Chemical Science

Accepted Manuscript

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View Article Online
DOI: 10.1039/D5SC00594A

ARTICLE

Atroposelective [4+1] Annulation for the Synthesis of Isotopic Isoindolinones Bearing both Central and Axial Chirality

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Isotopically chiral molecules have drawn much attention due to their practical applications in drug discovery. However, existing studies in this area are mainly limited to the centrally chiral molecules and H/D exchange. Herein, we report a chiral phosphoric acid-catalyzed atroposelective [4+1] annulation of ketoaldehyde and 1*H*-indol-1-amine. By means of this strategy, a series of D- and ^{18}O-labeled atropisomers featuring both central and axial chiralities are synthesized in high enantioselectivities and diastereoselectivities with good to excellent isotopic incorporation. Experimental and density functional theory studies suggest that the reaction involves a sequential condensation, cyclization and isomerization cascade, in which the second step is the enantiodetermining process.

Introduction

Isotope labeling strategy has been widely used in many fields such as quantitative proteomics, organic reaction mechanisms, and new drug discovery.[1] In this context, deuterium (D), as a nonradioactive isotope of hydrogen, was intentionally introduced into the bioactive molecules since the D-incorporation may not only improve the pharmacokinetic (PK) profile but provide an opportunity when bioactive molecules suffer from problems of metabolism-mediated toxicity, drug interactions and low bioactivation.[2] In 2017, the U.S. Food and Drug Administration (FDA) granted marketing approval for the first deuterated drug molecule deutetrabenazine, which is used to treat choreas associated with Huntington's disease and for tardive dyskinesias (Fig. 1a, left).[3] In addition, deucravacitinib, a tyrosine kinase 2 (TYK2) inhibitor approved for the treatment of psoriasis, represents another example of a deuterated FDA-approved drug in 2022 (Fig. 1a, right).[4] Therefore, much attention has been paid to synthesize the deuterated bioactive molecules.[5] Despite these advances, the synthesis of optically active isotopic molecules is mainly limited to H/D exchange based on either centrally or axially chiral compounds.[6] The efficient construction of deuterated molecules featuring multiple chiral elements is far more challenging and yet to be explored. More importantly, beyond the H/D exchange,[7] the other nonradioactive isotope (e.g. ^{18}O) incorporation of chiral molecules bearing multiple chiral elements are still undeveloped, despite the fact that these kinds of molecules may also have superior comprehensive performance compared to non-isotopic molecules.

Isotopic water (D_2O & $H_2{}^{18}O$) is one of the most desirable reagents for the synthesis of isotopically chiral molecules. In this regard, the water-participated reactions have the advantage for the efficient introduction of D or ^{18}O without the need for tedious synthetic procedures of isotopic starting materials. However, the asymmetric introduction of isotopes (D and ^{18}O) by using the isotopic water is still at the early stage.[8] To this end, we envision the strategy of asymmetric water-nucleophilic attack that could be used for the construction of chiral molecules featuring multiple chiral elements. As shown in Fig. 1b, by using compound **I** as the substrate, we posited that H_2O as the nucleophile could be introduced into compound **I** to initiate the asymmetric cyclization via chiral phosphoric acid (CPA) catalysis. This may cause the carbonyl moiety to first convert to corresponding hydroxyl group which affords the chiral intermediate **II**. The sequential elimination of one molecule of water would then give intermediate **III** thus achieving the deletion of carbonyl group of **I**. It should be noted that, if the X group is bulky enough, the axially chiral intermediate **II** can be afforded. Finally, the intramolecular isomerization would occur to generate the isoindolinones **IV** bearing both axial and central chirality which accomplishes the carbonyl relocation. More importantly, since H_2O is a key reactant of the reaction, the isotopically chiral **IV** may be easily afforded by simply adding D_2O or $H_2{}^{18}O$ into the reaction system.

Inspired by the reports on practical synthesis of isoindolinones,[9] we suppose that the reaction of acetylaldehyde **1** with 1*H*-indol-1-amine **2** by chiral phosphoric acid (CPA) catalysis could generate intermediate (**V**) featuring the active *N*-amine moiety[10] with the release of one molecule of H_2O (Fig. 1c). Herein, the extra isotopic D_2O could be added into the reaction system to exchange the H_2O and then reacts with **V**. On the other hand, due to the keto-enol tautomerism of **V** (or **1**), the D-incorporation at the benzylic site would also be expected. Similarly, the ^{18}O-labeled product could also be afforded by

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† Electronic supplementary information (ESI) available: Experimental details and characterization data for all new compounds, computational methods, and Cartesian coordinates. CCDC 2359270, 2354174, 2362138, and 2393057. For ESI and crystallographic data in CIF or other electronic format see See DOI: 10.1039/x0xx00000x

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subjecting $H_2{}^{18}O$ to the reaction mixture. In this regard, isotopically chiral isoindolinones bearing both carbon central and N-N axial chirality[11,12] would be produced that may possess potential applications in medicinal chemistry.

