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Highly Enantioselective Control of Dynamic Cascade Transformations by Dual Catalysis: Asymmetric Synthesis of Polysubstituted Spirocyclic Oxindoles

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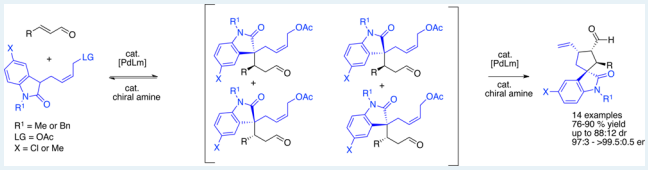
Supporting Information

ABSTRACT: The highly enantioselective (up to >99.5:0.5 er) synthesis of polysubstituted spirocyclic oxindoles with four new contiguous stereocenters, including the spiro all-carbon quaternary center, is disclosed. It is accomplished by the highly stereoselective control of a dynamic conjugate/intramolecular allylic alkylation relay sequence based on the synergistic cooperation of metal and chiral amine catalysts in which the careful selection of organic ligand, metal complex, and chiral amine is essential. The intramolecular C−C bond-forming step occurred only when both the metal and chiral amine catalysts were present.



KEYWORDS: *asymmetric cocatalysis, α,β-unsaturated aldehydes, dynamic transformations, polysubstituted, spirocyclic oxindoles, all-carbon quaternary stereocenter*

The biological activity and structural complex architectures found in nature have inspired chemists to design strategies for assembling challenging three-dimensional structures discovered in natural products.[1] Despite the tremendous advances in asymmetric synthesis technology, the creation of strained polycyclic structures and the generation of all-carbon quaternary stereocenters[2] are very difficult and need further development. Particularly intriguing is the spirocyclic oxindole structural motif,[3] which is present in a large number of natural and unnatural compounds with important biological activities, including potential treatment of malaria[3c] (Figure 1). This has led to the elegant development of structure-based design and diversity-oriented synthesis (DOS) for the preparation of spirocyclic oxindole derivatives.[4] However, because of their structural complexity described vide supra, it is a great challenge to do this in an asymmetric fashion. A few methods have recently been disclosed, which include cycloaddition processes and the intramolecular Heck reaction.[5]

Domino and cascade reactions are powerful methodologies for rapidly achieving molecular complexity and include "green chemistry" parameters.[6−9] In this context, sophisticated metal-free catalytic technologies have recently been developed for the asymmetric synthesis of spirocyclic oxindoles.[10]

The concept of using a transition metal catalyst together with an organocatalyst in one flask has begun to emerge as a new tool in organic synthesis.[11−15] In 2006, we discovered that transition metal catalysis can be merged with aminocatalysis.[12a] Although recently, several important advances have been made,[12−14] this research area is only in its infancy and faces challenges such as incompatibility between the transition metal/organocatalyst and catalyst inhibition.[12−14] Thus, there are very few reports on the synthesis of spirocyclic oxindoles using "organo/metal cooperative catalysis" and all of them include the formation of spirocyclic cyclopentene oxindoles as the key transformation.[16]

Inspired by the vide-supra-described challenges and our retrocatalytic analysis,[12] we envisioned a cocatalytic dynamic asymmetric Michael/α-allylic alkylation cascade relay sequence between oxindoles **1** and enals **2** using a simple combination of Pd and chiral amine **5** catalysts for the construction of polysubstituted spirocyclic oxindoles **4** with the all-carbon stereocenter (Scheme 1). However, there are chemoselectivity issues, such as the Pd-catalyzed intermolecular Tsuji−Trost reaction of **1** and polymerization or N-alkylation of the amine catalyst **5** instead of the preferred pathway.[17] Furthermore, our previous research has shown that the Pd/amine-cocatalyzed cascade transformations are reversible and can deliver a mixture of four stereoisomers of Michael adducts **3**.[12h] Thus, to get a predominant stereoisomer out of the possible 16, the dual catalyst system has to first react via enamine intermediate **II** at a higher rate as compared with all the other pathways via **IIa**−**IIc**, followed by oxidative addition of the Pd catalyst to generate π-allyl intermediate **III**. Next, a highly stereoselective intramolecular nucleophilic attack by its enamine moiety, followed

