Chemical
Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2025, **16**, 5735

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 23rd January 2025
Accepted 25th February 2025

DOI: 10.1039/d5sc00594a

rsc.li/chemical-science

Atroposelective [4+1] annulation for the synthesis of isotopic isoindolinones bearing both central and axial chirality†

Jun Gu, Li-Hong Zhang, Hong-Feng Zhuang and Ying He *

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 centrally chiral molecules and H/D exchange. Herein, we report a chiral phosphoric acid-catalyzed atroposelective [4+1] annulation of ketoaldehydes and 1*H*-indol-1-amines. By means of this strategy, a series of D- and ^{18}O-labeled atropisomers featuring both central and axial chiralities are synthesized with high enantioselectivities and diastereoselectivities and 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 enantio-determining process.

Introduction

The 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 bioactive molecules since D-incorporation may not only improve the pharmacokinetic (PK) profile but also provide a solution when bioactive molecules face 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 chorea associated with Huntington's disease and tardive dyskinesia (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 synthesizing 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 incorporation of other nonradioactive isotope (*e.g.* ^{18}O) into chiral molecules bearing multiple chiral elements is still undeveloped, despite the fact that these kinds of molecules may also have superior comprehensive performance compared to non-isotopic molecules.

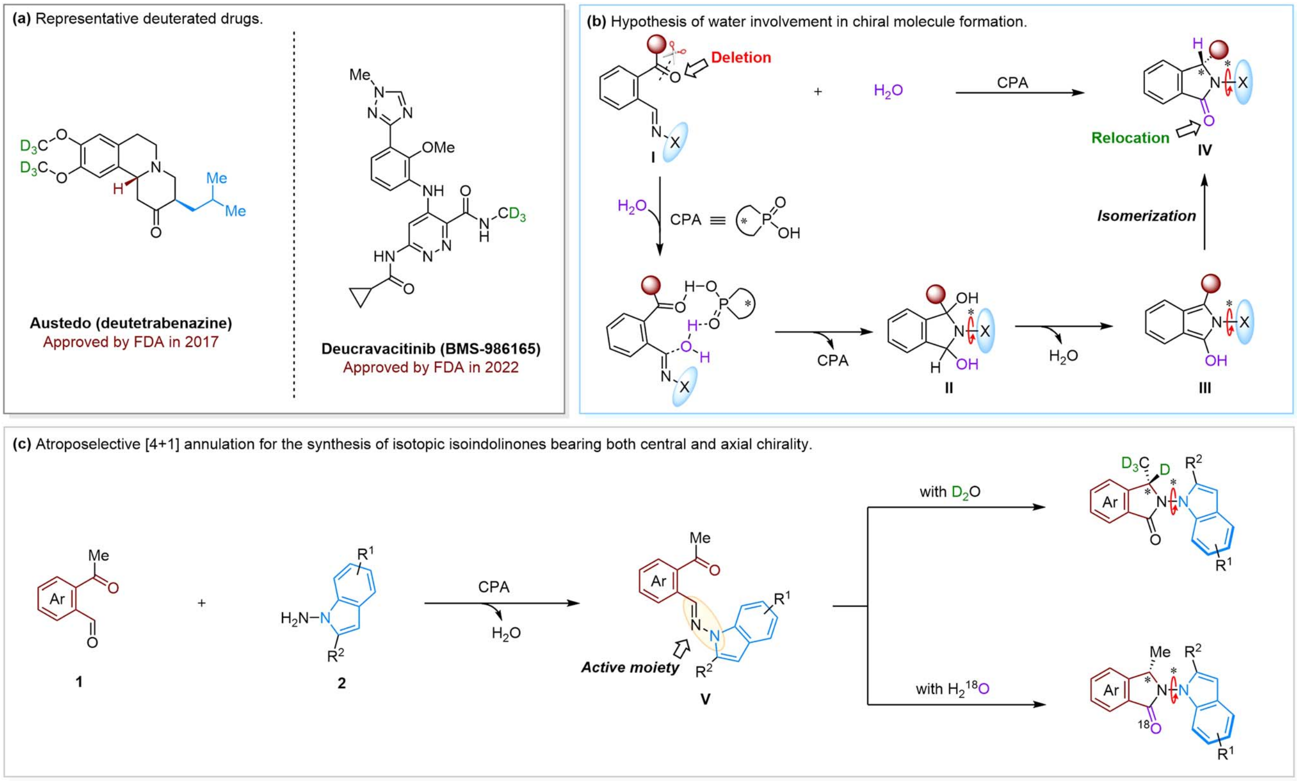
Isotopic water (D_2O and $H_2{}^{18}O$) is one of the most desirable reagents for the synthesis of isotopically chiral molecules. In this regard, water-involved reactions offer an efficient approach for introducing D or ^{18}O without the need for tedious synthetic procedures of isotopic starting materials. However, the asymmetric introduction of isotopes (D and ^{18}O) by using isotopic water is still in its early stages.[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 asymmetric cyclization *via* chiral phosphoric acid (CPA) catalysis. This may cause the carbonyl moiety to first convert to the 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 the 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 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 propose that the reaction of acetaldehyde **1** with 1*H*-indol-1-amine **2** by CPA catalysis could generate intermediate (**V**), featuring the active *N*-amine moiety[10] with the

---

School of Chemistry and Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China. E-mail: yhe@njust.edu.cn

† 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 DOI: **https://doi.org/10.1039/d5sc00594a**


(a) Representative deuterated drugs.