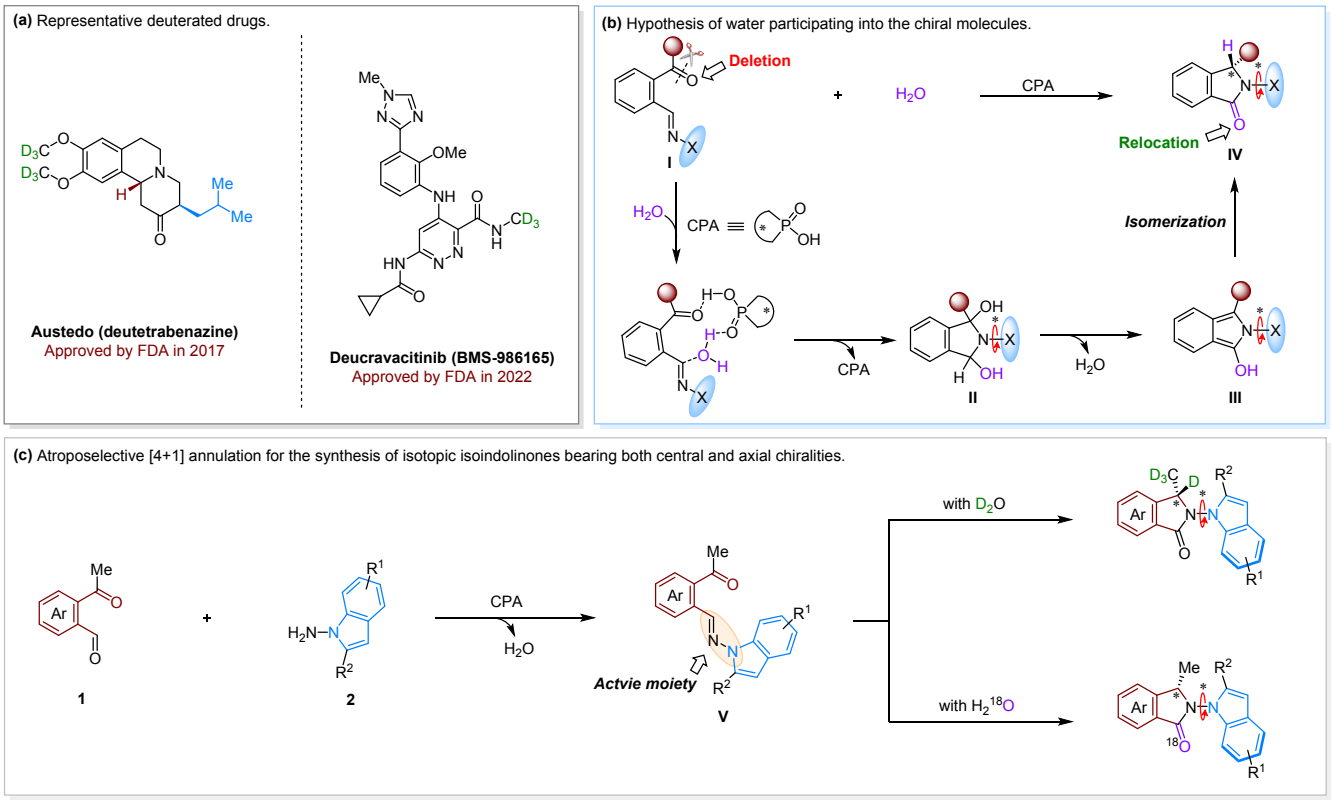

Fig. 1 State of the art for the synthesis of isotopically chiral molecules. (a) Representative deuterated drugs. (b) Hypothesis of water participating into the chiral molecules. (c) Atroposelective [4+1] annulation for the synthesis of isotopic isoindolinones bearing both central and axial chirality.

Results and discussion

We commenced our study by investigating the CPA-catalyzed reaction of 2-acetylbenzaldehyde **1a** with 2-(phenylsulfonyl)-1*H*-indol-1-amine **2a**, envisioning that the release of a molecular H_2O from the amine generation would participate in the asymmetric annulation to **3a** (Table 1). Gratifyingly, the reaction proceeded smoothly at 35 °C in toluene by **CPA1** catalysis, affording **3a** in 73% enantiomeric excess (ee) with 89% yield, albeit with low diastereomeric ratio (dr) of 3:1 (Table 1, entry 1). We then screened a variety of CPA for the reaction and identified **CPA4** as the optimal catalyst that gave **3a** in 94% ee and 91% yield with beyond 20:1 dr (entries 2-7). The absolute configuration of **3a** was determined to be (*P*, *S*) according to the single-crystal X-ray analysis. The use of other solvents such as CH_2Cl_2, $CHCl_3$, CCl_4, chlorobenzene or EtOAc gave no better results than toluene (entries 8-12). Lower concentration of the reaction resulted in comparable ee of **3a** but with relatively lower yield of 68% and 17:1 dr (entry 13). Moreover, as shown in entry 14-16, decreasing the reaction temperature and catalyst loadings both led to **3a** with lower ee (77-91%). When the SO_2Ph group was changed to H group, 68% ee of isoindolinone **3a** was obtained. On the other hand, in order to examine the axially configurational stability of **3a**, density functional theory (DFT) study was performed. As a result, the rotational barrier of **3a** around the N-N axis in toluene at room temperature is 31.5 kcal/mol, suggesting the high configurational stability of N-N moiety of **3a**.

With the optimal conditions in hand, the scope of the reaction was investigated. As shown in Table 2, the reaction proceeded smoothly when substrates **2** with substituents at C3 or C4 position, affording **3b**-**3e** in 62-80% yields and 86-94% ee with >20:1 dr in all cases. Substrates **2** bearing electron withdrawing and donating groups at C5 position were compatible with the reaction, providing the desired products (**3f**-**3k**) in good to excellent yields and high enantioselectivities (92-96%), with excellent to high levels of diastereomeric control (10:1 to >20:1 dr). However, relatively low ee and dr were obtained when substrates **2** possessing C6 substituents (**3l** and **3m**) were used. On the other hand, the phenylsulfonyl group could be verified by other groups including Ts, Fs and different ester groups, delivering products **3n**-**3r** in high ee and excellent to high dr. Moreover, the reaction also occurred when 2-(trifluoromethyl)-1*H*-benzo[d]imidazole was used as the substrate, leading to **3s** in 42% yield and 82% ee, but only with 2:1 dr. Finally, different ketoaldehydes **1** were examined for the reaction. To our delight, isoindolinones (**3t**-**3a'**) were readily

