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Design of C3-Alkenyl-Substituted 2-Indolylmethanols for Catalytic Asymmetric Interrupted Nazarov-Type Cyclization

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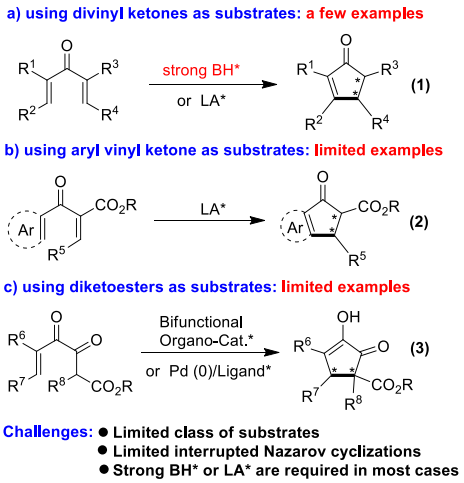
Abstract. The C3-alkenyl-substituted 2-indolylmethanols have been designed as a new class of substrates for catalytic asymmetric interrupted Nazarov-type cyclizations. In the presence of chiral phosphoric acid as a mild chiral Brønsted acid, the interrupted Nazarov-type cyclization of C3-alkenyl-substituted 2-indolylmethanols with nucleophiles occurred smoothly to construct cyclopenta[*b*]indole frameworks in generally excellent diastereo- and enantioselectivities (up to >95:5 dr, >99% ee).

Keywords: asymmetric organocatalysis; cyclization; enantioselectivity; indolylmethanol; tandem reaction

The Nazarov cyclization belongs to a class of 4π-electrocyclizations, which is a powerful method for constructing five-membered rings and has important applications in synthesizing natural products.[1-2] However, catalytic asymmetric Nazarov cyclization is underdeveloped due to the difficulty in controlling the enantioselectivity of the reaction (Scheme 1).



Scheme 1. Profile of catalytic asymmetric Nazarov cyclizations and the challenges.

Currently, the established catalytic asymmetric Nazarov cyclizations mainly utilize divinyl ketones as substrates to perform the reactions under the catalysis of chiral strong Brønsted acids (BH*) such as chiral *N*-triflylphosphoramide (CPN) or chiral Lewis acids (LA*) (eq. 1).[3-4] In addition, there are only limited examples employing aryl vinyl ketones as substrates to undergo catalytic asymmetric Nazarov cyclizations in the presence of chiral Lewis acids (eq. 2).[5] Besides, very limited examples used diketoesters as substrates to perform the Nazarov cyclization under the catalysis of chiral bifunctional organocatalyst or Pd (0)/chiral ligand (eq. 3).[6] So, great challenges still remain in catalytic asymmetric Nazarov cyclizations, including: 1) the limited substrates classes for Nazarov cyclizations; 2) the requirement of using strong Brønsted acids or Lewis acids as chiral catalysts in most cases; 3) the limited interrupted Nazarov-type cyclizations involving multiple transformations.[7-9]

Survey of the literature reveals there are only limited examples of catalytic asymmetric interrupted Nazarov-type cyclizations (Scheme 2).[7] For example, Rueping and coworker reported a domino Nazarov cyclization/halogenation reaction sequence (eq. 4),[7a] and the Tu group devised an interrupted Nazarov cyclization/semipinacol rearrangement (eq. 5).[7b] In spite of their elegant work, both of the reactions require a strong chiral Brønsted acid (CPN) as a chiral catalyst and the substrate class is confined to divinyl ketones. Therefore, it has become an urgent task to develop new class of substrates for catalytic asymmetric Nazarov cyclizations, which are not only easily activated by mild chiral Brønsted acids but also favorable for undergoing interrupted Nazarov-type cyclizations.