(b) Hypothesis of water involvement in chiral molecule formation.

(c) Atroposelective [4+1] annulation for the synthesis of isotopic isoindolinones bearing both central and axial chirality.

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

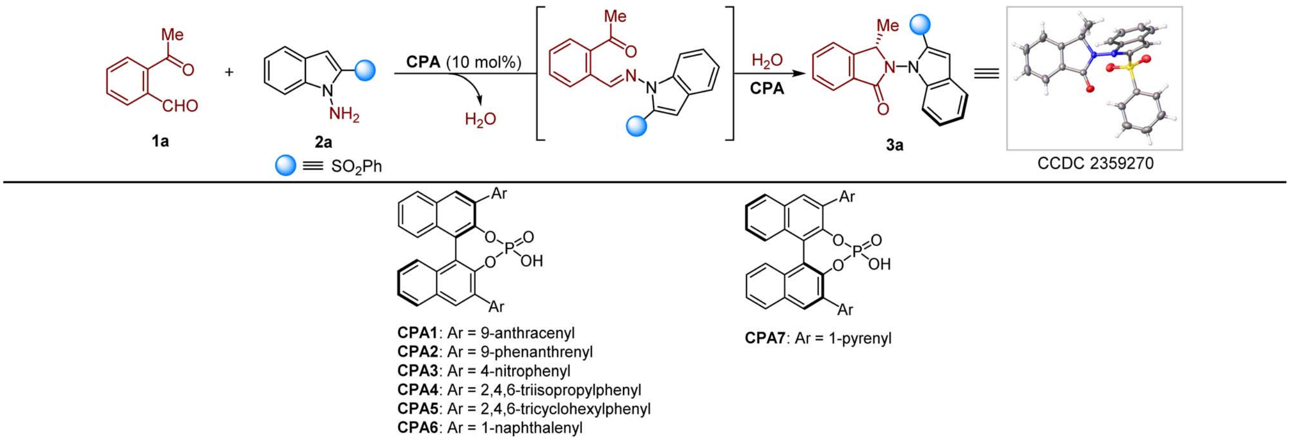
release of one molecule of H_2O (Fig. 1c). Herein, extra isotopic D_2O could be added to the reaction system to replace the H_2O and then react with **V**. On the other hand, due to the keto–enol tautomerism of **V** (or **1**), D-incorporation at the benzylic site would also be expected. Similarly, the ^{18}O-labeled products could also be afforded by 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.[13]

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 molecular H_2O released during 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 a low diastereomeric ratio (dr) of 3 : 1 (Table 1, entry 1). We then screened a variety of CPA catalysts for the reaction and identified **CPA4** as the optimal catalyst that gave **3a** in 94% ee and 91% yield with a dr of over 20 : 1 (entries 2–7). The absolute configuration of **3a** was determined to be (*P*, *S*) by 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). A lower concentration of the reaction mixture resulted in comparable ee of **3a** but with a relatively lower yield of 68% and 17 : 1 dr (entry 13). Moreover, as shown in entries 14–16, decreasing the reaction temperature and catalyst loading both led to **3a** with lower ee (77–91%). When the SO_2Ph group was replaced with the H group, 68% ee of isoindolinone **3a** was obtained. In order to examine the axial configurational stability of **3a**, a 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^{-1}, suggesting the high configurational stability of the 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 the 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 the C5 position were compatible with the reaction, providing the desired products (**3f–3k**) in good to excellent yields and high enantioselectivities (92–96% ee), with excellent to high levels of diastereomeric control (10 : 1 to >20 : 1 dr). However, relatively lower 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

Table 1 Optimized conditions for the reaction[a]



