Asymmetric Catalysis

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A Palladium/Chiral Amine Co-catalyzed Enantioselective Dynamic Cascade Reaction: Synthesis of Polysubstituted Carbocycles with a Quaternary Carbon Stereocenter

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Domino and cascade reactions that give access to multiple C–C bonds and multiple contiguous stereocenters with high chemo- and stereoselectivity are important for chemical synthesis and are performed in nature by multi-enzymatic pathways.[1] Cascade reactions enable the synthesis of complex molecules in a minimal number of synthetic steps and with lower amounts of waste and solvents (green chemistry).[2] Catalytic asymmetric cascade transformations are most commonly catalyzed by single metal complexes.[3] However, recently the use of organic catalysts has resulted in important advances in this research field.[4]

The concept of using a transition metal catalyst together with a metal-free catalyst in one flask ("organo/metal cooperative catalysis") is gaining increasing interest.[5–9] The reactivity and advantages of both metal and organic catalyst systems are combined and thereby can result in unique reactivity. However, this research field is still in its infancy with challenges such as incompatibility between the transition metal and organocatalyst (e.g. catalyst inhibition and different optimal reaction conditions). In 2006, we disclosed the merging of transition metal and aminocatalysis for the α-allylic alkylation of aldehydes.[6a] Since disclosure of this synergistic catalysis strategy there has been increasing number of reports on the development of the concept of organo/metal cooperative catalysis.[5–8]

The construction of quaternary carbon stereocenters with high enantioselectivity is important and challenging goal in organic synthesis.[10] In this context, new methods for the catalytic construction of polysubstituted carbocycles with contiguous stereocenters, including an all-carbon stereocenter, are desirable but difficult to achieve. Based on our previous research on organo/metal cooperative catalysis,[6] we envisioned a novel dynamic catalytic asymmetric Michael/α-allylic alkylation cascade reaction between compounds **1** and enals **2** mediated by a combination of Pd and chiral amine **5** catalysts (Scheme 1). Thus, initial reversible conjugate addition via an iminium intermediate **I** would give the corresponding enamine intermediate **II**, which upon hydrolysis would provide Michael adduct **3**. This process is reversible, however, oxidative addition of the Pd catalyst to intermediate **II** would generate π-allyl intermediate **III**, ready for intramolecular nucleophilic stereoselective attack by its enamine moiety. Subsequent C–C bond formation, hydrolysis, and protonation would deliver polysubstituted carbocycles **4** as well as regenerate the amine and Pd catalysts. However, there are a few main challenges to address. For example, chemoselectivity issues, as substrates **1** could undergo a Pd-catalyzed intermolecular Tsuji–Trost reaction, polymerization, or N-alkylation with amine **5** instead of the desired pathway.[11] We also know from our previous research that the Pd/amine co-catalyzed conjugate additions can deliver racemic Michael products.[6g–i] Thus, the reaction via enamine intermediate **II** has to occur at a higher rate compared to the that via **IIa**. Moreover, the equilibration between *ent*-**3** and **3** (racemization) must be faster than the carbocyclization for this reaction to become a dynamic kinetic transformation (DYKAT).[12] If no racemization occurred, the overall process would have a maximum theoretical yield of 50% (kinetic resolution). With respect to the construction of carbocycles **4** ($E \neq E^1$), the cascade transformation is also complex and difficult to control as Michael adducts (**3** having 2 stereocenters) are formed as four stereoisomers. Herein, we disclose a novel highly enantioselective dynamic Michael/α-allylic alkylation cascade transformation that gives polysubstituted cyclopentanes and cyclohexanes, which have a quaternary carbon stereocenter, in high yields with excellent enantiomeric ratios (99.5:0.5→99:0.5 e.r.).