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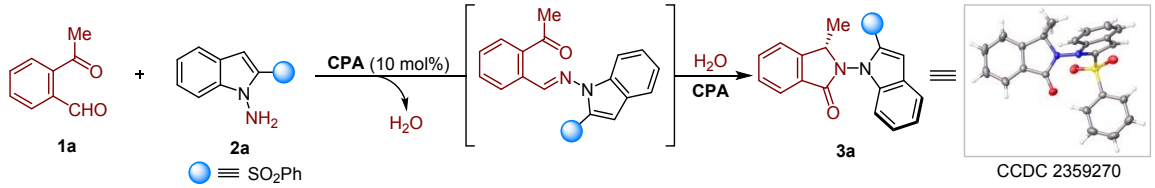
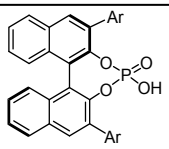
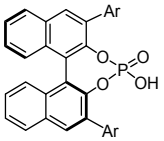
isolated in high ee (88-98%) with 10:1 to 20:1 dr, but only 37% yield and 60% ee of **3b'** were obtained when 2-acetyl-6-chlorobenzaldehyde was used as the substrate. Notably, the long-chain ketones also tolerated the reaction, delivering **3c'** and **3d'** in 94% ee and 92% ee with 18:1 and 14:1 dr, respectively. However, no desired product **3e'** was generated when 2-benzoylbenzaldehyde was used for the reaction under the optimal conditions.

Table 1. Optimized conditions for the reaction.[a]





CPA1: Ar = 9-anthracenyl
CPA2: Ar = 9-phenanthrenyl
CPA3: Ar = 4-nitrophenyl
CPA4: Ar = 2,4,6-triisopropylphenyl
CPA5: Ar = 2,4,6-tricyclohexylphenyl
CPA6: Ar = 1-naphthalenyl



CPA7: Ar = 1-pyrenyl

Entry	Catalyst	Solvent	ee (%)	Yield (%)	dr
1	**CPA1**	Toluene	73	89	3:1
2	**CPA2**	Toluene	27	71	4:1
3	**CPA3**	Toluene	-75	76	12:1
4	**CPA4**	Toluene	94	91	>20:1
5	**CPA5**	Toluene	94	91	17:1
6	**CPA6**	Toluene	-51	88	15:1
7	**CPA7**	Toluene	5	80	11:1
8	**CPA4**	CH_2Cl_2	91	91	>20:1
9	**CPA4**	$CHCl_3$	90	90	>20:1
10	**CPA4**	CCl_4	71	91	20:1
11	**CPA4**	Cl-Ph	80	88	18:1
12	**CPA4**	EtOAc	80	44	10:1
13[b]	**CPA4**	Toluene	93	68	17:1
14[c]	**CPA4**	Toluene	91	80	15:1
15[d]	**CPA4**	Toluene	83	66	16:1
16[e]	**CPA4**	Toluene	68	36	-

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA** catalyst (10 mol%), solvent (1.0 mL), 35 °C for 24 h. Isolated yield, ee values were determined by high performance liquid chromatography (HPLC), and dr values were determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Toluene (2.0 mL), [c] The reaction was carried out at 25 °C. [d] 5 mol% of **CPA4** was used. [e] $PhSO_2$ group was changed by H.

Having established the strategy for the synthesis of chiral isoindolinones **3**, we next explored the potential isotopic incorporation of **3** by adding D_2O or $H^{18}O$ into the reaction mixture. As shown in Table 3, the use of D_2O led to D-incorporation at two different sites, affording D-labeled isoindolinones **4** featuring both central and axial chirality. Substrates **2** bearing substituents with electron-neutral, -withdrawing and -donating groups at C3, C4 or C5 position were well tolerated to produce corresponding products in high yields with good to high dr (**4a**-**4e**). In addition, ketoaldehydes **1** bearing different groups at phenyl ring were accommodated to the reaction conditions affording **4f**-**4h** in good yield, high ee and excellent dr. It should be noted that, in all cases, the isoindolinones **4** were obtained in high D-incorporation at methyl group (89-91%) with moderate D-incorporation at benzylic position (63-70%). The moderate D-incorporation at benzylic position may be attributed to the fact that the H/D exchange of keto-enol tautomerism of **1** would generate extra

H_2O rebounded into the reaction system, thus decreasing the D-incorporation at the benzylic position. On the other hand, replacing the Me to C_7H_{15} group gave **4i** in high ee and dr with only benzyl D-incorporation.