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	—

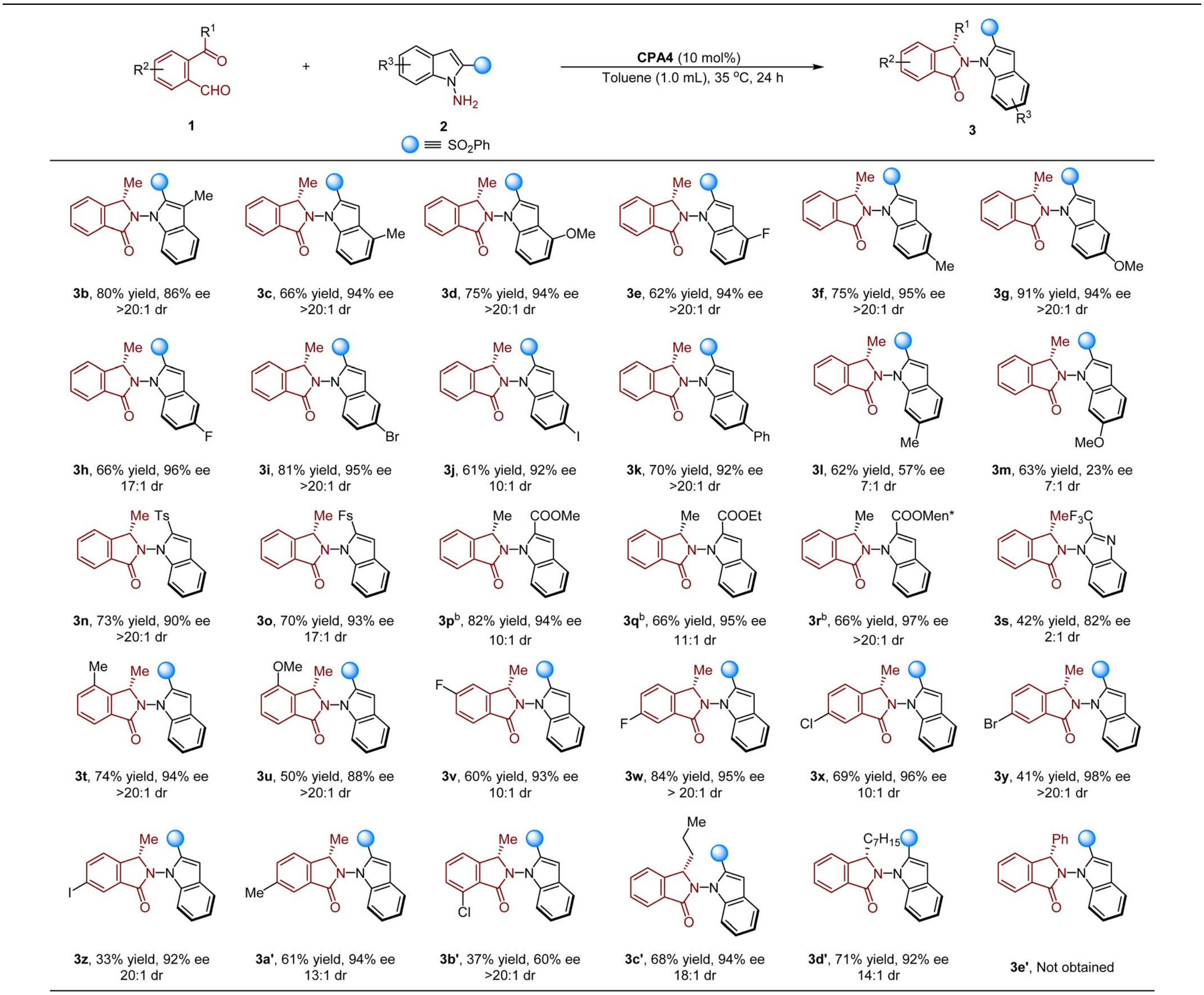
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA** catalyst (10 mol%), solvent (1.0 mL), 35 °C and 24 h. Isolated yield, ee values were determined by high performance liquid chromatography (HPLC), and dr values were determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] 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 replaced with H.

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 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, 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.

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 the C3, C4 or C5 position were well tolerated to produce the corresponding products in high yields with good to high dr (**4a–4e**). In addition, ketoaldehydes **1** bearing different groups at the phenyl ring were tolerated under 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 with high D-incorporation at the methyl group (89–91%) and moderate D-incorporation at the benzylic position (63–70%). The moderate D-incorporation at the 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 with the C_7H_{15} group gave **4i** in high ee and dr with moderate D-incorporation.

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

Table 2 Substrate scope[a]



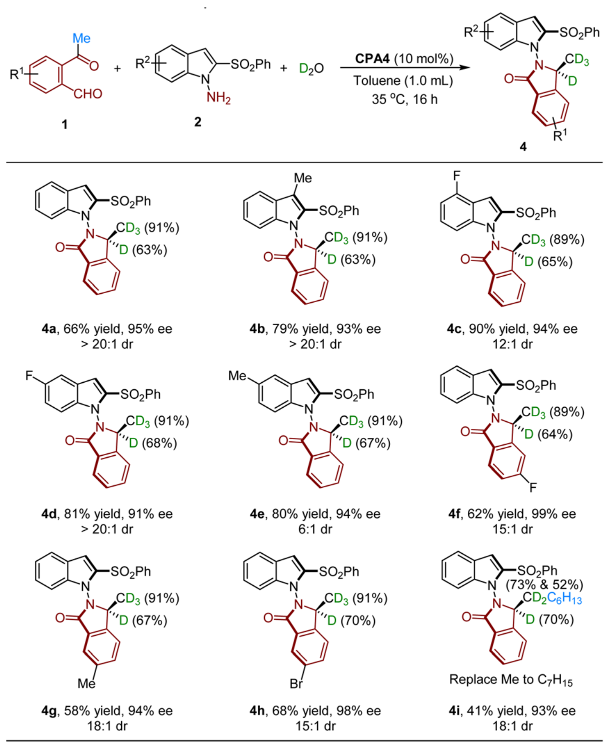
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **CPA4** (10 mol%), toluene (1.0 mL), 35 °C and 24 h. Isolated yield, ee values were determined by HPLC, and dr values were determined by ^{1}H-NMR analysis of the crude reaction mixture. Ts = tosyl and Fs = *p*-fluorobenzenesulfonyl. [b]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