Initially we investigated the dynamic cascade transformation between (*Z*)-**1a** and cinnamic aldehyde **2a** under different reaction conditions in the presence of chiral amines **5** and different Pd co-catalysts. Representative results are shown in Table 1. To our delight, the corresponding cyclopentane **4a** was formed in good conversion with high d.r. (91:9) and e.r. (up to 98:2) when chiral amine **5a**[13] (20 mol%) was used in combination with $[Pd(PPh_3)_4]$ (5 mol%) in toluene and acetonitrile (entries 3 and 4). The Michael intermediate **3a** was formed as a racemate (**3a**/*ent*-**3a** 50:50 e.r.). Thus, the

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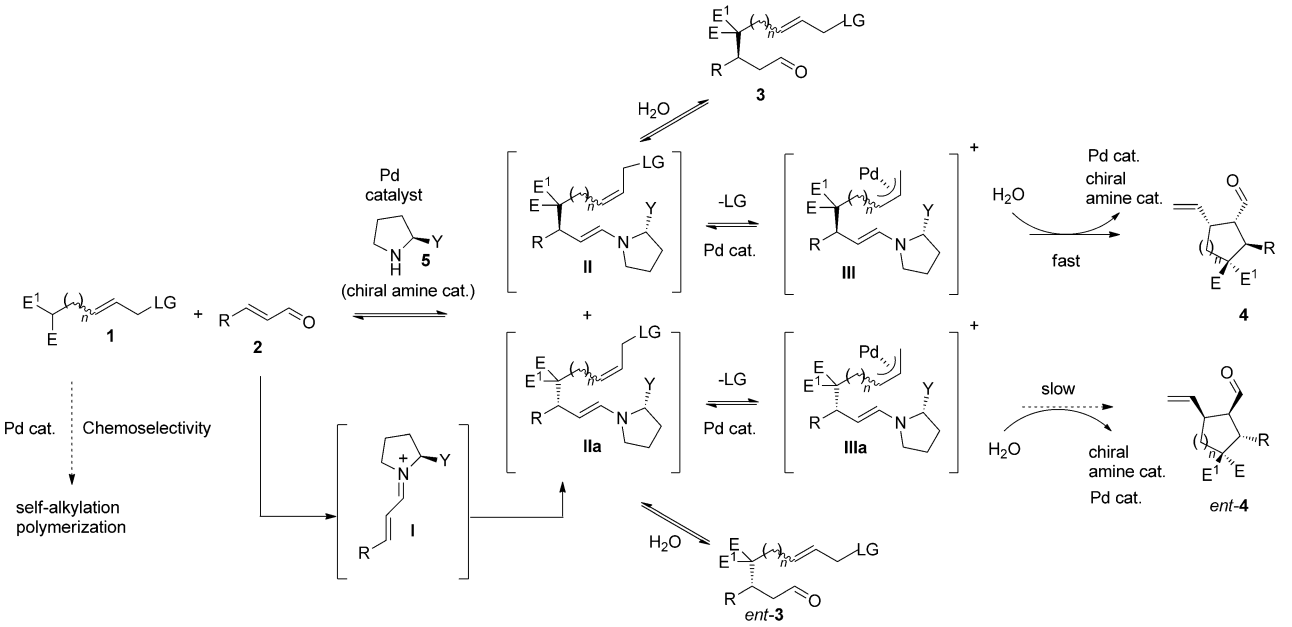
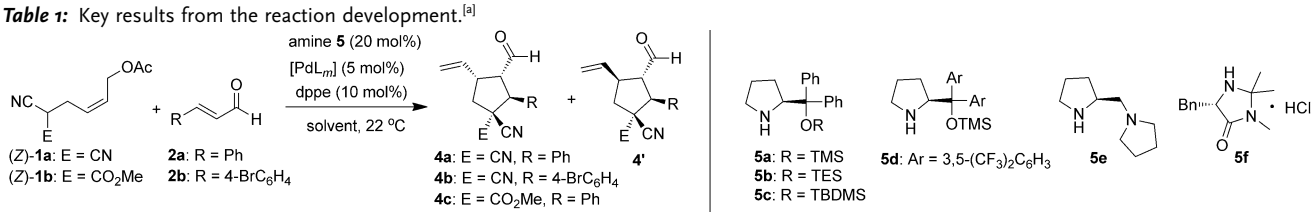


Scheme 1. Pd/chiral amine co-catalytic dynamic cascade reaction between **1** and **2**. Only two of the possible four stereoisomers of **3** are shown. LG = Leaving group.

