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Article

Efficient Stereoselective Carbocyclization to *cis*-1,4-Disubstituted Heterocycles Enabled by Dual Pd/Electron Transfer Mediator (ETM) Catalysis

Can Zhu,*,# Jie Liu,# Binh Khanh Mai, Fahmi Himo,* and Jan-E. Bäckvall*

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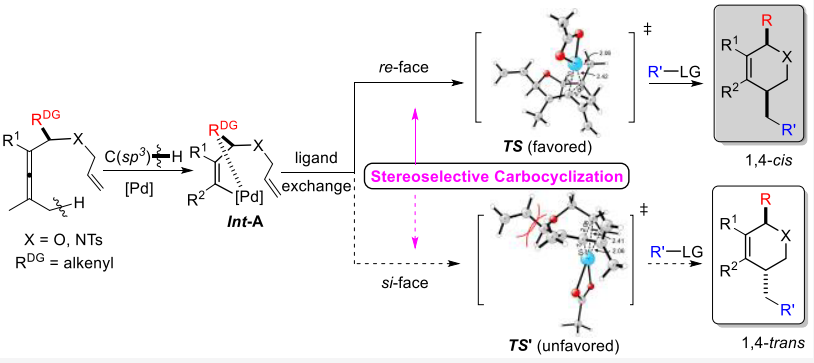

ABSTRACT: An efficient Pd/ETM (ETM = electron transfer mediator)-cocatalyzed stereoselective oxidative carbocyclization of dienallenes under aerobic oxidation conditions has been developed to afford six-membered heterocycles. The use of a bifunctional cobalt complex [Co(salophen)-HQ] as hybrid ETM gave a faster aerobic oxidation than the use of separated ETMs, indicating that intramolecular electron transfer between the hydroquinone unit and the oxidized metal macrocycle occurs. In this way, a class of important *cis*-1,4-disubstituted six-membered heterocycles, including dihydropyran and tetrahydropyridine derivatives were obtained in high diastereoselectivity with good functional group compatibility. The experimental and computational (DFT) studies reveal that the pendent olefin does not only act as an indispensable element for the initial allene attack involving allenic C(sp^3)−H bond cleavage, but it also induces a face-selective reaction of the olefin of the allylic group, leading to a highly diastereoselective formation of the product. Finally, the deuterium kinetic isotope effects measured suggest that the initial allenic C(sp^3)−H bond cleavage is the rate-limiting step, which was supported by DFT calculations.

INTRODUCTION

Six-membered heterocycles are ubiquitous core structures in various natural products, as well as in pharmacologically active substances.[1] Glucose, the monosaccharide made during photosynthesis from water and carbon dioxide, is one of the most important compounds in the life sciences.[2] α-D-glucopyranose bears the core structure of tetrahydropyran with substituents stereochemically arranged, including 1,2-, 1,3-, and 1,4-*cis* configurations of two different hydroxyl groups (Scheme 1a). The similar stereochemistry can also be found in many other natural products, such as (−)−*centrolobine*, *ophiocerin* B, (−)−*brevisamide*, and *pyranicin*.[3] For 1,2- and 1,4-disubstituted six-membered rings, a *cis* configuration will have one substituent in the equatorial position and the other one in the axial position, where the latter suffers from 1,3-diaxial interaction(s) with the axial C−H bond(s) (Scheme 1b).[4] Moreover, the distance between the two substituents in *cis*-1,4-disubstituted six-membered rings is much greater than that in the corresponding *cis*-1,2- or 1,3-disubstituted compounds, which is unfavorable for the control of its stereochemistry when the second substituent is introduced.[5] Therefore, the development of methodologies for efficient synthesis of *cis*-1,4-disubstituted six-membered rings, including heterocycles, is greatly challenging and highly desirable.[6]

Hetero-Diels−Alder reactions of carbonyl compounds or imines with conjugated dienes constitute a reliable approach toward the synthesis of six-membered heterocycles.[7] However, for the preparation of *cis*-1,4-disubstituted products, the reaction requires stereoisomerically pure (*E*,*E*)- or (*Z*,*Z*)-1,3-dienes (Scheme 2a). Moreover, hetero-Diels−Alder reactions

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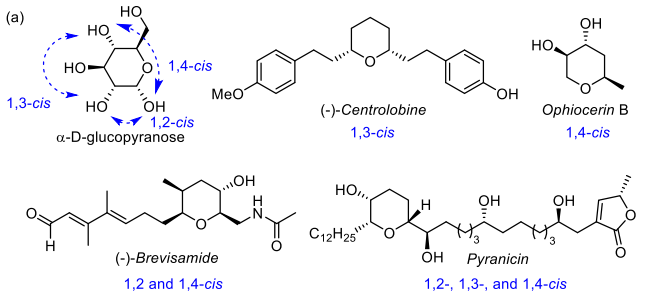
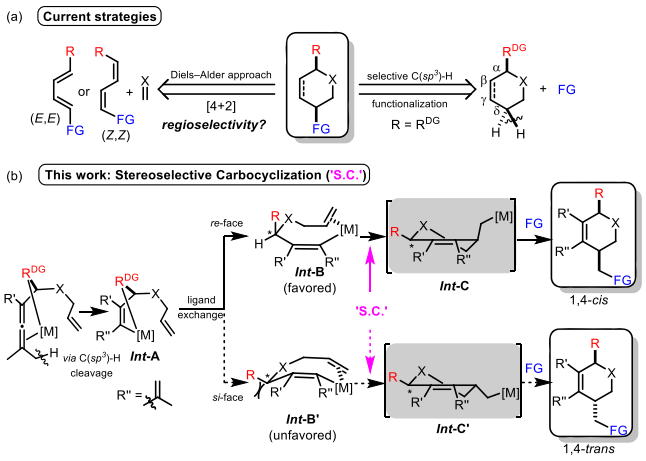
Scheme 1. (a) Selected Natural Products Bearing the Core Structure of Six-Membered Heterocycles with 1,2-, 1,3-, or 1,4-*cis* Configuration. (b) Comparison of the Difficulties on the Selectivity Control for the Synthesis of *cis*-1,2-, 1,3-, and 1,4-Disubstituted Six-Membered Rings (X, Y = C, O, N. etc.)