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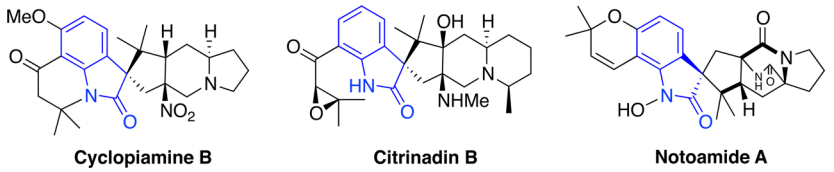
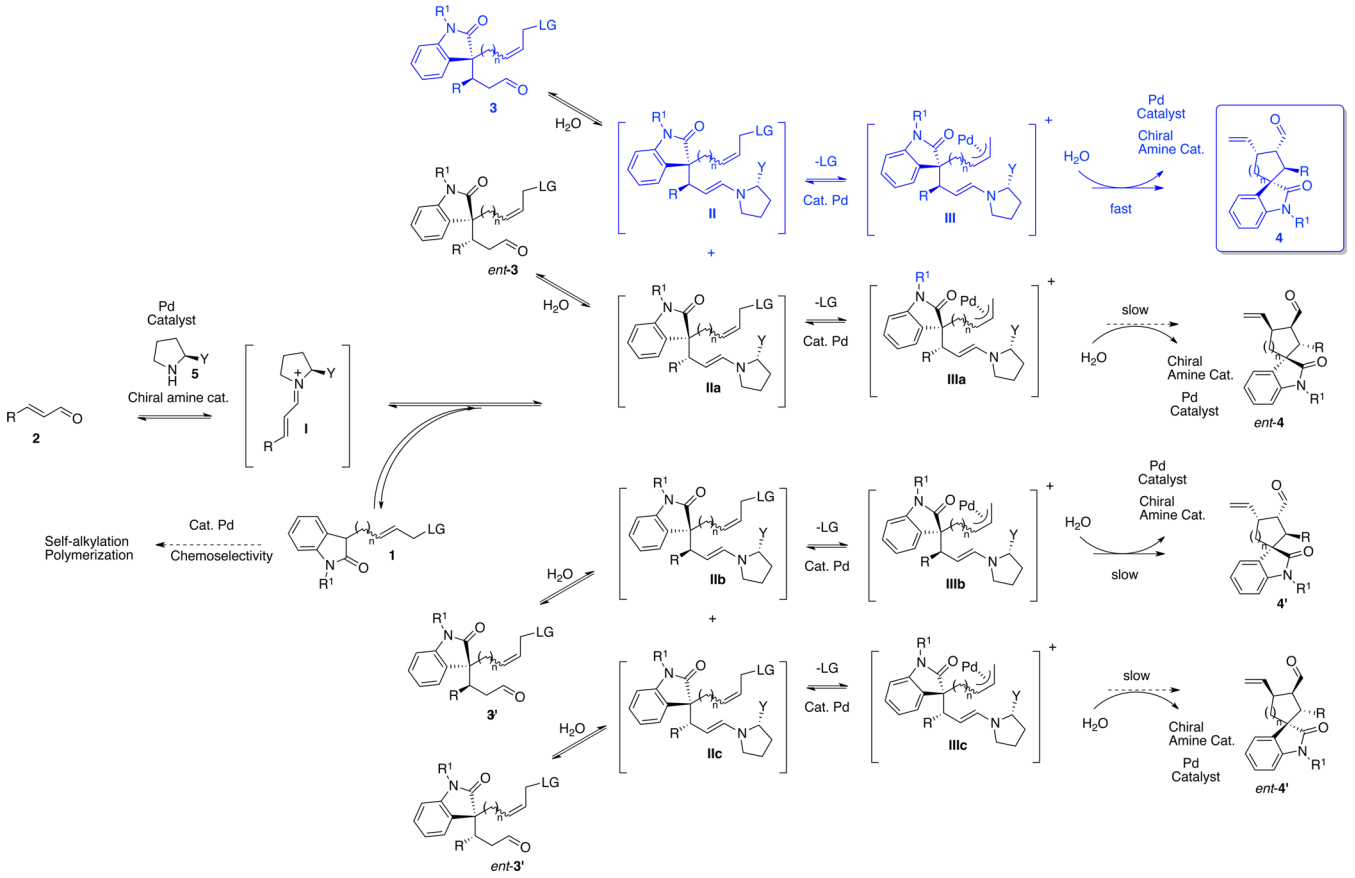


Figure 1. Examples of natural products containing the spirocyclopentane oxindole scaffold.