Table 1: Key results from the reaction development.[a]



Entry	5	Pd cat.	Solv.	4	T [h]	Conv. [%][b]	d.r.[b]	e.r.[c]	Entry	5	Pd cat.	Solv.	4	T [h]	Conv. [%][b]	d.r.[b]	e.r.[c]
1[d]	**5a**	–	CH_3CN	**4a**	48	57[e]	n.d.	n.d.	11	**5e**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	93	96:4	25:75
2	–	$[Pd_2(dba)_3]$	CH_3CN	**4a**	48	0	–	–	12	**5f**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	22[e]	n.d.	n.d.
3[d]	**5a**	$[Pd(PPh_3)_4]$	toluene	**4a**	17	55	91:9	98:2	13[f]	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	70[g]	96:4	>99.5:0.5
4[d]	**5a**	$[Pd(PPh_3)_4]$	CH_3CN	**4a**	8	62	91:9	97:3	14[f]	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4b**[g]	5	70[g]	85:15	>99.5:0.5
5	**5a**	$[Pd(OAc)_2]$	toluene	**4a**	22	72[e]	n.d.	n.d.	15[d,i]	**5a**	$[Pd(PPh_3)_4]$	CH_3CN	**4c**	24	95	84:16	98.5:2.5
6	**5a**	$[Pd_2(dba)_3]$	toluene	**4a**	8	95	91:9	>99.5:0.5	16[i]	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4c**	19	85	91:9	>99.5:0.5
7	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	90	96:4	>99.5:0.5	17[i]	**5b**	$[Pd_2(dba)_3]$	CH_3CN	**4c**	24	69	90:10	99.5:0.5
8	**5b**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	50	97:3	99:1	18[j]	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4c**	19	95	93:7	>99.5:0.5
9	**5c**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	27	91:9	98:2	19[j,k]	**5b**	$[Pd_2(dba)_3]$	CH_3CN	**4c**	24	58	92:8	>99.5:0.5
10	**5d**	$[Pd_2(dba)_3]$	CH_3CN	**4a**	5	14	91:9	92:8	20[l]	**5a**	$[Pd_2(dba)_3]$	CH_3CN	**4c**	24	91	95:5	>99.5:0.5

[a] The reaction was performed with (*Z*)-**1a** (0.15 mmol) and **2a** (0.1 mmol) in solvent (0.2 mL). [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Without dppe. [e] Conversion into the corresponding Michael adducts **3a** with 50:50 e.r. [f] The reaction was performed using (*Z*)-**1a** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL). [g] Yield of the isolated product. [h] The reaction was performed with *p*-bromocinnamic aldehyde **2b**. [i] The reaction was performed with (*Z*)-**1b** (0.15 mmol) and **2a** (0.1 mmol) in CH_3CN (0.2 mL). [j] The reaction was performed with (*Z*)-**1b** (0.15 mmol) and **2a** (0.1 mmol) in CH_3CN (0.5 mL). [k] 10 mol% of **5a**. [l] Reaction with (*E*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL). dba = dibenzylideneacetone, dppe = 1, 2-bis(diphenylphoshino)ethane, n.d. = not determined, TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