substitutents positions	R(equatorial)/R'(axial) (unfavored)	R(equatorial)/R'(equatorial) (favored)	R(equatorial)/R'(axial) (unfavored)
distance (R-R')	short (favored)	moderate (unfavored)	long (unfavored)

are usually associated with problems in the control of regioselectivity.[8]

Scheme 2. (a) State of the Art and (b) This Work (X = O, NR, etc.; DG = Directing Group; M = Metal)

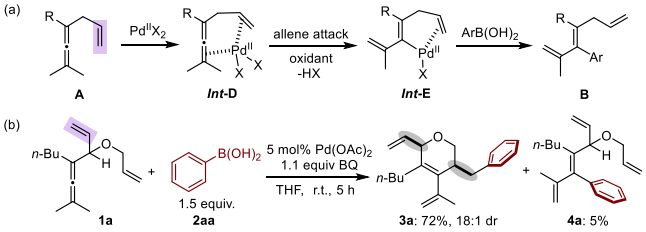


An alternative elegant solution for obtaining *cis*-1,4-disubstituted heterocycles is the utilization of transition metal-catalyzed C−H activation reactions (Scheme 2a). With a suitable directing group (DG) in the R group, the transannular δ-C(sp^3)−H functionalization can be realized with the remote selectivity starting from preformed heterocycles.[9,10] The newly introduced functional group will then be installed on the same face of the ring as the R group via a boat-conformation intermediate. However, high-temperature conditions are generally required to overcome the energy barrier for C(sp^3)−H activation.[9] Herein, we disclose an alternative efficient approach for the synthesis of *cis*-1,4-disubstituted heterocycles via a stereoselective carbocyclization. On the basis of our previous work,[11] we envisioned that a selective metalation of the C−H bond would produce **Int-A** (Scheme 2b) with a suitable directing/assisting substituent (R^{DG}). Subsequent intramolecular ligand exchange from the directing group in **Int-A** to the remote olefin leads to intermediates **Int-B** and/or **Int-B′**, due to the *re*- or *si*-facial coordination of the olefin to the metal. Initial computations indicated that the *re*-facial coordination in conformation **Int-B** would be favored over the *si*-facial coordination in **Int-B′** due to interactions between the R and R′ substituents in **Int-B′**. Surprisingly, the boatlike conformation (**Int-B** and **Int-B′**) was more stable than the corresponding chairlike conformations in both cases. Subsequent migratory insertion in the favored intermediate **Int-B** would generate **Int-C**, which further could undergo a coupling reaction to afford the corresponding *cis*-1,4-disubstituted heterocycle as the major product. The corresponding reaction of the less favored intermediate **Int-B′** would give the *trans*-1,4-disubstituted heterocycle **Int-C′**. In this overall transformation, both the ring-closing reaction and the installation of a new functional group (FG) can be efficiently realized in a one-step manner.

RESULTS AND DISCUSSION

A carbon−carbon double bond is a basic yet crucial functional group in organic chemistry.[12] It has been found as a useful directing group in organic transformations, for example, in C−H activation reactions.[13] Moreover, the alkene bond can be diversely transferred to many other functional groups, or easily reduced via hydrogenation.[14] In a previous study, we found that the pendent olefin unit is an indispensable element for the subsequent allene attack via C(sp^3)−H bond cleavage (Scheme 3a).[11] Therefore, an olefin unit was introduced on

Scheme 3. (a) Previous Studies and (b) Initial Attempts for this Work



the enallene moiety and evaluated as a directing group in the carbocyclization reaction (Scheme 3b). Our initial attempts began with the coupling reaction of dienallene **1a** with phenylboronic acid (**2aa**) under the catalysis of palladium with BQ (*p*-benzoquinone, 1.1 equiv) as the oxidant. Interestingly, the reaction in THF at room temperature (r.t.) for 5 h afforded the cyclic product **3a** in 72% yield, while the direct phenylation product **4a** was obtained only in 5% yield. Interestingly, the dihydropyran product **3a** was generated in high diastereoselectivity (d.r. = 18:1). From NOE studies of dihydropyran **3a**, it was found that the major stereoisomer is the product with *cis*-1,4-disubstitution.