positions of the indolyl ring were well-accommodated, affording ^{18}O-labeled isoindolinones **5a–5e** in high ee and dr with an 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 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**.

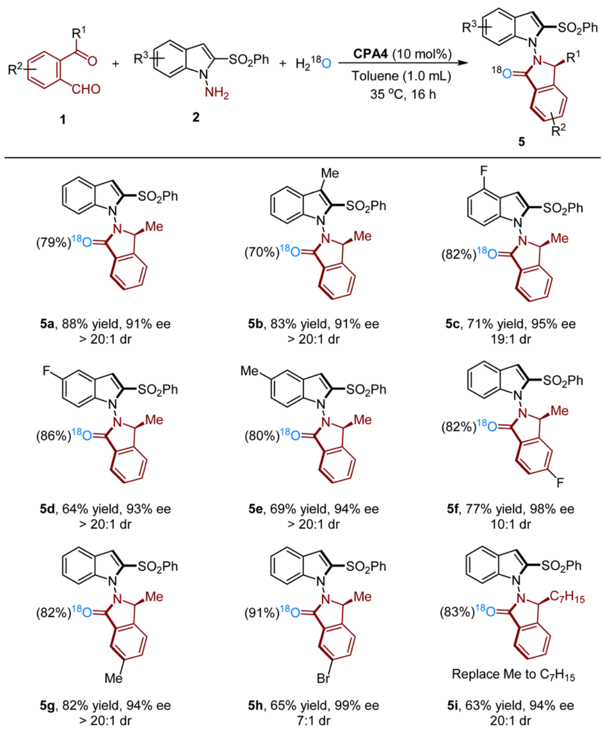
To probe the isotope introduction step of the reaction, we then performed D- and ^{18}O-labeling experiments (Fig. 2b). The reaction of **D-1a** with **2a** resulted in **3a** in 90% yield and 94% ee, but with no D-incorporation observed in **3a**. In addition, the reaction of **Int0** with D_2O or $H_2{}^{18}O$ yielded **4a** or **5a** with

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 and 24 h. Isolated yield and ee values were determined by HPLC. The dr values and D-incorporation were determined by ^1H-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 and 24 h. Isolated yield, ee values were determined by HPLC, and dr values were determined by ^1H-NMR analysis of the crude reaction mixture. The ^{18}O-incorporation was determined by high-resolution mass spectrometry (HRMS).

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 that the reaction may proceed *via* concerted or stepwise annulation (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 **6** since achiral **iii-6a** would be generated in this case (Fig. 2d). As a result, compound **7** 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, 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^{-1}, indicating that 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 gain 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 are shown in Fig. 3, and the coordination of **Int0** with **CPA4** was selected as the reference point. With H_2O participating in the reaction, the dual H-bonding effect was generated with an energy barrier of 16.0 kcal mol^{-1} (**Int0** + H_2O). The *Re*-face attack of the amine by water formed **Int1$_{R}$** *via* transition state **TS1$_{Re}$** with an energy barrier of 24.5 kcal mol^{-1}, whereas the *Si*-face attack formed **Int6$_{S}$** *via* transition state **TS6$_{Si}$** with a higher energy barrier of 28.4 kcal mol^{-1}. Thus, **Int1$_{R}$** is the more favorable intermediate, which undergoes sequential *N*-nucleophilic addition to the carbonyl group. In this case, four intermediates **Int2–5** may be generated accordingly, with **Int3$_{1S\text{-}Sa\text{-}3R}$** was superior to others because of the relatively lower energy barrier of **TS3$_{1Re\text{-}Sa\text{-}3R}$** (24.3 kcal mol^{-1}).