Scheme 1. Pd/Chiral Amine Co-Catalytic Dynamic Cascade Transformation between 1 and 2[a]



[a]LG = Leaving group. Only 4 of the possible 16 stereoisomers of **4** are shown.

by reductive elimination and hydrolysis, will deliver the spirocyclic oxindole **4** as well as regenerate the amine and Pd catalysts, respectively. Notably, the equilibration between the stereoisomers *ent*-**3**, *ent*-**3**′, **3**′, and **3** (eperimization, racemization) must occur because otherwise, the maximum theoretical yield of **4** and **4**′ would be 25%, respectively (kinetic resolution).[18]

Here, we disclose that highly enantioselective control of dynamic cascade relay sequences can be employed for the synthesis of polysubstituted spirocyclic oxindoles **4** in high yields and enantiomeric ratios (98.5:1.5 to >99:0.5) employing a simple dual catalyst system.

We first began to investigate the dynamic cascade transformation between oxindoles (*Z*)-**1**[19] and cinnamic aldehyde **2a** using different conditions in the presence of chiral amines **5** and different in-situ-generated Pd cocatalysts. Representative results are shown in Table 1.

To our delight, the extensive screening revealed that the corresponding spirocyclic oxindole **4a** was formed in good conversion with good dr and high er (98.5:1.5) when chiral amine **5a**[20] (20 mol %) was used in combination with $Pd_2(dba)_3$ and triarylphosphine **6b** or **6d** as the ligands, respectively, in acetonitrile (entries 9 and 11).[21] In comparison, when $Pd_2(dba)_3$ was used in combination with ligand **6a**, both the conversion and the enantioselectivity of the transformation increased (**4a**: 75% conversion, 99:1 er; entry 5); however, the dr decreased. Gratifyingly, when increasing the size of the N-protective group of the oxindole from methyl ((*Z*)-**1a**) to benzyl ((*Z*)-**1b**) using **5a** as the amine catalyst in combination with $Pd_2(dba)_3$ and ligand **6d**, both the conversion and the enantioselectivity of the transformation increased while keeping a good dr (**4b**: 80% conversion, >99.5:0.5 er, 64:36 dr; entry 16). It is noteworthy that when performing this condition at 40 °C, both the efficiency and diastereoselectivity of the transformation was further improved (**4b**: >95% conversion, 99.5:0.5 er, 77:23 dr; entry 18). The reaction performed with only the chiral amine **5a** as the catalyst gave the corresponding Michael adducts **3a** and **3a**′ in 57:43 ratio (entry 1). The reaction with only the Pd catalyst led to no product formation and only some intramolecular Tsuji−Trost reaction of **1** (entry 2). We also probed other chiral amines **5** under this reaction condition (entries 21−23); however, the highest stereo-

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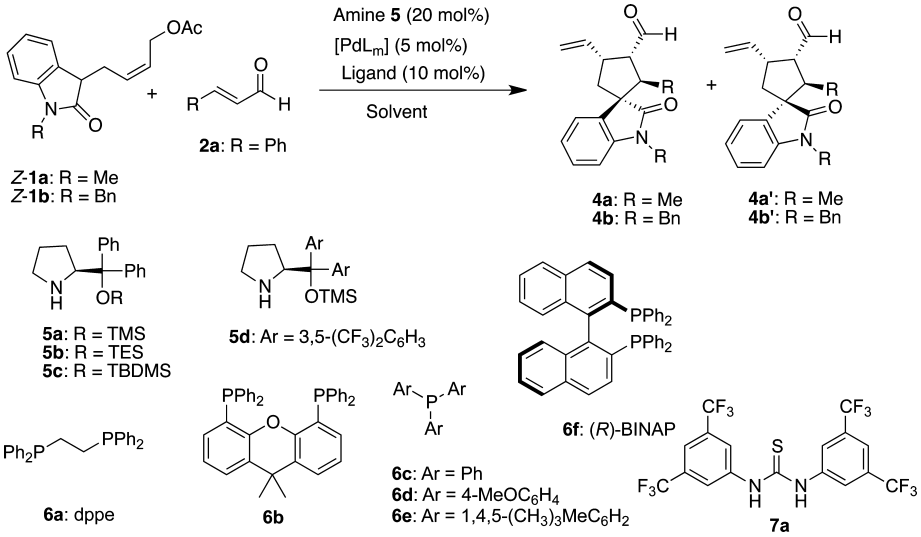
Table 1. Key results from the reaction development.[a]