With these initial results in hand, we turned to optimizing the reaction conditions. In the oxidation reactions, the goal was to use environmentally benign oxidants, such as molecular oxygen.[15] However, direct reoxidation of Pd(0) by molecular oxygen is expected to be unfavored due to the high-energy barrier for electron transfer under the reaction conditions of

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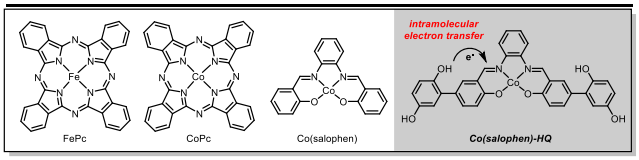
the carbocyclization.[16] Indeed, the attempted palladium-catalyzed oxidative reaction of **1a** using molecular oxygen as the only oxidant without any additives did not give any of the product **3a** or **4a**, and the starting material **1a** was recovered in 79% yield (Table 1, entry 1). A solution to this problem is to add various established electron transfer mediators (ETMs), including metal macrocyclic complexes and BQ to improve the reoxidation efficiency.[16,17] To our delight, in the presence of BQ (10 mol %) and catalytic amount of Fe(Pc) (Pc = phthalocyanine), a 14% yield of dihydropyran **3a** was obtained with an 18:1 d.r., while **1a** was recovered in 50% yield (Table 1, entry 2). The employment of Co(Pc) in place of Fe(Pc) led to a decrease of the yield of **3a** to 7% (Table 1, entry 3). Co(salophen) (5 mol %) together with BQ (10 mol %) showed slightly higher efficiency in this oxidative carbocyclization with formation of **3a** in 15% yield (d.r. = 18:1) and recovery of dienallene **1a** in 60% yield (Table 1, entry 4). Replacing BQ by HQ (hydroquinone) resulted in a lower yield of **3a** (4%) (Table 1, entry 5). Interestingly, the use of a hybrid catalyst Co(salophen)-HQ,[18] in which metal-macrocycle Co(salophen) (ETM_1) and two quinone moieties (ETM_2) are merged into one molecule, significantly improved the yield of the desired product **3a** to 45% (Table 1, entry 6). This improvement is probably due to the higher efficiency of the intramolecular electron transfer in the bifunctional cobalt catalyst [Co(salophen)-HQ], compared to that of the two separate ETMs in entry 5. Unfortunately, in this case, side product **4a** was also formed in 31% yield, implying a poor chemoselectivity during the reaction. Replacing phenylboronic acid by triphenyl boroxine did not lead to any improvement (entry 7). However, the chemoselectivity toward the formation of **3a** was dramatically improved by replacing phenylboronic acid by its neopentylglycol ester (PhBneo) as the arylating reagent (entry 8 vs entry 6). Similarly, PhBpin also showed good reactivity and selectivity albeit in slightly lower yield (46%, entry 9). Notably, stoichiometric amounts of H_2O significantly favored the transformation of dienallene **1a** to afford **3a** and **4a** (Table 1, entries 10–12).[19] When 2 equiv of H_2O was added to the reaction mixture, the yield of **3a** was further improved up to 75%, along with the phenylated product **4a** in 15% yield (Table 1, entry 12). Finally, by increasing the catalyst loading of Co(salophen)-HQ to 10 mol %, an optimal yield (85%) of **3a** was obtained in the presence of 1 equiv of H_2O, while side product **4a** was kept as low as 8% yield (Table 1, entry 13).

Next, the catalytic reaction under aerobic conditions (1 atm of O_2) at r.t. with different electron transfer mediators (ETMs) was examined using [5 mol % Co(salophen) + 10 mol % HQ], [5 mol % Co(salophen) + 10 mol % BQ], or [5 mol % Co(salophen)-HQ] in the presence of 5 mol % $Pd(OAc)_2$ (for details of the reaction conditions, see entries 4–6 in Table 1). As shown in Figure 1, the reaction with hybrid catalyst

Table 1. Optimization of the Reaction Conditions[a]

1a 2 3a 4a

Entry	ETM_1 (5 mol%)	ETM_2 (10 mol%)	'Ph-B' reagent **2**	Yield of **3a** (d.r.)	Yield of **4a**	Recovery of **1a**
1	-	-	$PhB(OH)_2$ (**2aa**)	0	0	79%
2	FePc	BQ	$PhB(OH)_2$ (**2aa**)	14% (18:1)	<1%	50%
3	CoPc	BQ	$PhB(OH)_2$ (**2aa**)	7% (18:1)	<1%	64%
4	Co(salophen)	BQ	$PhB(OH)_2$ (**2aa**)	15% (18:1)	<1%	60%
5	Co(salophen)	HQ	$PhB(OH)_2$ (**2aa**)	4% (18:1)	<1%	70%
6	Co(salophen)-HQ		$PhB(OH)_2$ (**2aa**)	45% (18:1)	31%	<1%
7	Co(salophen)-HQ		$(PhBO)_3$ (**2ca**)	39% (18:1)	31%	<1%
8	Co(salophen)-HQ		PhBneo (**2ba**)	48% (18:1)	2%	30%
9	Co(salophen)-HQ		PhBpin (**2da**)	46% (18:1)	2%	30%
10[b]	Co(salophen)-HQ		PhBneo (**2ba**)	66% (18:1)	5%	14%
11[c]	Co(salophen)-HQ		PhBneo (**2ba**)	72% (18:1)	7%	9%
12[d]	Co(salophen)-HQ		PhBneo (**2ba**)	75% (18:1)	15%	<1%
13[c,e]	***Co(salophen)-HQ***		***PhBneo (2ba)***	***85% (18:1)***	***8%***	<1%



[a]Unless otherwise noted, the following reaction conditions were employed: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (5 mol %), ETM_1 (5 mol %), ETM_2 (10 mol %), in 0.2 M THF, O_2 (balloon, 1 atm) at room temperature (23 °C) for 24 h. Yields and conversions were determined by ^{1}HNMR using anisole as internal standard. [b]H_2O (0.5 equiv) was added to the reaction mixture. [c]H_2O (1.0 equiv) was added to the reaction mixture. [d]H_2O (2.0 equiv) was added to the reaction mixture. [e]The reaction was run with 10 mol % of Co(salophen)-HQ for 36 h.