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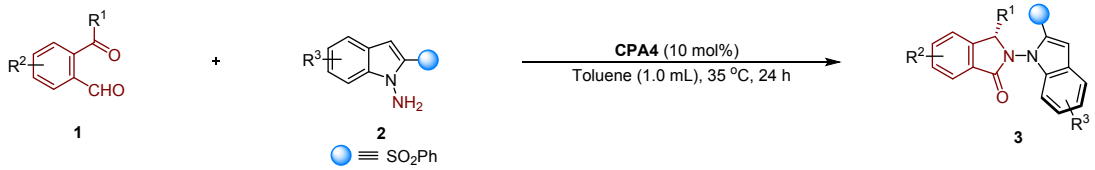
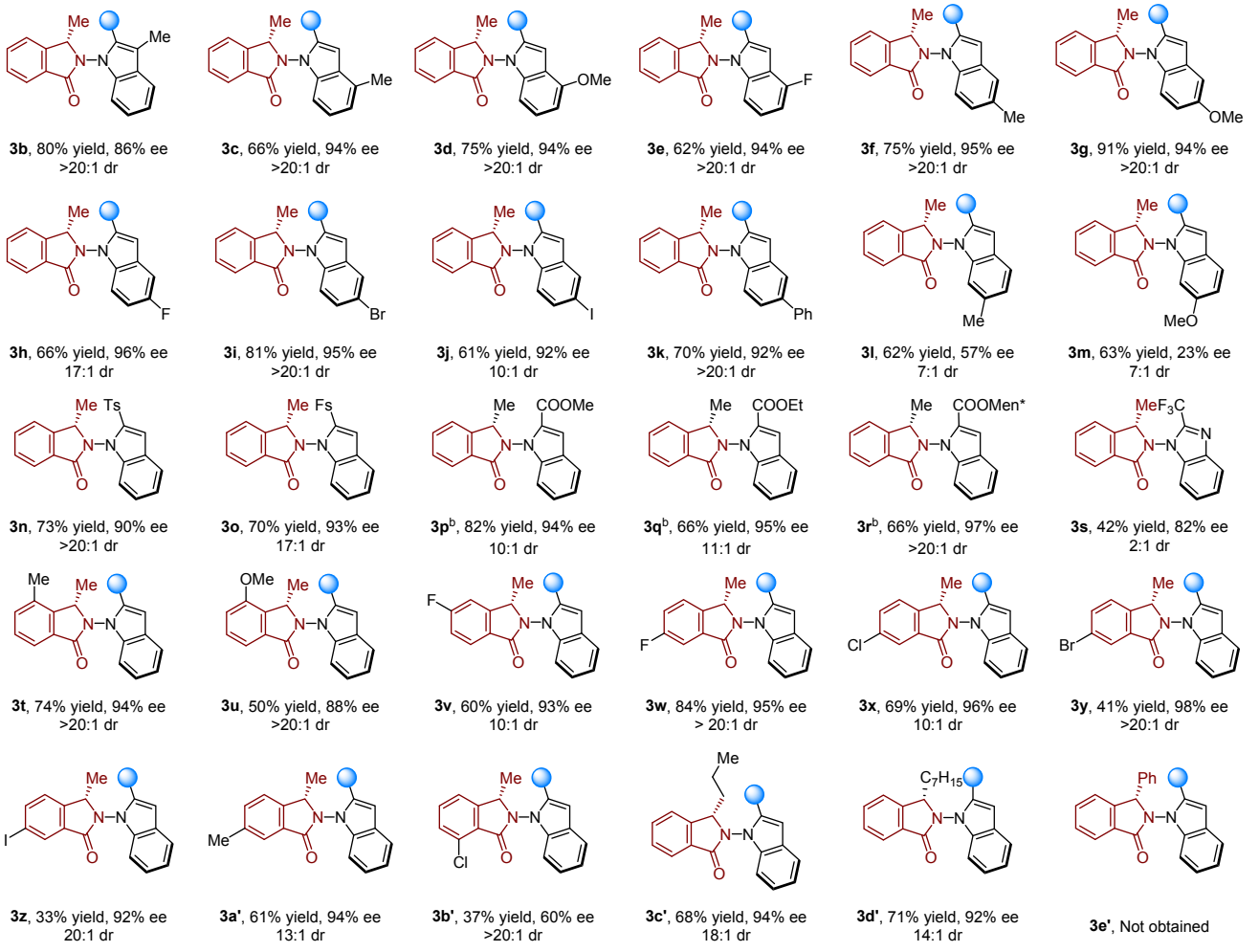
Table 2. Substrate scopea.[a]





[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA4** (10 mol%), toluene, (1.0 mL), 35 °C for 24 h. Isolated yield, ee values were determined by HPLC, and dr values were determined by ^{1}H-NMR analysis of the crude reaction mixture. Ts = tosyl, Fs = p-fluorobenzenesulfonyl. [b] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA** catalyst (10 mol%), solvent: chlorobenzene (1.0 mL), -10 °C for 12 h.

Subsequently, reactions of representative ketoaldehydes **1** and 2-(phenylsulfonyl)-1*H*-indol-1-amines **2** with $H_2{}^{18}O$ were studied (Table 4). As a result, substituents attached at different positions of indolyl ring were well-accommodated, affording ^{18}O-labeled isoindolinones **5a**-**5e** in high ee and dr with the excellent level of ^{18}O incorporation (70-86%). The 82-91% ^{18}O incorporation of **5** was also obtained in good yield, high ee and good to high dr (**5f**-**5i**). It should be noted that this reaction represents a very rare example of the synthesis of ^{18}O-labeled atropisomers bearing both central and axial chirality.

To gain some insight into the details of the reaction, we performed a series of experiments to probe the mechanism. As shown in Fig. 2a, we probed the reaction intermediates by performing the reaction of **1a** with **2a** at low temperature. As a result, compound **Int0** was readily afforded and isolated in *E*-configuration under either **CPA4** or *ent*-**CPA4** catalysis. The configuration of **Int0** was unambiguously determined by single crystal X-ray diffraction analysis. Moreover, **CPA4** catalyzed the reaction of **Int0** with H_2O converted to (*P, S*)-**3a** in 71% yield with 93% ee. The use of *ent*-**CPA4** for the reaction led to *(M, R)*-**3a** in 90% ee with >20:1 dr. It should be noted that, lower yield and

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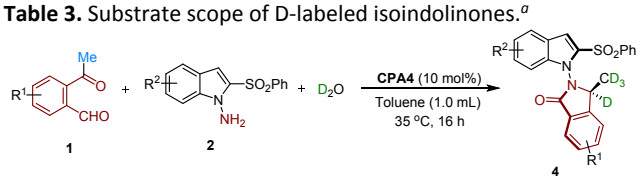
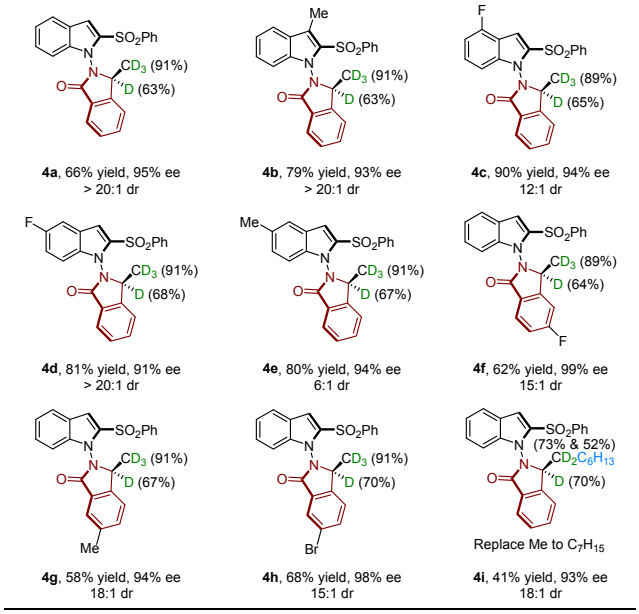
ee would be obtained when the reactions proceeded in the absence of extra H_2O in the system. All these results indicated that **Int0** is the key intermediate of the annulation, and the enantioselectivity and diastereoselectivity are derived from the transformation of **Int0** with H_2O to **3a**.