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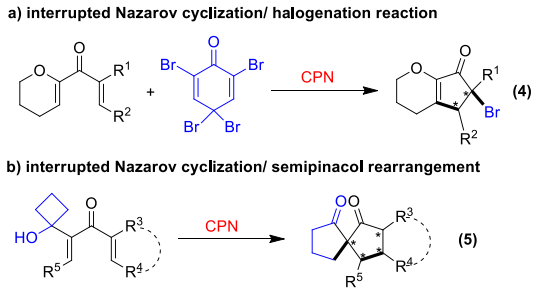
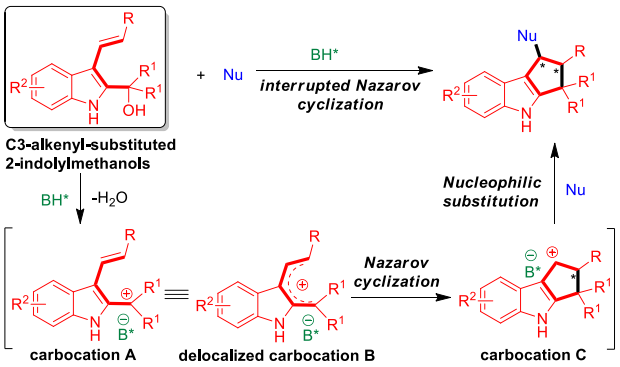


Scheme 2. Limited examples of catalytic asymmetric interrupted Nazarov cyclizations.

To fulfil this task, we designed C3-alkenyl-substituted 2-indolylmethanols as a new class of substrates for catalytic asymmetric interrupted Nazarov-type cyclizations (Scheme 3). This design was based on the consideration that C3-unsubstituted 2-indolymethanols could form delocalized carbocation in the presence of an acid.[10] If an alkenyl group was introduced to the C3-position of 2-indolymethanols, the carbocation **A** could be further delocalized to generate a 4π carbocation **B**, which is similar to the delocalized 4π cation intermediate produced from aryl vinyl ketone. So, this 4π carbocation **B** is able to perform an enantioselective Nazarov cyclization via the ion pair interaction with chiral Brønsted acid anion, thus giving rise to a cyclic carbocation **C**. Finally, this intermediate **C** can be rapidly trapped by nucleophiles (Nu) to accomplish the catalytic asymmetric interrupted Nazarov-type cyclization and to construct the cyclopenta[*b*]indole framework in a diastereo- and enantioselective fashion. It should be mentioned chiral cyclopenta[*b*]indole framework often exists in the structures of many natural products and pharmaceutically important compounds.[11]



Scheme 3. Design of new class of substrates for catalytic asymmetric interrupted Nazarov cyclization.

Based on this design and as our continuous interests in developing new catalytic asymmetric transformations,[10,12] we utilized chiral phosphoric acid (CPA)[13-14] as a mild chiral Brønsted acid to catalyze the interrupted Nazarov-type cyclization, which constructed cyclopenta[*b*]indole frameworks in excellent diastereo- and enantioselectivities. It should be noted, compared with CPN, a more significant advantage of CPA would be the shorter and easier synthesis of such a catalyst.