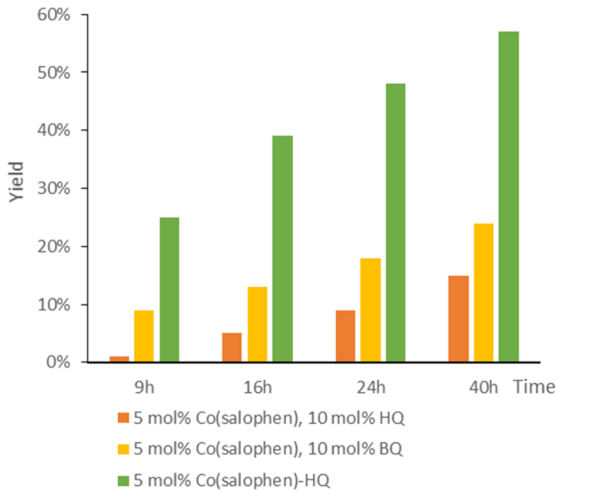


Figure 1. Comparison of catalytic efficiency of different electron transfer mediators (ETMs). Reaction conditions: The reaction was conducted at 25 °C in THF (0.5 mL) with **1a** (0.1 mmol), PhBneo (0.13 mmol), and H_2O (0.1 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) and ETM(s) under atmosphere of O_2.

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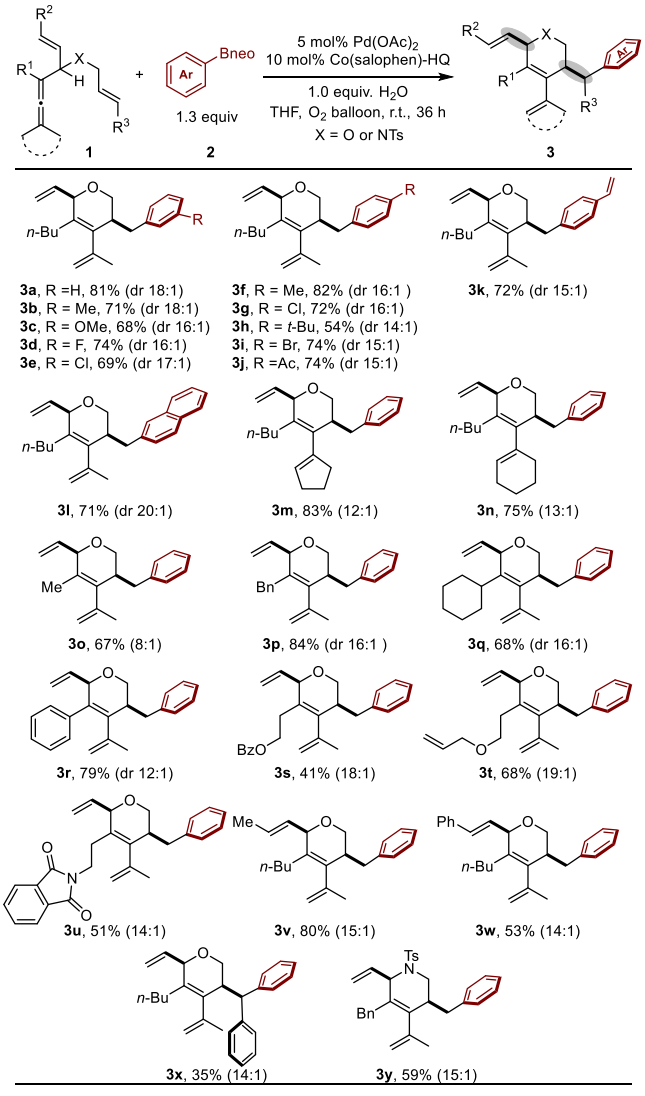
J. Am. Chem. Soc. 2020, 142, 5751−5759

Co(salophen)-HQ resulted in a much higher reaction rate compared to the reaction with separate use of Co(salophen) and HQ (or BQ). These results indicate that an intramolecular electron transfer between the hydroquinone unit and the oxidized metal macrocycle occurs in bifunctional hybrid catalyst Co(salophen)-HQ.