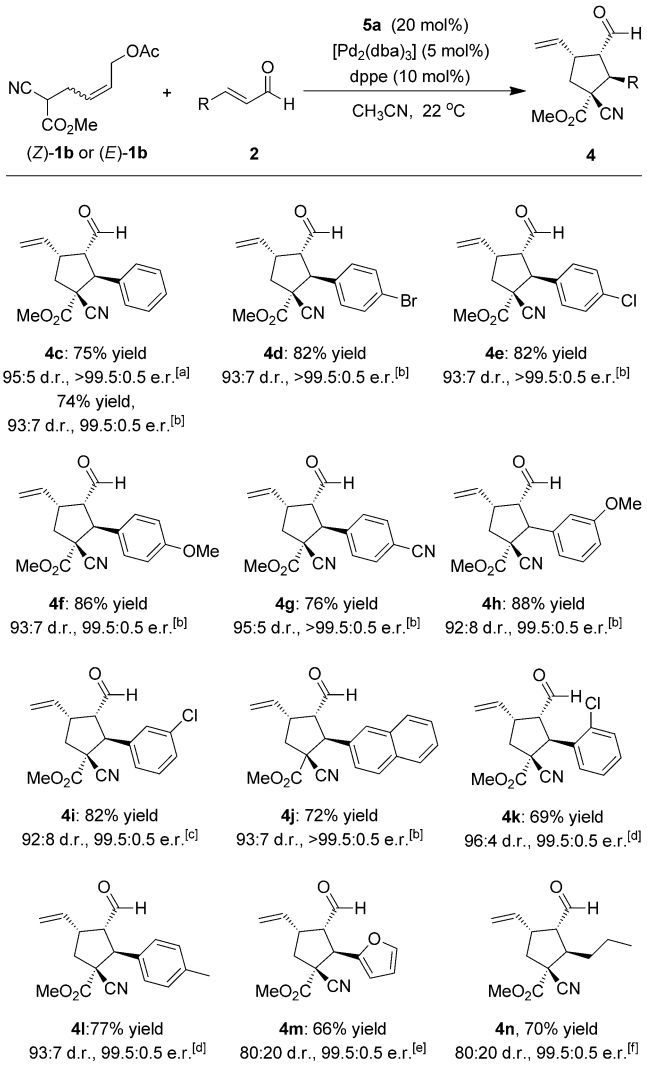
cascade reactions proceed through a DYKAT process.[12] The reactions performed with only chiral amine **5a** as the catalyst gave the corresponding Michael adducts **3a** as a racemate (entry 1). In the presence of only the Pd catalyst no desired product was obtained, only some product from the intramolecular Tsuji–Trost reaction of **1** was obtained (entry 2). Notably, when $[Pd_2(dba)_3]$ was used in combination with 1,2-bis(diphenylphosphino)ethane (dppe), as the ligand, both the conversion and the enantioselectivity of the transformation increased (**4a**: >90% conv., >99.5:0.5 e.r.; entries 6 and 7). The highest diastereoselectivity was obtained with CH_3CN as solvent (96:4 d.r.; entry 7). We next tested several chiral amines **5** under these reaction conditions (entries 7–12). The highest stereoselectivity was obtained when **5a** and **5b** were used as the co-catalysts. Moreover, cyclopentanes **4a** and **4b** were isolated in high yield with excellent e.r. when the

reaction scale was doubled (entries 13 and 14). Next, the cascade transformation between (*Z*)-**1b** and **2a** was investigated (entries 15–20). It is noteworthy that the reactions were highly stereoselective and the corresponding cyclopentane **4c** having a quaternary carbon stereocenter was formed with high e.r.. In addition, the highest efficiency was achieved when the concentration of the enal **2a** component was 0.2 M (**4c**: 95% conv., 93:7 d.r. and >99.5:0.5 e.r.; entry 18). When (*E*)-**1b** was used the diastereoselectivity (95:5 d.r.) of the co-catalytic cascade reaction improved while the excellent enantioselectivity (>99.5:0.5 e.r.; entry 20) was maintained. The stereoselectivity was not affected when the catalyst loading of the chiral amine **5a** was lowered, however, the reaction rate slightly decreased (entry 18 vs. 19). The Michael intermediates **3c** and **3c'**, were formed in 65:35 ratio during the reaction and were racemic. Thus, the reaction is a DYKAT of type IV.[12] With these results in hand, we investigated the co-catalytic dynamic asymmetric cascade reaction between **1b** and enals **2** with **5a**, as the amine catalyst, in combination with $[Pd_2(dba)_3]$ and dppe in CH_3CN (Scheme 2).