entry	amine	cat. Pd	ligand	solv.	prod.	t (h)	T (°C)	conv. (%)[b]	dr[b]	er[c]	er[d]
1	**5a**			CH_3CN	**4b**	12	40	0[e]			
2		$Pd_2(dba)_3$	**6a**	CH_3CN	**4b**	48	22	0			
3	**5a**	$Pd(PPh_3)_4$		toluene	**4a**	60	22	>95	58:42	98:2	90.5:9.5
4	**5a**	$Pd(PPh_3)_4$		CH_3CN	**4a**	65	22	20	57:43	n.d.	n.d.
5	**5a**	$Pd_2(dba)_3$	**6a**	CH_3CN	**4a**	38	22	75	58:42	99:1	95:5
6	**5a**	$Pd_2(dba)_3$	**6a**	CH_3CN	**4a**	104	−22	75	58:42	n.d.	n.d.
7	**5a**	$Pd_2(dba)_3$	**6a**	CH_3CN	**4a**	20	60	81	57:43	96:4	63:37
8	**5a**[f]	$Pd_2(dba)_3$	**6a**	CH_3CN	**4a**	75	22	<1	n.d.	n.d.	n.d.
9	**5a**	$Pd_2(dba)_3$	**6b**	CH_3CN	**4a**	38	22	68	67:33	98.5:1.5	98:2
10	**5a**	$Pd_2(dba)_3$	**6c**	CH_3CN	**4a**	72	22	22	57:43	>89.5:0.5	94:6
11	**5a**	**$Pd_2(dba)_3$**	**6d**	**CH_3CN**	**4a**	**36**	**22**	**59**	**74:26**	**98.5:1.5**	**94:6**
12	**5a**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4a**	24	40	54	64:36	97.5:2.5	96:4
13	**5a**	$Pd_2(dba)_3$	**6e**	CH_3CN	**4a**	80	22	63	50:50	99:1	>99.5:0.5
14	**5a**	$Pd_2(dba)_3$	**6f**	CH_3CN	**4a**	48	22	<10	50:50	n.d.	n.d.
15	**5a**	$Pd_2(dba)_3$	**6d**	toluene	**4a**	36	22	<5	n.d.	n.d.	n.d.
16	**5a**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	24	22	80	64:36	>89.5:0.5	99:1
17	**5a**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	4	60	>95	73:27	98.5:1.5	94:6
18	**5a**	$Pd_2(dba)_3$	**6d**	**CH_3CN**	**4b**	**12**	**40**	**>95**	**77:23**	**99.5:0.5**	**98:2**
19	**5a**[g]	**$Pd_2(dba)_3$**	**6d**	CH_3CN	**4b**	72	40	42	58:42	99:1	98:2
20	**5a**[h]	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	20	40	83	70:30	99.5:0.5	98:2
21	**5b**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	12	40	85	75:25	99.5:0.5	98:2
22	**5c**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	12	40	83	76:24	99.5:0.5	98:2
23	**5d**	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	12	60	<10	n.d.	n.d.	n.d.
24	**5a**	$Pd_2(dba)_3$	**6d**	DMF	**4b**	12	40	67	74:26	96:4	93:7
25	**5a**	$Pd_2(dba)_3$	**6d**	THF	**4b**	12	40	>85	71:29	96.5:3.5	88:12
26	**5a**	$Pd_2(dba)_3$	**6d**	CH2CI2	**4b**	12	40	61	56:44	96:4	93:7
27	**5a**	$Pd_2(dba)_3$	**6d**	DMSO	**4b**	12	40	>95	73:27	98:2	90.5:9.5
28	**5a**[i]	$Pd_2(dba)_3$	**6d**	CH_3CN	**4b**	12	40	>95	77:23	99.5:0.5	98:2

[a]The reaction was performed with (*Z*)-**1a** (0.2 mmol) or (*Z*)-**1b** (0.2 mmol) and **2a** (0.1 mmol) in solvent (0.5 mL). [b]Conversion to and Dr of **4** as determined by ^{1}H NMR analysis of the crude reaction mixture. [c]er of **4** as determined by chiral-phase HPLC analysis. [d]er of **4′** as determined by chiral-phase HPLC analysis. [e]66% conversion to the corresponding Michael adducts **3a** and **3a′** in 57:43 ratio. [f]Addition of **7a** (20 mol %). [g]Addition of benzoic acid (20 mol %). [h]Addition of TEA (25 mol %). [i]Reaction performed at the double scale. TMS = trimethylsilyl, TES = triethylsilyl, TBDMS = *tert*-butyldimethylsilyl, dppe =1,2-bis(diphenylphoshino)ethane, dba = dibenzylideneacetone, n.d. = not determined, TEA = triethylamine, Bn = Benzyl.

selectivity was obtained when **5a** was used as the cocatalysts. With these results in hand, we began to investigate the cocatalytic dynamic asymmetric cascade reaction between oxindoles **1b**−**1d** and enals **2** using **5a** as the amine catalyst in combination with $Pd_2(dba)_3$ and **6d** in CH_3CN at 40 °C (Scheme 2).