With the optimal reaction conditions in hand, we turned to investigating the substrate scope of this stereoselective carbocyclization reaction (Scheme 4). First, arylboronic acid

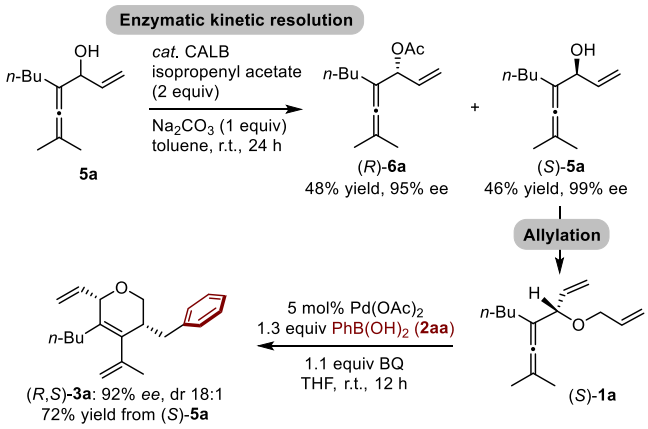
Scheme 4. Substrate Scope



neopentylglycol esters with a range of substituents in the *meta*-position of the benzene ring were examined: the *meta*-analogues with electron-donating substituents, such as Me and MeO, reacted smoothly in high diastereoselectivity (16:1 to 18:1). Substrates bearing electron-withdrawing functional groups in the *meta*-position, including F and Cl worked equally well, affording the corresponding products **3d** and **3e** in 74 and 69% yields, respectively. Moreover, substituent effects in the *para*-position were also studied: functional groups, including Me, Cl, ^{t}Bu, Br, acetyl, and vinyl groups, in the *para*-position of the benzene ring of arylboronic acid neopentylglycol esters led to the corresponding products **3f**–**3k** in good yields (54–82%). A higher diastereoselectivity was observed when a 2-naphthylboronic acid neopentylglycol ester was used, which afforded dihydropyran **3l** in a d.r. of 20:1. Furthermore, cycloalkylidene allenes could also be employed, yielding products **3m** and **3n** in 83 and 75% yields, respectively. The substituent on the allene moiety (R^1) can not only be an aliphatic group (R^1 = Me, Bn, or Cy), but also be an aromatic group (R^1 = Ph), and the corresponding dihydropyran derivatives **3o**–**3r** were obtained in 67–84% yields accordingly. Functional groups, such as an ester, an ether, and an imide were nicely tolerated under the catalysis of Pd and Co(salophen)-HQ, yielding products **3s**–**3u** in 41–68% yields. Not only can a terminal olefin act as the directing/assisting group, but also an internal olefin was found to promote the reaction as shown by the formation of products **3v** and **3w** in 80 and 53% yields, respectively. When a phenyl group was introduced on the distal olefin (R^3 = Ph), the corresponding dihydropyran **3x** was obtained in 35% yield. Finally, this stereoselective carbocyclization was successfully extended to the synthesis of a tetrahydropyridine derivative **3y**.

Enzymatic kinetic resolution (EKR) provides an efficient and scalable method for the preparation of chiral secondary alcohols.[20] EKR of α-allenol **5a** catalyzed by CALB (*Candida antarctica* lipase B) afforded 48% yield of chiral α-allenic acetate (*R*)-**6a** with 95% ee on a 1 g scale (Scheme 5).[21]

Scheme 5. Synthesis of Chiral Product (*S*)-5a by Using Enzymatic Kinetic Resolution



Meanwhile, chiral α-allenol (*S*)-**5a** was recovered in 46% yield with 99% ee. O-allylation of (*S*)-**5a** and subsequent stereoselective carbocyclization under the catalysis of palladium led to the chiral dihydropyran (*R*,*S*)-**3a** in 72% yield (from (*S*)-**5a**), with 92% ee and 18:1 d.r. using stoichiometric BQ as oxidant.

We believe that the erosion of the ee occurs in the carbocyclization step (second step) of the reaction sequence in Scheme 5.[22] This was supported by the observation that when the conditions of Scheme 4 were used for the carbocyclization, only 81% ee of (*R*,*S*)-**3a** was obtained.[23]

Next, to demonstrate the diversity of this stereoselective carbocyclization reaction, enallenyne **7**, bearing the moiety of an internal alkyne, was employed under aerobic oxidative conditions. The corresponding dihydropyran product **8** was isolated in 55% yield, indicating a selective arylating carbocyclization during the reaction (Scheme 6a). To further confirm the effect of the pendent olefin group in dienallene **1**, we carried out comparative experiments using enallene **1a′**, in which the vinyl group in **1a** had been replaced by an ethyl

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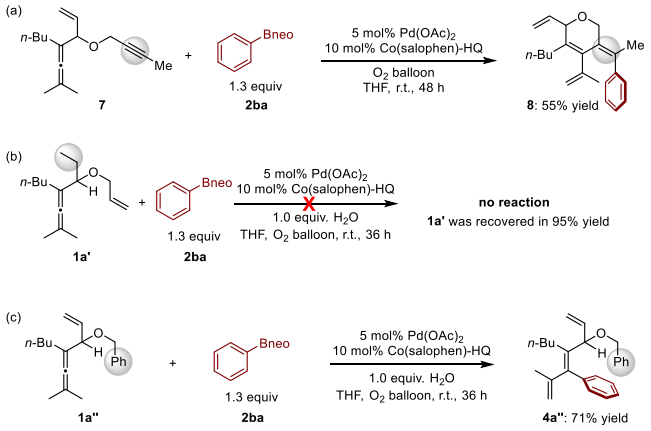
J. Am. Chem. Soc. 2020, 142, 5751−5759