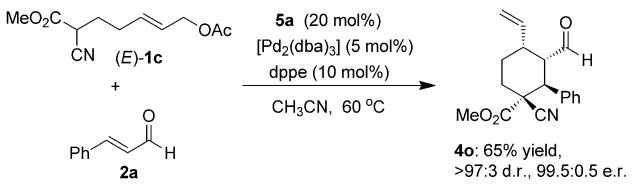
Both β-aryl and β-alkyl substituted enals **2** could be used as substrates to give the corresponding cyclopentanes **4c**–**4n** in high yield, d.r., and e.r. (99.5:0.5 e.r.–>99.5:0.5). We next investigated the transformation between (*E*)-**1c** and enal **2a** using the same co-catalyst system at 60 °C; this reaction had an increased rate (Scheme 3). Gratifying the transformation gave cyclohexane **4o** in 65% yield as a nearly enantiopure isomer (>97:3 d.r. and 99.5:0.5 e.r.). Thus, the co-catalytic reaction is both an entry to highly functionalized 5- and 6-membered carbocycles **4** with a quaternary carbon stereocenter.

The absolute and relative configuration of the chiral carbocycles **4** was determined by single-crystal X-ray analysis of **4k** (Figure 1).[14] The relative stereochemistry of the minor diastereoisomer was determined by NOE experiments of **6d′** (obtained by reduction of **4d′**, see the Supporting Information).

To further investigate the reaction mechanism, HRMS analysis was performed on the reaction mixtures.[15] HRMS determined the presence of iminium intermediates **I**, **II**, **III**, and **IV** (Scheme 4). We also confirmed that the Michael intermediates **3** derived from **1b** were formed as racemates (50:50 e.r.) with low d.r. under the investigated reaction conditions. Thus, the overall cascade reaction can be classified as a DYKAT of type IV.[12] We also investigated the sequential catalyst addition approach by first synthesizing the Michael adduct **3c** with **5a** as the catalyst in acetonitrile. The Michael adduct was formed as a racemic compound with 60:40 d.r. (**3c**/**3c′**). The subsequent addition of $[Pd_2(dba)_3]$ and dppe resulted in the formation of **4c** in 45% yield after 40 h with 91:9 d.r. and 98:2 e.r. together with the remaining starting cinnamic aldehyde **2a**. In comparison, **4c** was isolated in 74% yield with 93:7 d.r. and 99:0.5 e.r. with only trace amounts of cinnamic aldehyde **2a**, when our optimized one-pot procedure was used (Scheme 2). Thus, a significant synergistic effect is achieved when performing the one-pot operation with the two co-catalysts present from the beginning. Based on the absolute configurations and our experimental results,



Scheme 2. [a] Reactions performed using (*E*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 24 h. See the Supporting Information for details. [b] Using (*Z*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 24 h. [c] Using (*Z*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 23 h. [d] Using (*Z*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 28 h. [e] Using (*Z*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 30 h. [f] Using (*Z*)-**1b** (0.3 mmol) and **2a** (0.2 mmol) in CH_3CN (1.0 mL) for 60 h at 4 °C. The e.r. was determined by GC analysis using a chiral stationary phase.