Alternatively, if concerted annulation occurred, only four pathways might be experienced *via* transition states **TS11$_{1Re\text{-}Ra\text{-}3Re}$**, **TS12$_{1Si\text{-}Ra\text{-}3Si}$**, **TS17$_{1Re\text{-}Sa\text{-}3Re}$** or **TS18$_{1Si\text{-}Sa\text{-}3Si}$** (Fig. 4). This is mainly because the bulky indole moiety existing in **Int0** induced exclusive suprafacial activation by **CPA4**. In this regard, the annulation that proceeded *via* **TS18$_{1Si\text{-}Sa\text{-}3Si}$** has an overcome energy barrier of 30.5 kcal mol^{-1}, a finding that is not possible. On the other hand, although **Int3$_{1S\text{-}Sa\text{-}3R}$** could be easily afforded *via* **TS3$_{1Re\text{-}Sa\text{-}3R}$**, the sequential dehydration step has an extremely high energy barrier of 38.8 kcal mol^{-1} *via* **TS19$_{1S\text{-}Sa\text{-}3R}$**, which is not possible either. This result also ruled

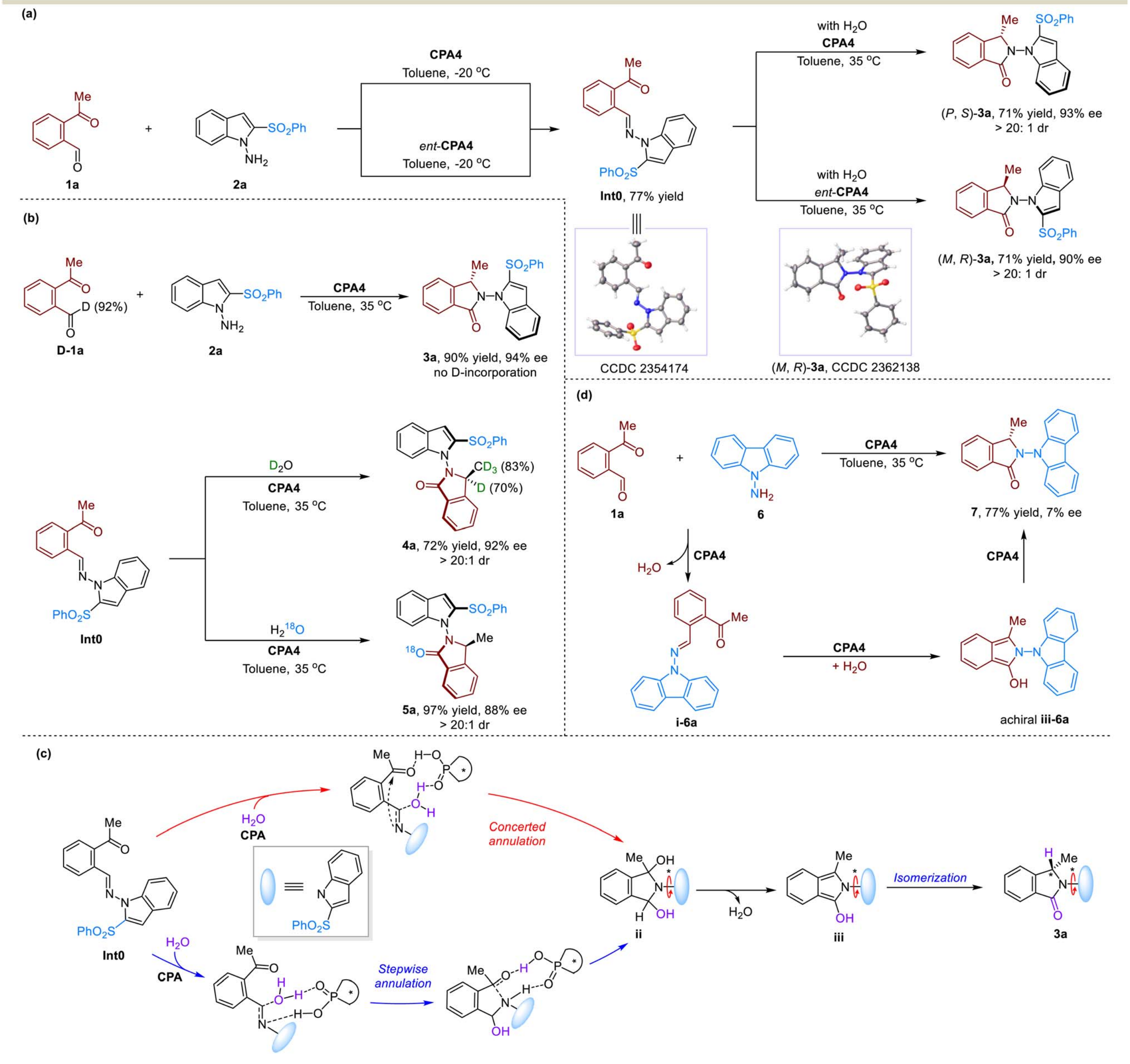


Fig. 2 Mechanistic studies. (a) Control experiments. (b) Deuterium- and ^{18}O-labeling experiments. (c) Proposed reaction pathway. (d) Enantio-determining-step investigation.