The cocatalytic dynamic asymmetric cascade reaction exhibited a broad scope and both *β*-aryl- and *β*-alkyl-substituted enals **2** could be used as substrates. It is noteworthy that the reactions were highly stereoselective and the corresponding polysubstituted spirocyclic oxindoles **4b**-**4n** with their all-carbon quaternary stereocenter were formed in high yields and er's (98.5:1.5 - >99.5:0.5). The dr was good to high in most

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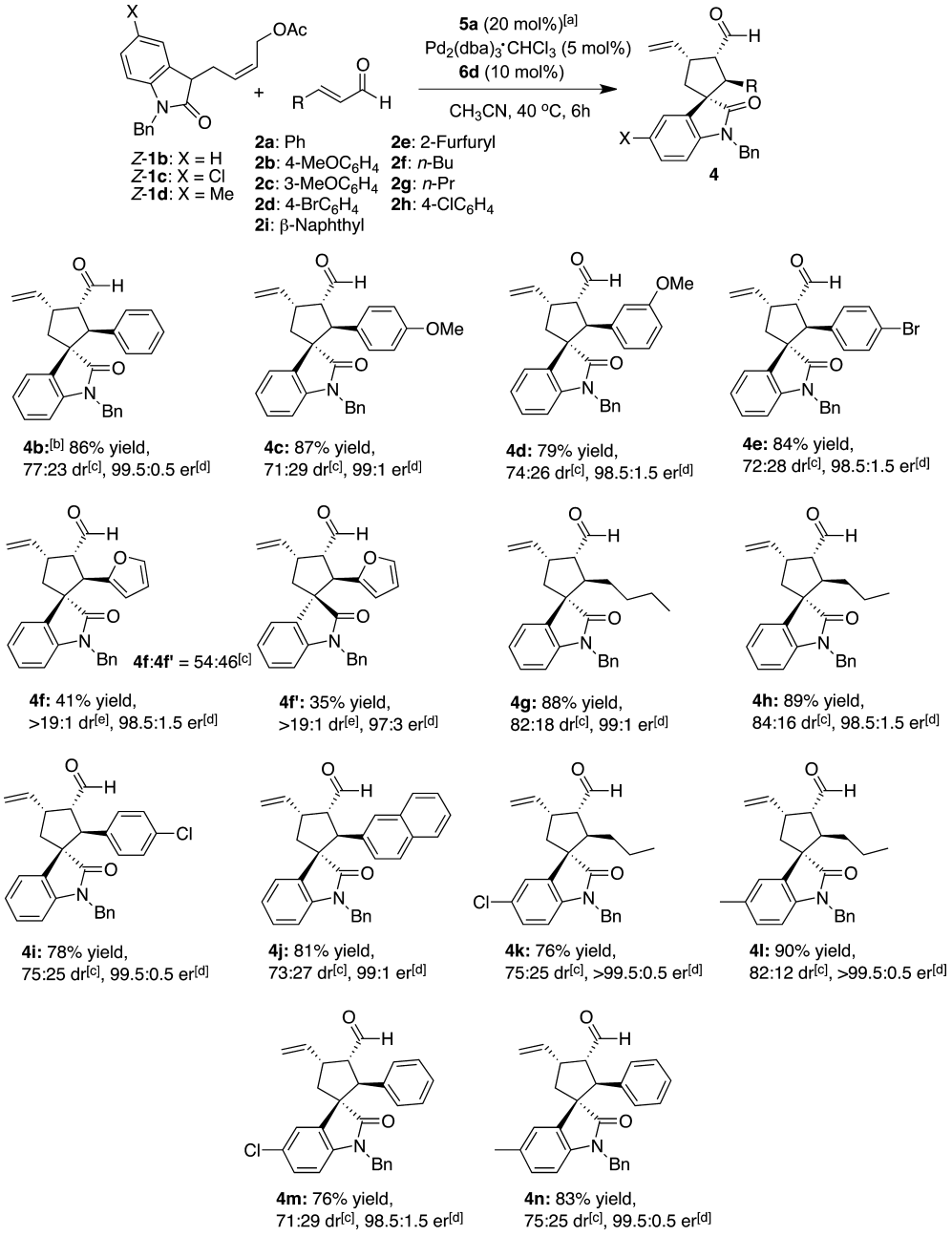
Scheme 2[a]