Scheme 3. Pd/chiral amine co-catalyzed asymmetric synthesis of cyclohexane **4o**.

we propose the following mechanism. Thus, initial reversible conjugate addition of **1b** or **1c** to the in situ generated iminium intermediate **I** results in an initial rapid equilibration between the four stereoisomers **3**, *ent*-**3**, **3′**, and *ent*-**3′** via the

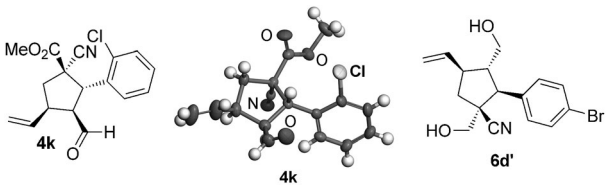


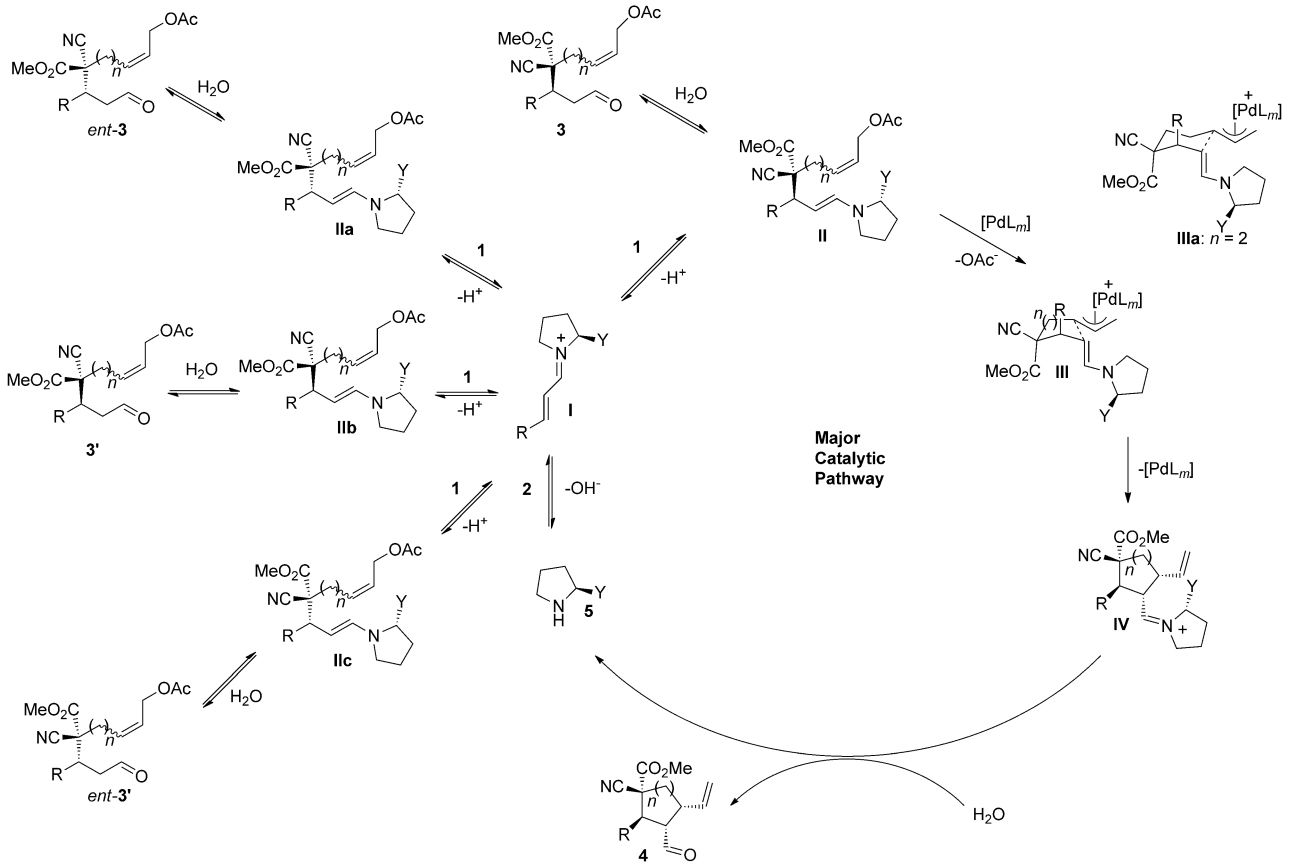
Figure 1. Ortep diagram of crystal **4k** (with thermal ellipsoids set at 90% probability) and structure of **6d'**.