Initially, we employed indole **2a** as a nucleophile to react with C3-alkenyl-substituted 2-indolylmethanol **1a** in the presence of CPA **4a** in toluene to testify the possibility of our hypothesis (Scheme 4). Gratifyingly, the interrupted Nazarov cyclization indeed occurred to afford the desired product **3aa** in a moderate yield of 49% and an excellent diastereoselectivity of >95:5 dr although the enantioselectivity was extremely low. This preliminary result demonstrated the feasibility of our hypothesis. However, there are two obvious challenges embedded in this reaction. The first one is to control the stereoselectivity, especially the enantioselectivity of the Nazarov cyclization; the second one is to control the chemoselectivity of the interrupted reaction. Actually, the moderate yield of product **3aa** was largely ascribed to the formation of two byproducts **7** and **8**. As shown in Scheme 4, in the reaction process, indole **2a** has a tendency to directly attack the carbocation **A**, thus generating byproduct **7**. In addition, the cyclic carbocation **C**, which was formed from the Nazarov cyclization, can generate byproduct **8** via deprotonation instead of being attacked by indole **2a** to give the desired product **3aa**. So, in order to settle these challenges, we performed condition optimization to improve the yield and the enantioselectivity of product **3aa** (see SI for details). Screening of BINOL-derived CPAs revealed catalysts **4d**-**4e** bearing two bulky substituents were superior to others in terms of controlling the enantioselectivity. Then, the backbone of CPAs **4d**-**4e** was changed from BINOL to H_8-BINOL and SPINOL, which found H_8-BINOL-derived CPA **5a** could catalyze the interrupted Nazarov-type cyclization in the highest enantioselectivity of 80% ee albeit the yield was still in a moderate level (48%) due to the generation of byproducts **7** and **8**. In order to improve the yield as well as the enantioselectivity of product **3aa**, the reaction temperature was altered in the presence of the optimal catalyst **5a**. However, it was found either lowering or elevating the reaction temperature was detrimental to the generation of product **3aa**. This is because byproduct **7** would become a main product when lowering the temperature; while the amount of byproduct **8** would increase when elevating the temperature. So, at room temperature, a series of solvents were carefully evaluated, which disclosed that chloroform could deliver the desired product **3aa** in a much higher yield of 78% with maintained good enantioselectivity of 82% ee. Finally, it was found the addition of 3Å molecular sieves (MS) as additives could further improve the yield of **3aa** to 87% and enhance the enantioselectivity to 94% ee. So, this condition was chosen as the optimal one for the interrupted Nazarov cyclization. It should be mentioned only one diastereomer of product **3aa** was observed during the condition optimization.

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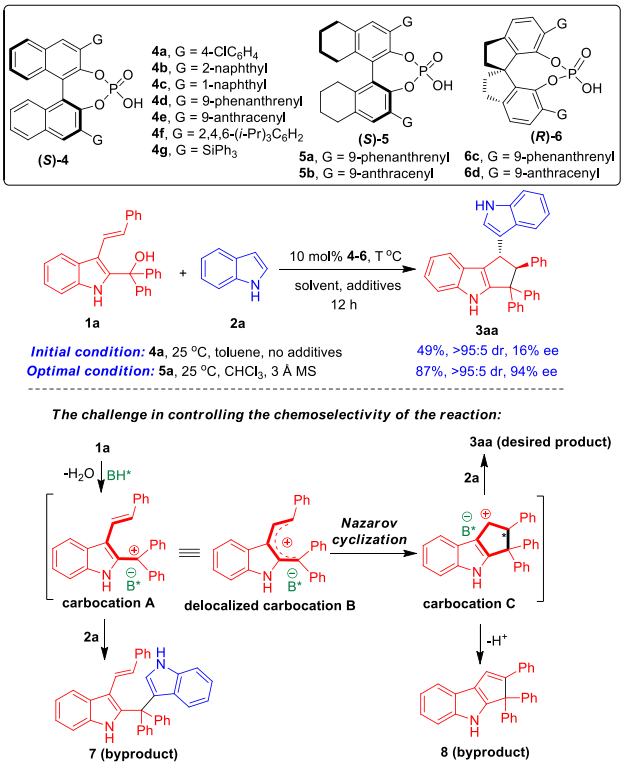
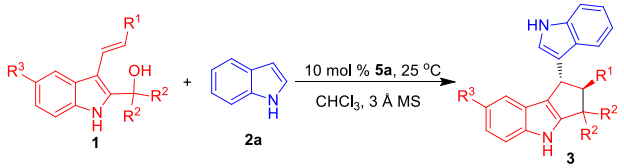


Scheme 4. Condition optimization and the challenge in controlling the chemoselectivity of the reaction.

With the optimal reaction conditions known, we then investigated the substrate scope of C3-alkenyl-substituted 2-indolylmethanols **1** by the reactions with indole **2a**. As shown in Table 1, this approach was applicable to a variety of substrates **1** bearing different $R^1/R^2/R^3$ substituents, which smoothly underwent the interrupted Nazarov cyclization in generally considerable yields (50%-87%), excellent diastereoselectivities (all >95:5 dr) and high enantioselectivities (80% to >99% ee). In detail, *ortho*-, *meta*- or *para*-substituted phenyl groups could serve as suitable R^1 groups (entries 2-7). Moreover, R^2 and R^3 groups could be altered with different electronic nature (entries 8-12).