[a][a] Reactions performed using (*Z*)-**1** (0.3 mmol) and **2** (0.15 mmol) in CH_3CN (1.0 mL) for 6 h. See the Supporting Information for details. [b] Same as [a] but reaction time 12 h. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] determined by chiral-phase HPLC analysis. [e] Determined by ^1H NMR analysis of the isolated pure compound.

cases, demonstrating a faster intramolecular α-allylic alkylation of isomer **3** over **3′** by the dual catalyst system. Only the cascade reaction with the β-furfuryl-substituted enal **2e** provided the corresponding spirocyclic oxindoles **4f** and **4f′** in a 54:46 ratio with high er's (98.5:1.5 and 97:3, respectively). The absolute and relative configuration of the chiral carbocycles **4** was determined by X-ray analysis of (1*S*,2*R*,3*R*,4*S*)-**4i** (Figure 2).[22] The relative stereochemistry of the minor diastereoisomer was determined by NOE experiments of **4d′** (see the SI).

To further establish the reaction mechanism, HRMS analysis was performed on the crude reaction mixtures for the cocatalyzed transformation between oxindole (*Z*)-**1c** and **2g**.[23] The HRMS determined the presence of iminium and enamine intermediates **I**, **II**, and **IV**, respectively (Scheme 3). We also found that the isolated intermediates **3** can undergo retro-Michael reactions to enals **1** in the presence of the dual catalyst system. They were also formed in a significantly lower er as compared with the spirocycles **4**. For example, after 4h, **3b** was formed with 73.5:26.5 er (47% ee) as compared with the >99.5:0.5 er (>99% ee) of **4a**. Moreover, the Michael intermediates **3** did not undergo carbocyclization to **4** without the presence of the chiral amine catalyst **5a**. We also performed a crossover experiment and found that starting with a mixture of Michael adducts **3b**, **3b′**, and 4-Br-cinnamic aldehyde **2d** in the presence of the Pd/chiral amine **5a** system led to the exclusive conversion to spirocyclic oxindole **4e** (67%

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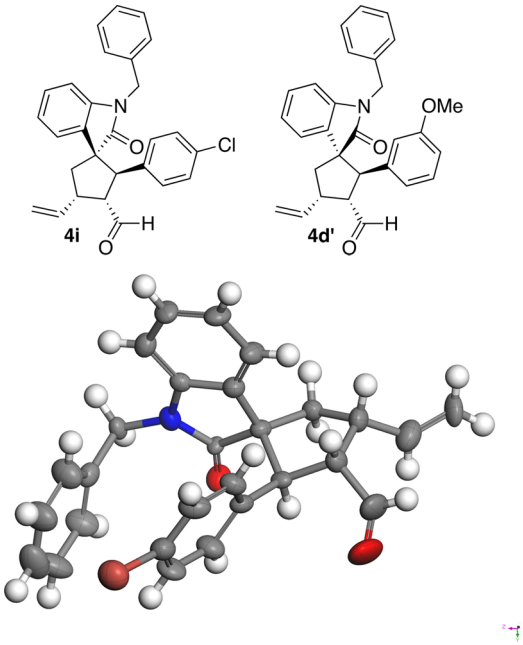
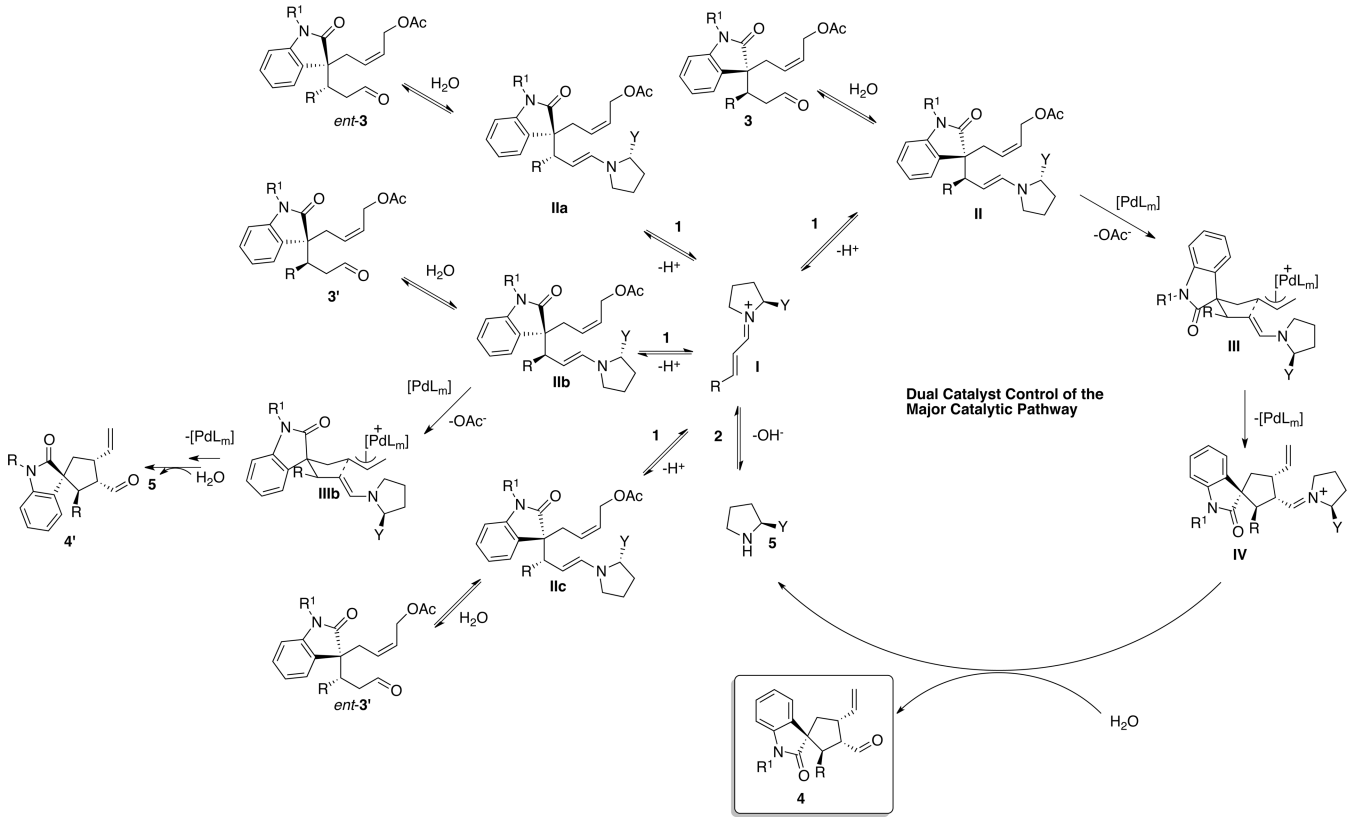