out the only possible stepwise pathway that occurred from **Int3**$_{\mathbf{1}\boldsymbol{S}\text{-}\boldsymbol{Sa}\text{-}\mathbf{3}\boldsymbol{R}}$ (Fig. 3, blue line). In contrast, our calculation revealed that **Int2**$_{\mathbf{1}\boldsymbol{S}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{R}}$ and **Int8**$_{\mathbf{1}\boldsymbol{R}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{S}}$ are more favorable intermediates, which are generated *via* **TS11**$_{\mathbf{1}\boldsymbol{Re}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{Re}}$ and **TS12**$_{\mathbf{1}\boldsymbol{Si}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{Si}}$ with energy barriers of 23.4 and 24.3 kcal mol^{-1}, respectively. However, the dehydration from **Int2**$_{\mathbf{1}\boldsymbol{S}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{R}}$ required overcoming a relatively higher energy barrier than that of **Int8**$_{\mathbf{1}\boldsymbol{R}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{S}}$. Therefore, the reaction preferred to undergo dehydration *via* **TS14**$_{\mathbf{1}\boldsymbol{R}\text{-}\boldsymbol{Ra}\text{-}\mathbf{3}\boldsymbol{S}}$ to afford **Int11**$_{\boldsymbol{P}}$. The intramolecular isomerization then occurred *via* **TS15**$_{\boldsymbol{P}\text{-}\boldsymbol{Re}}$ to afford (*P*, *S*)-**3a** with an energy barrier of 26.9 kcal mol^{-1}. This result is consistent with our experimental observation that isoindolinone **3a** was obtained in preferential (*P*, *S*) configuration.

Finally, 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.

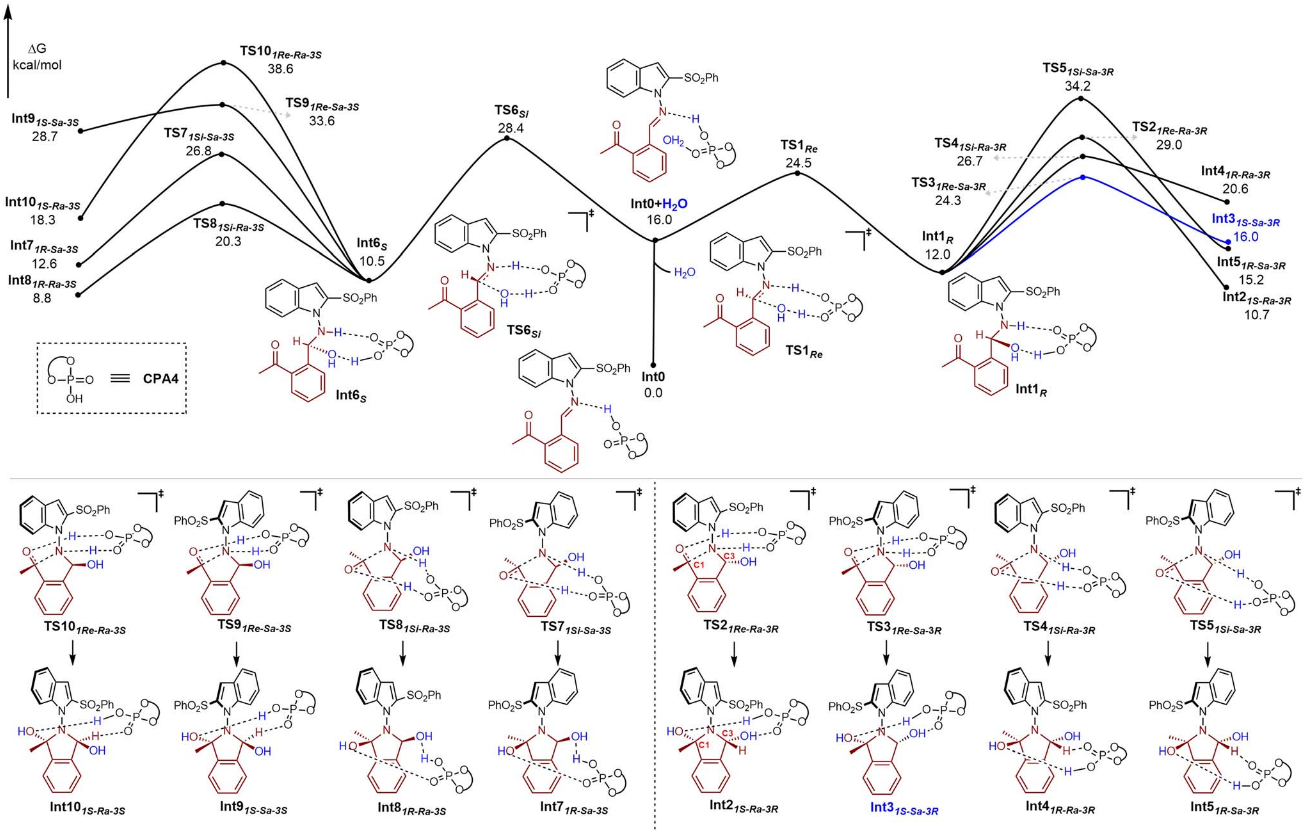


Fig. 3 DFT studies of stepwise annulation. Free energy diagrams of the chiral phosphoric acid-catalyzed stepwise mechanism in asymmetric annulation. Gibbs free energy obtained at the M06-2X/def2-TZVPP(SMD, Toluene)//M06-2X/def2-SVP level. The meaning of the corner mark in the structure name: ***Re***: 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.

