantioselectivity is considered to stem from both the steric hindrance of the bulky 1,3,5-triisopropyl phenyl group of Trip moiety and the hydrogen-bond interactions between the phenolic hydroxyl group of substrate **2** with the P═O functionality of Trip. As a net result, two new C−C bonds and one C−O bond are stereoselectively generated from this cascade annulation, as well as two new rings.

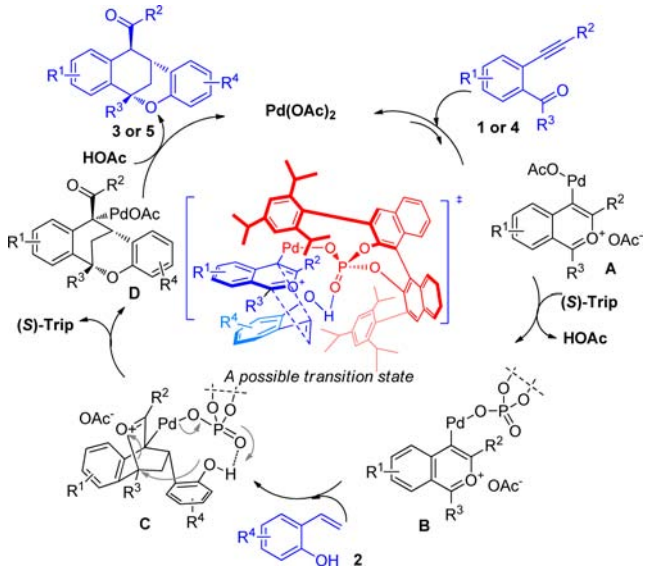


Figure 3. Proposed reaction mechanism.

CONCLUSION

The first successful example of catalytic asymmetric cascade transformation has been achieved on the basis of an enantioselective oxa-Diels−Alder reaction of metallo-isochromenylium intermediate with *o*-hydroxystyrene with good to excellent enantioselectivities (up to >99.5% ee) in a broad spectrum of substrates. The developed metallo/organo binary catalytic methodology showed great efficiency in multiple-bond formation and establishing bridged-ring systems with densely multiple stereogenic centers including quaternary carbons, and therefore provides a convenient one-step access to enantiopure complex tetrahydronaphthalene natural product-like derivatives of medicinal interest.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterizations, copies of NMR spectra for new compounds, chiral HPLC analyses for products **3** and **5** (PDF), and X-ray data of **3ac**, **3aj**, **3ak**, **5ca**, and **5fa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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