Table 1. Substrate scope of C3-alkenyl-substituted 2-indolylmethanols **1**[a]

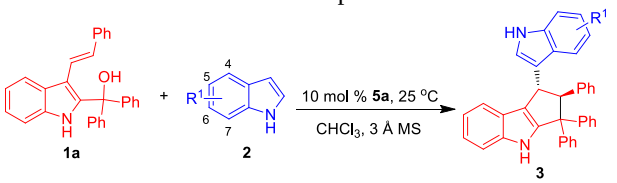


en-try	3	$R^1/R^2/R^3$ (1)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3aa**	Ph/Ph/H (**1a**)	87	>95:5	94
2	**3ba**	*o*-FC_6H_4/Ph/H (**1b**)	50	>95:5	92
3	**3ca**	*o*-MeC_6H_4/Ph/H (**1c**)	61	>95:5	96
4	**3da**	*m*-MeC_6H_4/Ph/H (**1d**)	68	>95:5	94
5	**3ea**	*p*-$MeOC_6H_4$/Ph/H (**1e**)	59	>95:5	94
6	**3fa**	*p*-ClC_6H_4/Ph/H (**1f**)	57	>95:5	94
7	**3ga**	*p*-FC_6H_4/Ph/H (**1g**)	51	>95:5	>99
8	**3ha**	Ph/*m*-MeC_6H_4/H (**1h**)	59	>95:5	88
9	**3ia**	Ph/*m*-FC_6H_4/H (**1i**)	55	>95:5	80
10	**3ja**	Ph/Ph/MeO (**1j**)	55	>95:5	82
11	**3ka**	Ph/Ph/Cl (**1k**)	54	>95:5	92
12	**3la**	Ph/Ph/Br (**1l**)	52	>95:5	90

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in chloroform (2 mL) with 3 Å MS (100 mg) at 25 °C for 12 h, and the molar ratio of **1**:**2a** was 1:1.2. The absolute configuration of compound **3ba** was determined to be (*7R,8S*) by single crystal X-ray diffraction analysis (see SI for details).[15] [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. [d]The enantiomeric excess (*ee*) was determined by HPLC.

Then, we studied the substrate scope of indoles **2** by the reactions with C3-alkenyl-substituted 2-indolylmethanols **1a**. As listed in Table 2, this interrupted Nazarov cyclization was amenable to a wide range of substituted indoles **2**, affording the desired products **3** in overall good yields (51%-88%), excellent diastereoselectivities (all >95:5 dr) and high enantioselectivities (80% to 98% ee). Specifically, C4-C7 substituted indoles regardless of their electronic nature could be applicable to the reaction. It seemed that the position of the substituents exerted some effect on the enantioselectivity because C4- and C5-methyl substituted indoles (**2b** and **2d**) offered the products **3** in higher enantioselectivity than C6-methyl substituted indole **2h** (entries 2 and 4 vs 8). Notably, all the products **3** were generated in uniformly excellent diastereoselectivities.

Table 2. Substrate scope of indoles **1**[a]



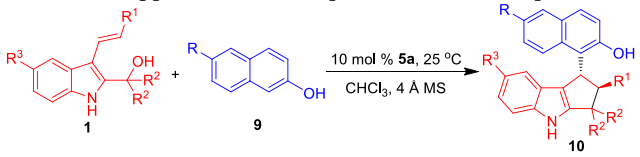
en-try	3	R^1 (2)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3aa**	H (**2a**)	87	>95:5	94
2	**3ab**	4-Me (**2b**)	79	>95:5	96
3	**3ac**	4-Br (**2c**)	86	>95:5	90
4	**3ad**	5-Me (**2d**)	62	>95:5	96
5	**3ae**	5-MeO (**2e**)	59	>95:5	90
6	**3af**	5-Br (**2f**)	87	>95:5	98
7	**3ag**	5-Cl (**2g**)	78	>95:5	80

8	**3ah**	6-Me (**2h**)	53	>95:5	90
9	**3ai**	6-Cl (**2i**)	88	>95:5	94
10	**3aj**	7-F (**2j**)	51	>95:5	98

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in chloroform (2 mL) with 3 Å MS (100 mg) at 25 °C for 12 h, and the molar ratio of **1a**:**2** was 1:1.2. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. [d]The enantiomeric excess (*ee*) was determined by HPLC.