Figure 2. Ortep picture of crystal **4i** and structures **4i** and **4d′**.

conversion, 59:41 dr, 98:2 er) and cinnamic aldehyde **2a** (Scheme 4). It is noteworthy that product **4b** was not formed. Thus, the retro-Michael reaction of **3b** was faster than the intramolecular C−C bond-forming step of **3b**, and subsequent Michael/carbocyclization cascade of **1b** with enal **2d** was favored over **2a**.

The above results demonstrate that the reaction is a dynamic cascade relay process in which the Pd and chiral amine catalyst operate in synergy during the carbocyclization step. However, as compared with our previous carbocyclization using less bulky donors,[12h] which proceeds via a DYKAT of type IV[18] mechanism, the Michael intermediates **3** were not racemic. On the basis of the absolute configurations and our experimental results, we propose the following mechanism to account for the stereochemical and product outcome of the spirocyclic oxindoles **4** with an all-carbon stereocenter (Scheme 3). Thus, initial reversible stereoselective conjugate addition of **1**, preferably to the less sterically hindered Si face (R = Aryl) of the in-situ-generated iminium intermediate **I**, results in predominant formation of the major stereoisomers **3** and **3′** over the minor stereoisomers *ent*-**3** and *ent*-**3′**, which are in a slow equilibration via the corresponding enamine intermediates (**II-IIc**). Next, oxidative addition of the Pd catalyst occurs predominantly to enamine intermediate **II** and delivers the corresponding electrophilic π-allyl palladium complex **III**. Subsequent irreversible stereoselective intermolecular nucleophilic Si-facial attack by the chiral enamine via a 5-membered transition state followed by protonation and reductive elimination generates iminium intermediate **IV** and releases the Pd catalyst. Next, hydrolysis of **IV** delivers spirocyclic oxindole **4** and regenerates the chiral amine catalyst **5**. Our proposal for the reaction pathway to be much faster via enamine **II** as compared with the pathway via **IIb** is that less-steric repulsion between the axial aryl group and the R-group in transition state **III** favors it, whereas for the latter one, the bulkier *N*-alkyl amido group is less favored and in closer proximity to the R-group when the right ligand **6** for the catalytically active Pd complex is employed.