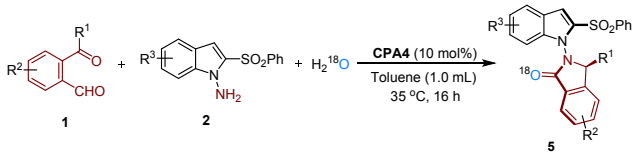
Table 3. Substrate scope of D-labeled isoindolinones.[a]

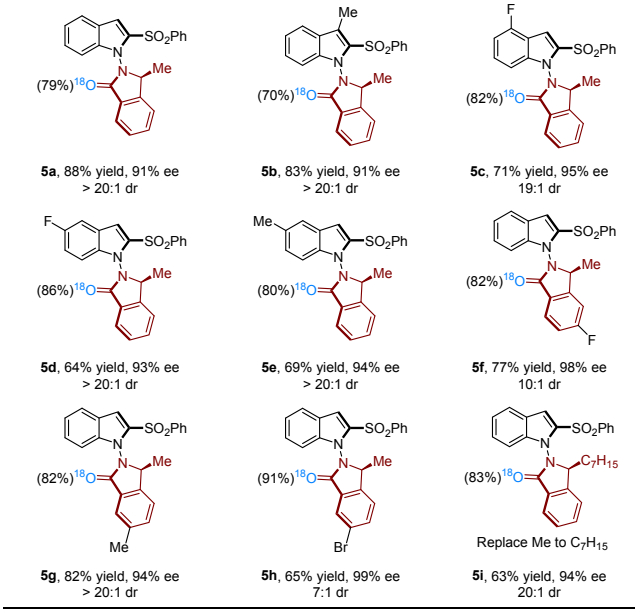




[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA4** (10 mol%), toluene, (1.0 mL), D_2O (50 μL), 35 °C for 24 h. Isolated yield, ee values were determined by HPLC. The dr values and D-incorporation were determined by ^{1}H-NMR analysis of the crude reaction mixture.

Table 4. Substrate scope of ^{18}O-labeled isoindolinones.[a]





[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA4** (10 mol%), toluene, (1.0 mL), $H_2{}^{18}O$ (50 μL), 35 °C for 24 h. Isolated yield, ee values were determined by HPLC, and dr values were determined by ^{1}H-NMR analysis of the crude reaction mixture. The ^{18}O-incorporation were determined by high-resolution mass spectra (HRMS).

To probe the isotope introduction step of the reaction, we then performed the D- and ^{18}O-labeling experiments (Fig. 2b). The reaction of **D-1a** with **2a** resulted in **3a** in 90% yield and 94% ee, but with no D-incorporation observed in **3a**. In addition, the reaction of **Int0** with D_2O or $H_2{}^{18}O$ yielded **4a** or **5a** with excellent D- or ^{18}O-incorporation, respectively. These results suggested that H_2O participated in the reaction and is responsible for the isotope introduction of isoindolinones. Finally, we explored the origin of enantioselectivity. Based on these results, we proposed the concerted or stepwise annulation may occur for the reaction (Fig. 2c). However, currently, the isolation of this intermediate **ii** or **iii** has failed. Nevertheless, we explored the reaction of **1a** with 9*H*-carbazol-9-amine **6a** since the achiral **iii-6a** would be generated in this case (Fig. 2d). As a result, compound **7a** was obtained in 77% yield but only with 7% ee. This result indicated that the generated axial chirality is a key factor for the efficient synthesis of isoindolinones **3** in high ee. Thus, the origin of enantioselectivity for the reaction of **1** and **2** is mainly attributed to the axially chiral generation which derived from the chiral intermediate **ii** (Fig. 2c). Our calculation suggested that the rotational barrier of **ii** at room temperature is 30.7 kcal/mol indicating the axial chirality is generated in this step. Furthermore, the high diastereoselectivity is attributed to the stereospecific intramolecular isomerization induced by axial information rather than the chiral induction catalyzed by CPA.

DFT studies were then performed to deep insight into the reaction mechanism. We first examined whether the annulation of **Int0** and H_2O occurred stepwise or concertedly to afford the intermediate **ii** (Fig. 2c). The energy profiles of the stepwise process were shown in Fig. 3, and the coordination of **Int0** with **CPA4** was selected as the reference point. With the H_2O participating into the reaction, the dual H-bonding effect was generated with an energy barrier of 16.0 kcal/mol (**Int0** + H_2O). The *Re*-face attack of amine by water formed **Int1R** via transition state $\mathbf{TS1}_{Re}$ with an energy barrier of 24.5 kcal/mol, whereas *Si*-face attack formed $\mathbf{Int6}_S$ *via* transition state $\mathbf{TS6}_{Si}$ with a higher energy barrier of 28.4 kcal/mol. Thus, $\mathbf{Int1}_R$ is the more favorable intermediate which undergoes the sequential N-nucleophilic addition to the carbonyl group. In this case, four

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intermediates **Int 2-5** maybe generated accordingly, from which **Int3**$_{1S\text{-}Ra\text{-}3R}$ was superior to others because of the relatively lower energy barrier of **TS3**$_{1Re\text{-}Ra\text{-}3R}$ (24.3 kcal/mol).