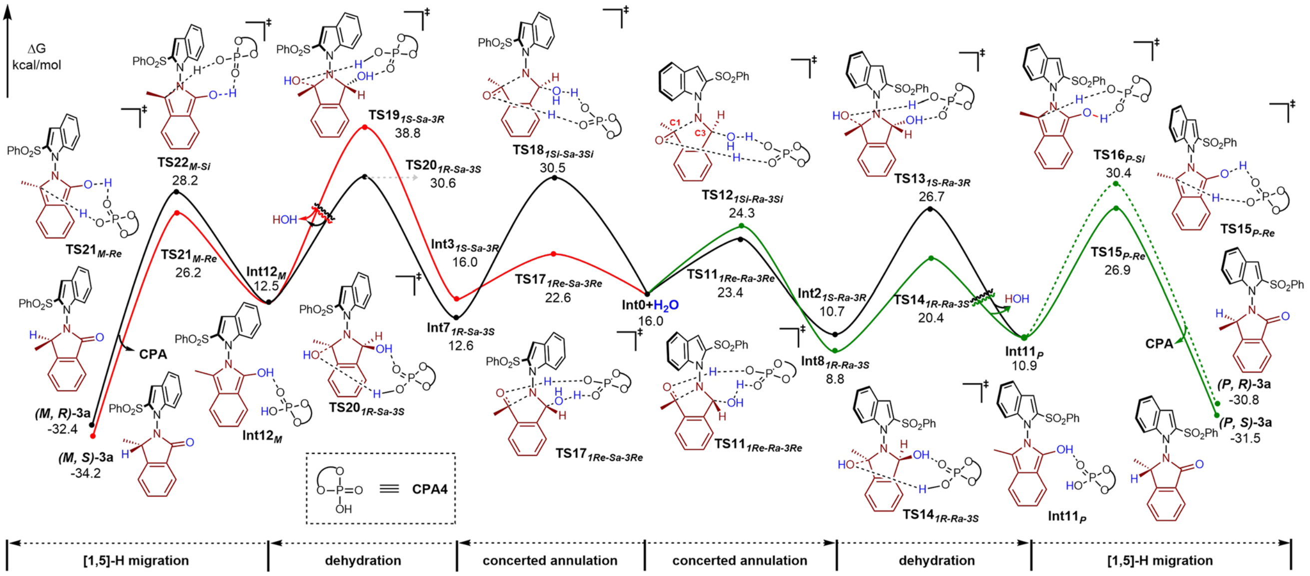


Fig. 4 DFT studies of concerted annulation. Free energy diagrams of the chiral phosphoric acid-catalyzed concerted mechanism for asymmetric annulation, and the investigation of enantioselectivity. ***M*** and ***P*** were used to replace the ***R*** and ***S*** configurations of axial chirality, respectively.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

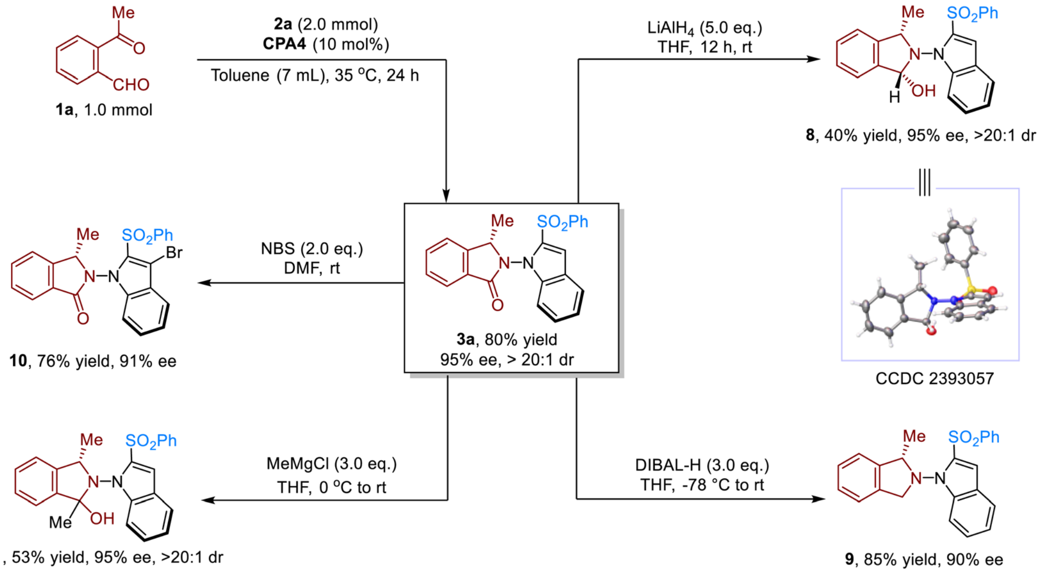


Fig. 5 Synthetic transformations.