Next, in order to examine the applicability of this catalytic asymmetric interrupted Nazarov cyclization, we employed 2-naphthols **9** as another class of nucleophiles to react with C3-alkenyl-substituted 2-indolylmethanols **1** under the similar reaction conditions (Table 3). To our satisfaction, the desired domino Nazarov cyclization occurred smoothly by using 2-naphthols **9** as nucleophiles, which afforded the corresponding products **10** in moderate to good yields, acceptable diastereoselectivities and high enantioselectivities.

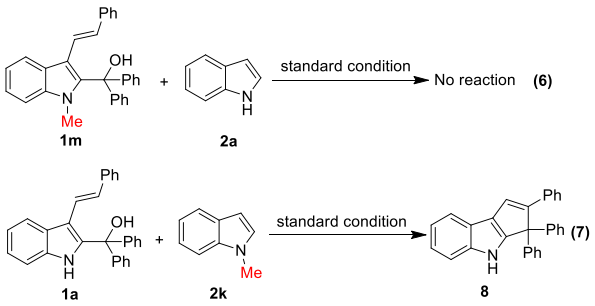
Table 3. Application of 2-naphthols **9** as nucleophiles[a]



en-try	**10**	$R^1/R^2/R^3$ (**1**)	R (**9**)	yield (%)[b]	dr[c]	ee (%)[d]
1	**10aa**	Ph/Ph/H (**1a**)	H (**9a**)	72	90:10	93
2	**10fa**	*p*-ClC$_6$H$_4$/Ph/H (**1f**)	H (**9a**)	56	90:10	92
3	**10ia**	Ph/*m*-FC$_6$H$_4$/H (**1i**)	H (**9a**)	87	88:12	93
4	**10ka**	Ph/Ph/Cl (**1k**)	H (**9a**)	74	85:15	96
5	**10ab**	Ph/Ph/H (**1a**)	Me (**9b**)	70	88:12	94

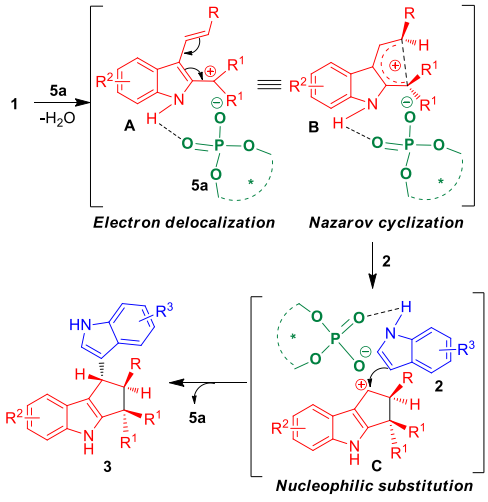
[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in chloroform (2 mL) with 4 Å MS (100 mg) at 25 °C for 12 h, and the molar ratio of **1**:**9** was 1.1:1. [b]Isolated yield. [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. [d]The enantiomeric excess (*ee*) was determined by HPLC.

In order to gain some insights into the activation mode of the catalyst to the substrates, we performed some control experiments (Scheme 5). First, *N*-methyl protected 2-indolylmethanol **1m** was employed to the reactions with indole **2a** under the standard reaction conditions (eq. 6). In this case, no reaction occurred, which indicated the N-H group of substrates **1** played a crucial role in controlling the reactivity. Namely, the hydrogen-bonding interaction between the N-H group of substrates **1** and the CPA anion was necessary for performing the first step of Nazarov cyclization. Secondly, we utilized *N*-methyl protected indole **2k** as a substrate to react with 2-indolylmethanol **1a** (eq. 7), which found no desired interrupted Nazarov cyclization occurred and only byproduct **8** was generated. This result demonstrated that the N-H group in substrates **2** was very important for carrying out the second step of interrupted Nazarov cyclizations by forming a hydrogen bond with the CPA anion. All these results suggested the CPA catalyst might form dual hydrogen-bonding interaction with the N-H groups of the two reaction partners.