Alternatively, if concerted annulation occurred, only four pathways might be experienced via transition states **TS11**$_{Re\text{-}Sa\text{-}3Re}$, **TS12**$_{1Si\text{-}Sa\text{-}3Si}$, **TS17**$_{1Re\text{-}Ra\text{-}3Re}$ or **TS18**$_{1Si\text{-}Ra\text{-}3Si}$ (Fig. 4). This is mainly because the bulky indole moiety existing in the **Int0** induced the exclusive suprafacial activation by **CPA4**. In this regard, the annulation which proceeded via **TS18**$_{1Si\text{-}Ra\text{-}3Si}$ has an overcome energy barrier of 30.5 kcal/mol, a finding that is not possible. On the other hand, although **Int3**$_{1S\text{-}Ra\text{-}3R}$ could be easily afforded via **TS3**$_{1Re\text{-}Ra\text{-}3R}$, the sequential dehydration step has an extremely high energy barrier of 38.8 kcal/mol *via* **TS19**$_{1S\text{-}Ra\text{-}3R}$ which is not possible either. This result also ruled out the only possible stepwise pathway that occurred from **Int3**$_{1S\text{-}Ra\text{-}3R}$ (Fig. 3, blue line). In contrast, our calculation revealed that **Int2**$_{1S\text{-}Sa\text{-}3R}$ and **Int8**$_{1R\text{-}Sa\text{-}3S}$ are more favorable intermediates which are generated *via* **TS11**$_{1Re\text{-}Sa\text{-}3Re}$ and **TS12**$_{1Si\text{-}Sa\text{-}3Si}$ with the energy barrier of 23.4 and 24.3 kcal/mol respectively. However, the dehydration from **Int2**$_{1S\text{-}Sa\text{-}3R}$ required to overcome a relatively higher energy barrier than that of **Int8**$_{1R\text{-}Sa\text{-}3S}$. Therefore, the reaction preferred to undergo dehydration *via* **TS14**$_{1R\text{-}Sa\text{-}3S}$ to afford **Int11**$_{P}$. The intramolecular isomerization then occurred via **TS15**$_{P\text{-}Re}$ to afford (*P*, *S*)-**3a** with the energy barrier of 26.9 kcal/mol. This result is consistent with our experimental observation that isoindolinone **3a** was obtained in preferential (*P*, *S*) configuration.

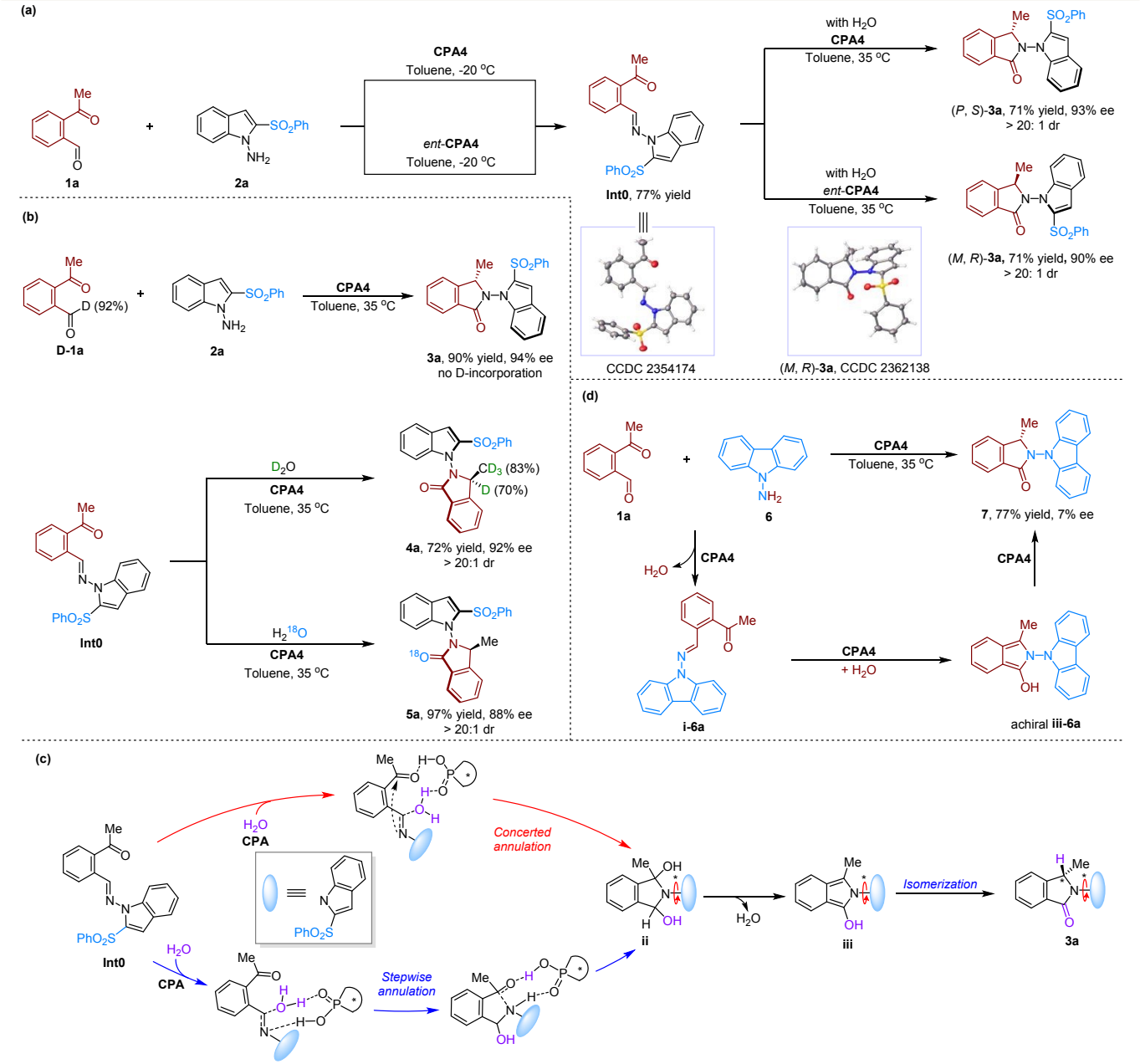

Fig. 2 Mechanistic studies. (a) Control experiments. (b) Deuterium- and ^{18}O-labeling experiments. (c) Proposed catalytic cycle. (d) Enantiodetermining-step investigation.