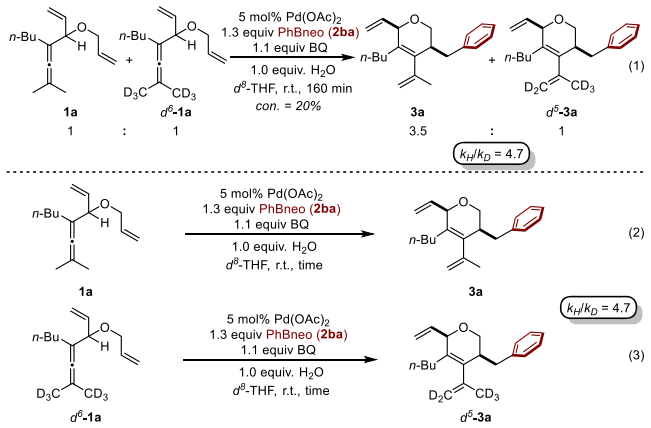
Scheme 6. Mechanistic Studies



group (Scheme 6b). Attempted reaction of **1a′** under standard conditions for 36 h did not give any product, and neither the pyran derivative **3a′** nor the triene product **4a′** could be detected. The starting material **1a′** was recovered in 95% yield. This result indicates that the pendent olefin is an indispensable element for the overall transformations.[11] Under the standard reaction conditions, direct phenylated product **4a″** was obtained in 71% yield by using enallene **1a″**, in which the distal vinyl group in **1a** had been replaced by a phenyl group (Scheme 6c). This observation again shows the importance of the pendent olefin for the initial activation of the allene via C(sp^3)−H bond cleavage.[11]

To gain a deeper insight into the mechanism of this stereoselective carbocyclization reaction, the deuterium kinetic isotope effects (KIE) were studied.[24] An intermolecular competition experiment was carried out using a 1:1 mixture of dienallene **1a** and d_6-**1a** at r.t. for 160 min in the presence of stoichiometric amounts of BQ (eq 1, Scheme 7). The product

Scheme 7. Kinetic Isotope Effects



ratio **3a**/d_5-**3a** (ca. 20% conversion) was measured as 3.5:1. From the product ratio and the reaction conversion, the competitive KIE for this reaction was determined to be k_H/k_D = 4.7.[25] Moreover, two parallel experiments with **1a** and d_6-**1a** gave the same level of KIE (k_H/k_D from initial rate) value of 4.7 (eqs 2 and 3, Scheme 7). These observed kinetic isotope effects indicate that the allenic C−H bond cleavage is the rate-limiting step. The large competitive isotope effect in the allenic C−H bond cleavage (k_H/k_D = 4.7) requires that this step is the first irreversible step.

To gain a better insight into the role of the pendent olefin[11,26] and the origin of the stereoselectivity, we performed density functional theory (DFT) calculations with the dispersion-corrected B3LYP functional (see Supporting Information for computational details) using substrate **1o** (R = Me) as a representative case. On the basis of the DFT calculations (Figure 2), the catalytic cycle for the reaction shown in Scheme 8 is proposed.[27] The reaction starts with the dissociation of the Pd(II) acetate trimer to monomer, to which **1o** coordinates, giving **Int-1**.[11,28] The lowest-energy binding mode is found to be the coordination of the allene moiety and the pendent olefin of **1o** (see the Supporting Information for optimized structures). The energy of **Int-1** is calculated to be 12.5 kcal/mol relative to the Pd(II) acetate trimer (Figure 2a). To proceed, the allenic C(sp^3)−H bond cleavage via transition state **TS-1** can then take place, generating **Int-2**. The activation barrier of **TS-1** is calculated to be 8.8 kcal/mol relative to **Int-1**, i.e., 21.3 kcal/mol relative to the Pd(II) acetate trimer, which constitutes the rate-determining barrier of the reaction (Figure 2a).[29] This is consistent with the above KIE experiments for substrate **1a** (Scheme 7), showing that this step is the rate-limiting step.[30] This step is also the first irreversible step of the reaction as can be seen from Figure 2. In addition, the calculated KIE for the C−H cleavage step from DFT calculation is 3.3, which is consistent with the large competitive isotope effect measured (k_H/k_D = 4.7).

It is interesting to mention that the allenic C(sp^3)−H cleavage transition state **TS-1′**, in which the distal olefin of **1o** is coordinated to palladium in place of the pendent olefin, was also located (see the Supporting Information for details). The barrier of **TS-1′** was calculated to be 11.1 kcal/mol higher in energy than that of **TS-1**, i.e., 32.4 kcal/mol relative to Pd(II) acetate trimer. This result is consistent with the fact that C(sp^3)−H cleavage does not occur if the pendent olefin is removed.[11]

Direct coupling of **Int-2** with arylboronic acid neopentylglycol ester gives side product **4**. In the major pathway, the coordination to the palladium ion is changed from the pendent olefin to the distal olefin to form **Int-3c**, which is calculated to be 9.1 kcal/mol higher in energy than **Int-2**. Subsequent carbocyclization via transition state **TS-2c** (Figure 2b) is shown to take place, giving six-membered ring intermediate **Int-4c**, which leads to the formation of product **3o** through transmetalation and reductive elimination steps.[31,32] The activation energy of **TS-2c** is calculated to be 15.7 kcal/mol relative to **Int-2** (Figure 2a). Finally, the released Pd^0 is reoxidized to Pd^{II} by the intramolecular ETM system with molecular oxygen as the terminal oxidant, which closes the catalytic cycle (Scheme 8).[33] These reoxidation steps were not explicitly studied by the current calculations.