Scheme 3. Proposed Catalytic Cycle



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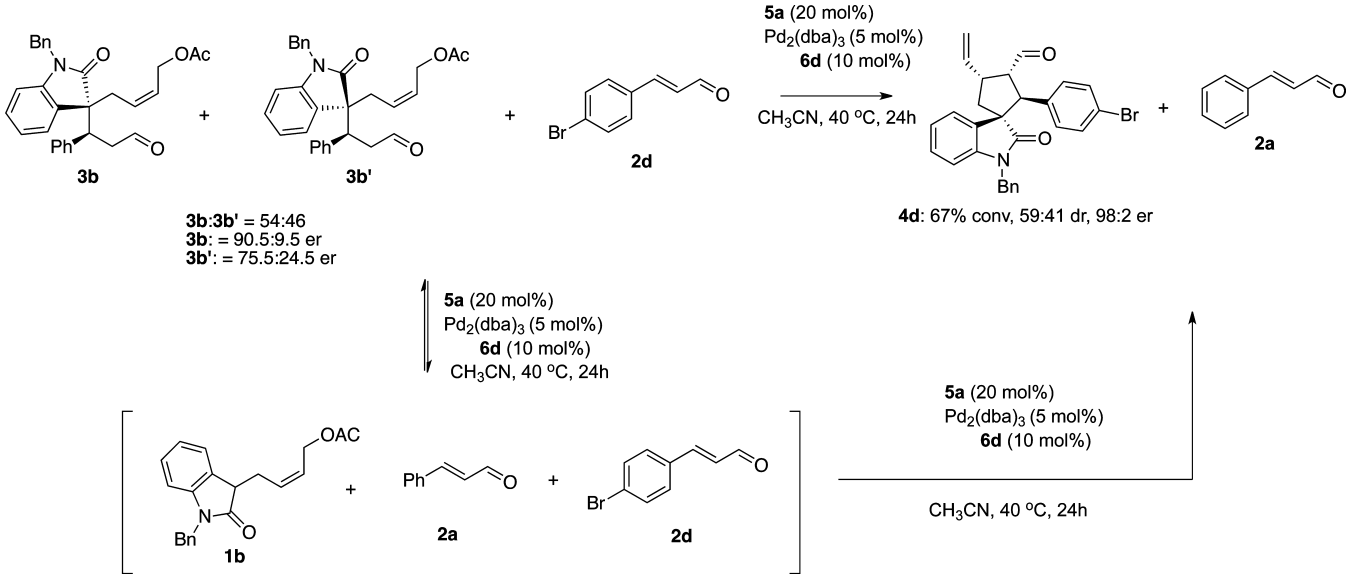
Scheme 4. Crossover Experiment



In summary, we have designed, optimized, controlled, and executed a dynamic Michael/α-allylic alkylation cascade relay sequence for the synthesis of polysubstituted spirocyclic oxindoles with four new contiguous stereocenters, including the spiro all-carbon quaternary center, from simple starting materials employing a dual Pd/chiral amine catalyst system. It is noteworthy that this valuable class of functionalized molecules is constructed in one pot with high chemo- and enantioselectivity from a mixture of stereoisomeric intermediates, which is possible by the synergistic catalysis generated from the "right" combination of ligand, metal complex, and chiral amine. The simplicity, high enantioselectivity, and modularity of the disclosed cocatalysis concept make it suitable for the synthesis of highly functionalized molecules and DOS. Thus, further expansion of it along these research themes as well as mechanistic studies are ongoing and will be disclosed in due course.

EXPERIMENTAL SECTION

Representative procedure: An oven-dried vial (8 mL) equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ $CHCl_3$ (10.4 mg, 0.01 mmol, 5 mol %) and ligand **6d** (7.0 mg, 0.02 mmol, 10 mol %), fitted with a septum, sealed, and flushed with a stream of N_2 for 10 min. Next, anhydrous CH_3CN (200 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 a stream of N_2, oxindole **1** (0.4 mmol, 2.0 equiv in CH_3CN (800 μL)) was added followed by enal **2** (0.2 mmol) under N_2 atmosphere. After stirring at room temperature for 7 min, the resulting mixture was transferred to the vial containing the mixture of palladium catalyst and ligand via a syringe (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 ^{1}H NMR analysis of the crude reaction mixture. Upon completion, the mixture was directly loaded onto a silica-gel column, and immediate flash chromatography (petroleum ether/EtOAc mixtures) gave the pure products **4** as yellowish oils.

ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501975u

Experimental procedures, preparation of starting materials, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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