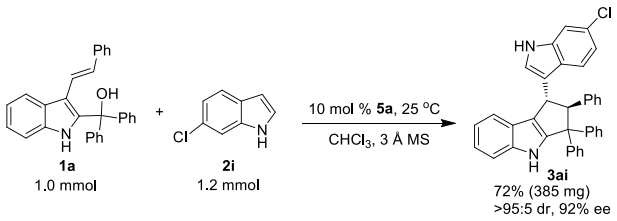
Scheme 5. Control experiments.

Based on the control experiment, we suggested a possible reaction pathway and activation mode of the catalyst to the substrates. As illustrated in Scheme 6, in the presence of CPA **5a**, C3-unsubstituted 2-indolymethanols **1** transformed into carbocation **A** via dehydration. Then, due to electron delocalization, a 4π carbocation **B** was generated to perform an enantioselective Nazarov cyclization via ion pair and hydrogen-bonding interaction imposed by the anion of CPA **5a**, thus leading to the formation of cyclic carbocation **C**. At this moment, the anion of CPA **5a** simultaneously activated both the nucleophile (indoles **2**) and the cyclic carbocation **C** via ion pair and hydrogen-bonding interaction, therefore facilitating the nucleophilic substitution to give the final products **3** with observed absolute configuration.



Scheme 6. Suggested reaction pathway and activation mode.

Finally, we performed a one mmol scale reaction (Scheme 7), which afforded product **3ai** in a nearly maintained good yield and high stereoselectivity. This result indicated this reaction could be scaled up.



Scheme 7. One mmol scale synthesis.

In summary, we have designed C3-alkenyl-substituted 2-indolylmethanols as a new class of substrates for catalytic asymmetric interrupted Nazarov-type cyclizations. In the presence of chiral phosphoric acid as a mild chiral Brønsted acid, the interrupted Nazarov-type cyclization of C3-alkenyl-substituted 2-indolylmethanols with nucleophiles occurred smoothly to construct cyclopenta[*b*]indole frameworks in generally excellent diastereo- and enantioselectivities. This approach has not only provided a new class of substrates for developing interrupted Nazarov-type cyclizations, but also enriched the research contents of catalytic asymmetric Nazarov cyclizations. In addition, this reaction also serves as a powerful method for constructing enantioenriched cyclopenta[*b*]indole frameworks.

Experimental Section

General

^{1}H and ^{13}C NMR spectra were measured respectively at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Enantiomeric excesses (*ee*) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric excesses by chiral HPLC were Chiralpak columns. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single crystal X-ray diffraction analysis of compounds **3ba** was CuKα (λ = 1.54178), and the thermal ellipsoid was drawn at the 30% probability level. Analytical grade solvents for the column chromatography were distilled before use. All starting materials commercially available were used directly.

General procedure for the synthesis of products 3

To the mixture of C3-alkenyl-substituted 2-indolylmethanols **1** (0.1 mmol), indoles **2** (0.12 mmol), catalyst **5a** (7.1 mg, 0.01 mmol) and 3 Å MS (100 mg) was added chloroform (2 mL). After being stirred at 25 °C for 12 h which indicated the completion of the reaction by TLC, the reaction mixture was filtered to remove the molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography to afford pure products **3**.

General procedure for the synthesis of products 10

To the mixture of C3-alkenyl-substituted 2-indolylmethanols **1** (0.11 mmol), 2-naphthols **9** (0.1 mmol), catalyst **5a** (7.0 mg, 0.01 mmol) and 4 Å MS (100 mg) was added chloroform (2 mL). After being stirred at 25 °C for 12 h which indicated the completion of the reaction by TLC, the reaction mixture was filtered to remove the molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through preparative thin layer chromatography to afford pure products **10**.

Acknowledgements

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[15] CCDC 1577461 (**3ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif. See the Supporting Information for details.

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Design of C3-Alkenyl-Substituted 2-Indolylmethanols for Catalytic Asymmetric Interrupted Nazarov-Type Cyclization

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