Importantly, we also considered the formation of the *trans*-isomer of **3o** via the carbocyclization transition state **TS-2t**, which is calculated to be 2.6 kcal/mol higher in energy than **TS-2c**. This result is consistent with the experimental finding that the *cis*-isomer **3o** is the main product for this palladium-catalyzed carbocyclization. By scrutiny of the optimized structures of **TS-2c** and **TS-2t**, one source of the energy differences could be identified as being the steric repulsion of the pendent olefin with the methyl moiety (Figure 2b). This interaction appears in **TS-2t**, but not in **TS-2c**, resulting in the higher energy of the former.

It is interesting to mention that other carbocyclization transition states, where the forming ring adopts a more

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J. Am. Chem. Soc. 2020, 142, 5751−5759

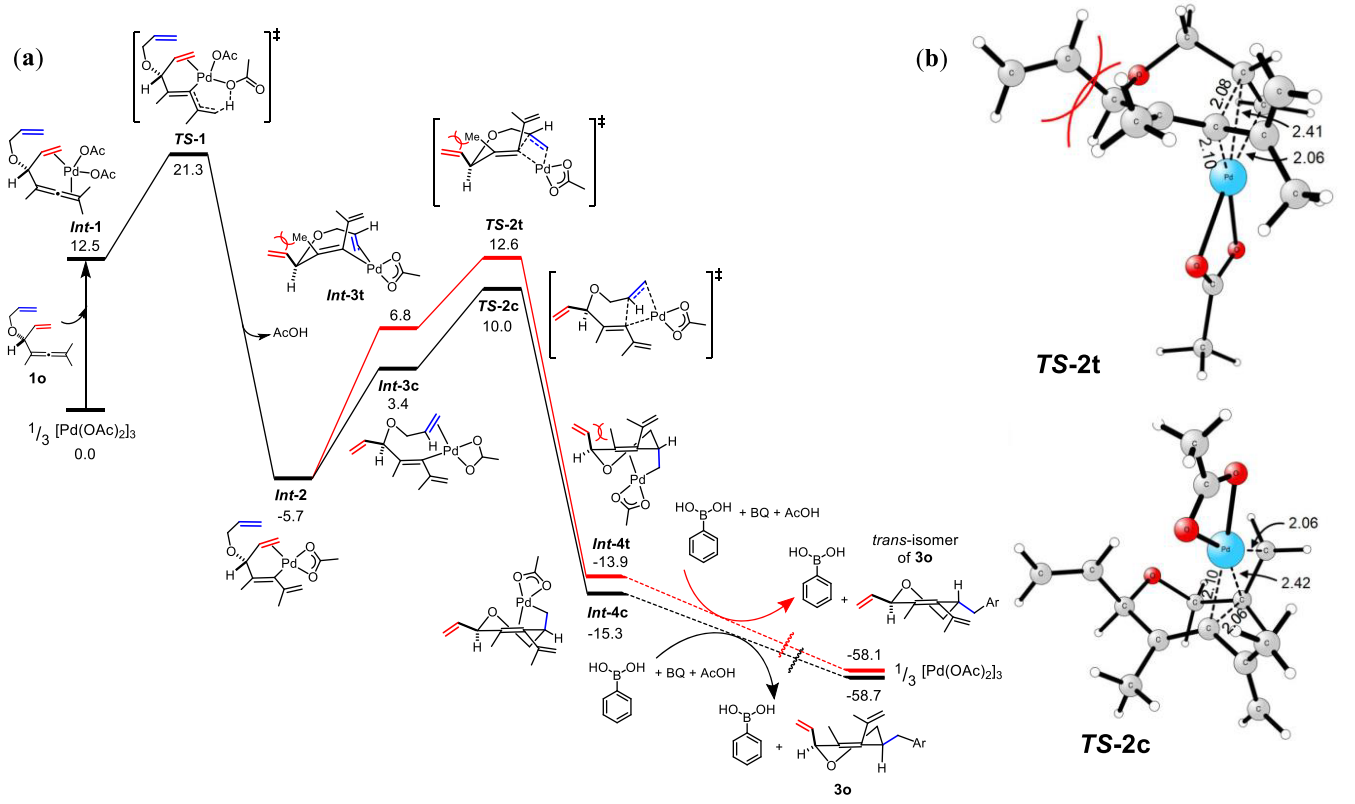
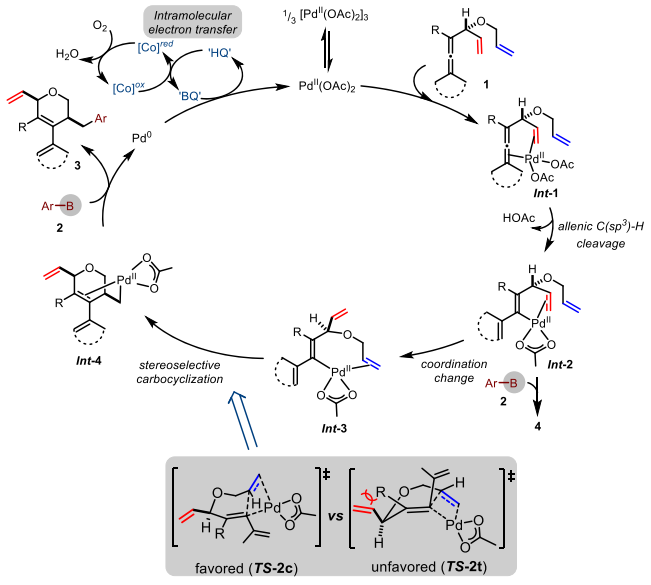


Figure 2. (a) Calculated free energy profile (kcal/mol) and (b) optimized structures of carbocyclization transition states for the Pd-catalyzed stereoselective carbocyclization. Bond distances are in Å.