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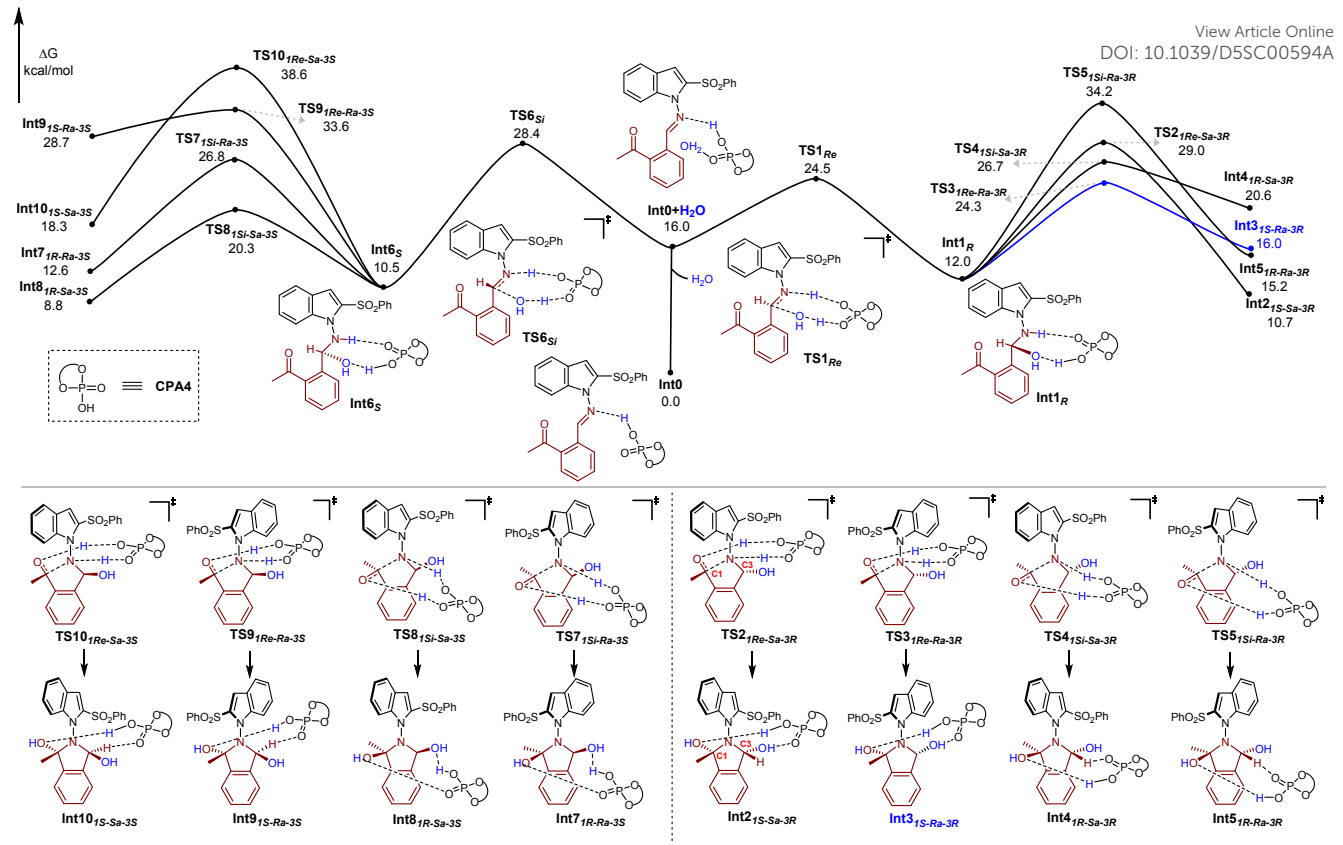

Fig. 3 DFT studies of stepwise annulation. Free energy diagrams of chiral phosphoric acid-catalyzed stepwise mechanism in asymmetric annulation. Gibbs free energy obtained at the M06-2X/def2-TZVPP(SMD, Toluene)// M06-2X/def2-SVP level. The meaning for the corner mark in the structure name: ***Re***: the rectus face; ***Si***: the sinister face; ***Ra***: the potential *R*-configuration for the N-N axis; ***Sa***: the potential *S*-configuration for the N-N axis; ***R***: the *R*-configuration for the central chirality; ***S***: the *S*-configuration for the central chirality.