corresponding enamine intermediates (**II**–**IIc**). Next, oxidative addition of the Pd catalyst occurs predominantly to enamine intermediate **II** and results in the corresponding electrophilic π-allyl palladium complex **III**. Subsequent irreversible stereoselective intermolecular nucleophilic *Si*-facial attack by the chiral enamine (via a Zimmerman–Traxler-type[16] transition state **IIIa** when $n=2$), followed by protonation and reductive elimination generates iminium intermediate **IV** and releases the Pd catalyst. Next, hydrolysis of **IV** gives carbocycle **4** and regenerates the chiral amine catalyst **5**. We believe that the reaction pathway via enamine **II** is much faster compared to those via **IIa**–**IIc,** because transition state **III** is favored owing to less steric repulsion between the equatorial CN and the axial R group, whereas for in the transition states for the pathways via **IIa**–**IIc** the bulkier ester group would be in closer proximity to the R group.

In summary, we have designed, developed, and used a conceptually novel highly chemo- and enantioselective Pd/chiral amine co-catalytic dynamic kinetic asymmetric cascade process for the concise synthesis of polysubstituted cyclopentane and cyclohexane products from structurally simple starting materials. Mechanistically, the co-catalytic reaction is a dynamic kinetic asymmetric transformation that proceeds through a Michael/α-allylic alkylation reaction sequence and generates four stereocenters in a one-pot operation with excellent enantioselectivity (99.5:0.5–>99.5:0.5 e.r.). Notably, the co-catalytic dynamic cascade reaction can be applied for the synthesis of carbocycles with an all-carbon stereocenter with up to >99.5:0.5 e.r. We believe that this co-catalysis cascade concept will be additionally explored and utilized for the synthesis of highly functionalized molecules. Research towards these goals will be undertaken in due course.

Experimental Section

Representative procedure: An oven-dried vial (8 mL) equipped with a magnetic stir bar was charged with $[Pd_2(dba)_3]\cdot CHCl_3$ (10.4 mg, 0.01 mmol, 5 mol%), and 1,2-bis(diphenylphoshino)ethane (dppe) (8.0 mg, 0.02 mmol, 10 mol%), fitted with a septum, sealed and flushed with N_2 for 10 min. Next, anhydrous CH_3CN (300 μL) was added and the resulting mixture was stirred at room temperature for 7 min. In parallel, an oven-dried vial (8 mL) was charged with catalyst **5a** (13.0 mg, 0.04 mmol, 20 mol%) and sealed. After flushing with N_2, allyl acetate **1** (0.3 mmol, 1.5 equiv in CH_3CN (300 μL)) was added followed by enal **2** (0.2 mmol, in CH_3CN (300 μL)) under N_2 atmosphere. After stirring at room temperature for 7 min, the resulting mixture was transferred to the vial containing the mixture



Scheme 4. Proposed catalytic cycle.

of palladium catalyst and ligand by a syringe. More anhydrous CH_3CN was added to transfer all the solution and reach a final volume of 1.0 mL ([**2**] = 0.2 M). Next, the mixture was stirred at room temperature for the time shown in Scheme 2. The conversion and diastereomeric ratio were monitored by ^1H NMR spectroscopy of the reaction mixture. Upon completion, the mixture was directly loaded on a silica-gel column purified by flash chromatography (petroleum ether/EtOAc mixtures) to give the pure products **4** as colorless or yellowish oils.

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