Scheme 8. Proposed Mechanism



chairlike conformation, were also located (see Supporting Information, Figures S8 and S9). However, these transition states were calculated to be more than 4 kcal/mol higher in energy than the **TS-2c** and can therefore be ruled out as feasible conformations for the cyclization.

CONCLUSIONS

In conclusion, we have developed an efficient Pd/ETM-cocatalyzed stereoselective carbocyclization of dienallenes under aerobic oxidation condition that provides access to important *cis*-1,4-disubstituted six-membered heterocycles. The bifunctional cobalt catalyst [Co(salophen)-HQ] showed high efficiency in this oxidative reaction where molecular oxygen serves as the terminal oxidant. The pendent olefin was shown to be an indispensable element by comparative experiments, and its role is not only to trigger the initial allenic C(sp^3)−H bond cleavage but also to control the stereochemical outcome of the carbocyclization as confirmed by the DFT calculations. Dihydropyran and tetrahydropyridine derivatives with *cis*-1,4-disubstitution were obtained in high diastereoselectivity. The studies on the kinetic isotope effects, both in competition and in parallel experiments show that the initial allenic C(sp^3)−H bond cleavage is the first irreversible step and also the rate-limiting step as confirmed by the DFT calculations. The second chiral center in the product was successfully induced by the preformed chiral center in the dienallene, which was obtained via enzymatic kinetic resolution. This methodology provides a novel synthesis of *cis*-1,4-disubstituted six-membered heterocycles, with potential applications in the synthesis of natural products and pharmacologically active substances.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13700.

Additional experimental results and procedures and characterization data (NMR, GC, and HPLC spectra, structures), kinetic isotope effect experiments, computational methods, absolute energies, Cartesian coordinates) (PDF)

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AUTHOR INFORMATION

Corresponding Authors

Can Zhu − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;* orcid.org/0000-0001-6604-6173; Email: zhucaner@gmail.com

Fahmi Himo − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;* orcid.org/0000-0002-1012-5611; Email: fahmi.himo@su.se

Jan-E. Bäckvall − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden; Department of Natural Sciences, Mid Sweden University, SE-851 79 Sundsvall, Sweden;* orcid.org/0000-0001-8462-4176; Email: jeb@organ.su.se

Authors

Jie Liu − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;* orcid.org/0000-0002-3105-4840

Binh Khanh Mai − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.9b13700

Author Contributions

[#]C. Zhu and J. Liu contributed equally to this work.

Notes

The authors declare no competing financial interest.

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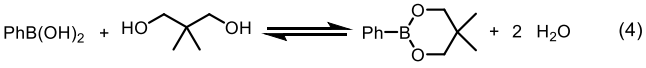
(19) There is an equilibrium between $PhB(OH)_2$ and the corresponding neopentyl glycol boronic ester (eq 4).)



Addition of water can promote hydrolysis of this ester toward the formation of $PhB(OH)_2$, therefore increasing the reaction rate and yield of the product. For a similar effect by water see: Bartholomeyzik, T.; Pendrill, R.; Lihammar, R.; Jiang, T.; Widmalm, G.; Bäckvall, J.-E. Kinetics and Mechanism of the Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes. *J. Am. Chem. Soc.* **2018**, *140*, 298−309.

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(22) It is likely that some C−H bond cleavage by Pd(II) occurs at the chiral center during carbocyclization. Since we were not able to determine the ee value of the product (*S*)-**1a** by chiral GC or HPLC, we cannot rule out that some erosion of ee also occurs in the first step.

(23) In the reaction of enantioenriched substrate (*S*)-**1a** (99% ee) to give (*R*,*S*)-**3a**, a greater ee erosion occurs when using the Co/Pd system of Scheme 4. In this case only 81% ee of the product (*R*,*S*)-**3a** was obtained from enantioenriched substrate (*S*)-**5a**, with similar yield (71% yield) and diastereoselectivity (d.r. 18:1).

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(29) We also calculated the eight-membered TS for the allenic C−H bond cleavage, in which the other acetate oxygen is involved. This TS is calculated to be 2.5 kcal/mol higher in energy than **TS-1**. An agostic interaction, which occurs in **TS-1** but not in the eight-membered TS, is one of the factors that stabilizes **TS-1**. For details, see the Supporting Information, Figure S7.

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(31) In principle transmetalation could occur before carbocyclization. However, the activation barrier for transmetalation from **Int-2** is calculated to be 21.0 kcal/mol relative to **Int-2**, which is 5.3 kcal/mol higher in energy than **TS-2c**. Moreover, transmetalation from **Int-3** has an even higher barrier, 10.5 kcal/mol higher than the

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J. Am. Chem. Soc. 2020, 142, 5751−5759

transmetalation from **Int-2**. Thus, the DFT results support that the carbocylization step occurs before transmetalation.

(32) The β-H elimination products were not observed in the experiments. The DFT calculations show that alkene complexation in **Int-4c** is stabilized by the olefin coordination to Pd. The *trans* relationship between Pd and H would disfavor the β-H elimination process. As a result, a fast trapping of **Int-4c** by PhBneo occurs and generates the corresponding cyclization product.

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