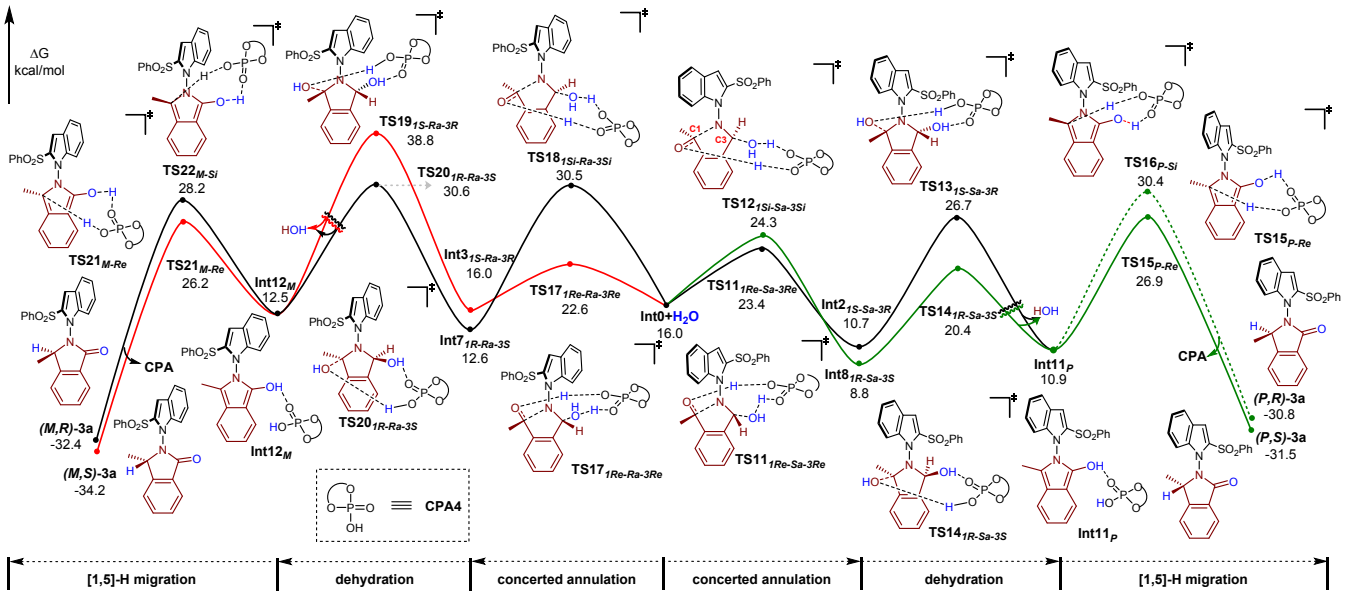

Fig. 4 DFT studies of concerted annulation. Free energy diagrams of chiral phosphoric acid-catalyzed concerted mechanism for the asymmetric annulation, and the investigation of enantioselectivity. ***M*** and ***P*** were used to replace the ***R*** and ***S*** configurations of axial chirality, respectively. The structures of **Int2**, **Int3**, **Int7** and **Int8** were shown in **Fig. 3**.

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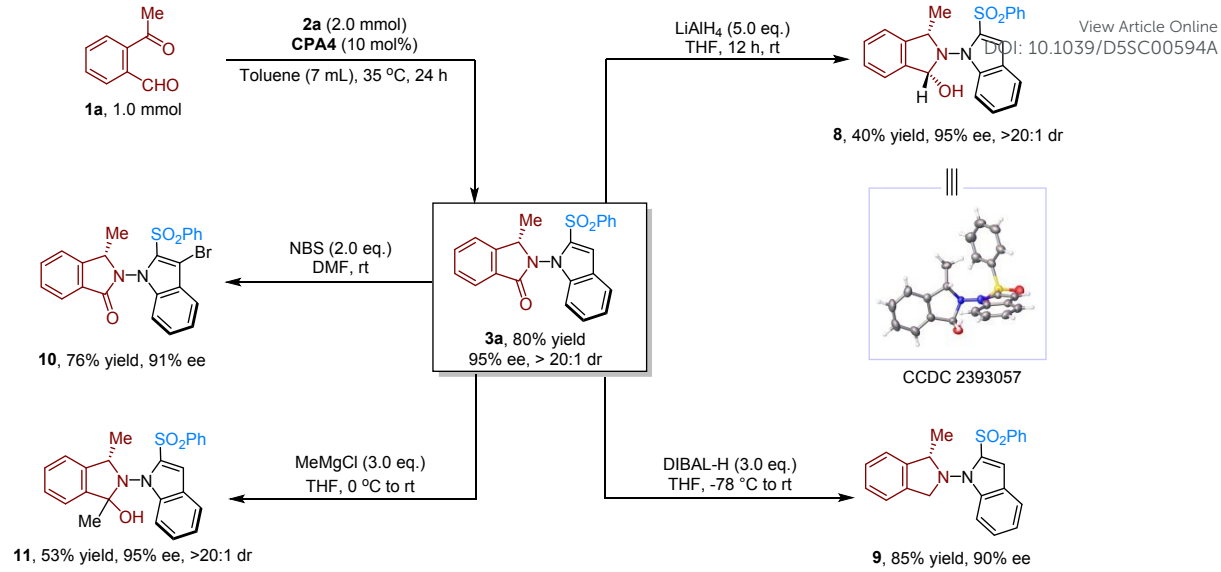

Fig. 5 Synthetic transformations.

At last, synthetic transformations of isoindolinones **3a** were performed (Fig. 5). First, the large-scale experiment of **3a** was carried out which afforded **3a** in 80% yield with 95% ee. Interestingly, treatment of **3a** with $LiAlH_4$ resulted in semi-reduction, affording centrally chiral product **8** in 95% ee with > 20:1 dr. When the reduction was performed with diisobutylaluminium hydride (DIBAL-H) in THF, complete reduction of the carbonyl moiety was observed producing compound **9** in 85% yield with 90% ee. Additionally, the bromo group was easily introduced via the bromination of **3a** with NBS, affording **10** in 76% yield with 91% ee. The stereospecific addition of **3a** could be achieved by using MeMgCl which furnished **11** in 53% yield with 95% ee and >20:1 dr.

Conclusions

In conclusion, we have reported the atroposelective [4+1] annulation of ketoaldehydes with 1*H*-indol-1-amines for the synthesis of centrally and axially chiral isoindolinones bearing N-N axes. By subjecting the D_2O or $H_2{}^{18}O$ to the reaction system, a series of isotopically chiral isoindolinones could be easily obtained with D- or ^{18}O-incorporation in good to excellent levels, respectively. Control experiments and DFT studies indicated that the reaction proceeded through the condensation to *E*-imine intermediates, followed by the nucleophilic addition- driven CPA-catalyzed enantioselective cyclization and isomerization. We anticipate that the strategy herein could inspire more studies on the synthesis of isotopically chiral molecules with multiple chiral elements.

Author contributions

H. Y. conceived and designed the experiment. G. J., Z. L.-H. and Z. H.-F. performed experiments and collected the data. G. J. provided the DFT calculations. H. Y. wrote the manuscript with the revision of all authors.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting this article have been included as part of the ESI.†

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (22201131) and the Natural Science Foundation of Jiangsu Province (BK20220137).

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DOI: 10.1039/D5SC00594A

The data that support the findings of this study are available in the Supplementary Information of this article.