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 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 condensation to *E*-imine intermediates, followed by 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.

Data availability

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

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.

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).

Notes and references

1 (*a*) C. S. McCaughey, J. A. van Santen, J. J. J. van der Hooft, M. H. Medema and R. G. Linington, *Nat. Chem. Biol.*, 2022, **18**, 295–304; (*b*) M. Miyagi and K. C. S. Rao, *Mass Spectrom. Rev.*, 2007, **26**, 121–136; (*c*) X. Tian, H. P. Permentier and R. Bischoff, *Mass Spectrom. Rev.*, 2023, **42**, 546–576; (*d*) X. Chen, Y. Sun, T. Zhang, L. Shu, P. Roepstorff and F. Yang, *Genomics, Proteomics Bioinf.*, 2021, **19**, 689–706; (*e*) J. Liu, Y. Shan, Y. Zhou, Z. Liang, L. Zhang and Y. Zhang, *Trac. Trends Anal. Chem.*, 2020, **124**, 115815; (*f*) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge and M. Beller, *Chem. Rev.*, 2022, **122**, 6634–6718; (*g*) J. Atzrodt, V. Derdau, W. J. Kerr and M. Reid, *Angew. Chem., Int. Ed.*, 2018, **57**, 1758–1784; (*h*) A. Labiche, A. Malandain, M. Molins, F. Taran and D. Audisio, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303535.

2 (*a*) R. M. C. Di Martino, B. D. Maxwell and T. Pirali, *Nat. Rev. Drug Discovery*, 2023, **22**, 562–584; (*b*) T. Pirali, M. Serafini, S. Cargnin and A. A. Genazzani, *J. Med. Chem.*, 2019, **62**, 5276–5297; (*c*) T. M. Belete, *Drug Des., Dev. Ther.*, 2022, **16**, 3465–3472; (*d*) T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595–3611.

3 S. H. DeWitt and B. E. Maryanoff, *Biochemistry*, 2018, **57**, 472–473.

4 (*a*) S. M. Hoy, *Drugs*, 2022, **82**, 1671–1679; (*b*) T. M. Truong, G. N. Pathak, A. Singal, V. Taranto and B. K. Rao, *Ann. Pharmacother.*, 2024, **58**, 416–427.

5 For selected examples on the synthesis of deuterated drugs, see: (*a*) H. M. C. Mouli, A. Vinod, S. Kumari, A. K. Tiwari, M. K. Kathiravan, V. Ravichandiran and R. Peraman, *Bioorg. Chem.*, 2023, **135**, 10649; (*b*) F. Liu, B. Wang, Y. Liu, W. Shi, X. Tang, X. Wang, Z. Hu, Y. Zhang, Y. Guo, X. Chang, X. He, H. Xu and Y. He, *ACS Med. Chem. Lett.*, 2022, **13**, 1730–1738; (*c*) F. Liu, B. Wang, Y. Liu, W. Shi, Z. Hu, X. Chang, X. Tang, Y. Zhang, H. Xu and Y. He,

Bioorg. Med. Chem. Lett., 2023, **86**, 129235; (*d*) Z. Zhang, Y. Lv, W. Renee Ong, X. Zhao, Z. Jia and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2024, **63**, e202408509; (*e*) P. Ma, T. Guo and H. Lu, *Nat. Commun.*, 2024, **15**, 10190.

6 (*a*) S. De Witt, A. W. Czarnik and V. Jacques, *ACS Med. Chem. Lett.*, 2020, **11**, 1789–1792; (*b*) B. Barabás, L. Caglioti, K. Micskei, C. Zucchi and G. Pályi, *Origins Life Evol. Biospheres*, 2008, **38**, 317–327; (*c*) X. Chang, X. Cheng and C.-J. Wang, *Chem. Sci.*, 2022, **13**, 4041–4049; (*d*) J. S. Rowbotham, M. A. Ramirez, O. Lenz, H. A. Reeve and K. A. Vincent, *Nat. Commun.*, 2020, **11**, 1454; (*e*) A. Li, X. Song, Q. Ren, P. Bao, X. Long, F. Huang, L. Yuan, J. Steve Zhou and X. Qin, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301091; (*f*) S. Miwa, R. Senda, K. Saito, A. Sato, Y. Nakamura and O. Kitagawa, *J. Org. Chem.*, 2022, **87**, 13501–13507; (*g*) K. Saito, S. Miwa, A. Iida, Y. Fujimoto, E. Caytan, C. Roussel and O. Kitagawa, *Org. Lett.*, 2021, **23**, 7492–7496.

7 (*a*) R. Senda, Y. Watanabe, S. Miwa, A. Sato and O. Kitagawa, *J. Org. Chem.*, 2023, **88**, 9579–9583; (*b*) Z. Zhu, X. Wu, G. T. Bida, H. Deng, X. Ma, S. Qian, Z. Wu, Z. Li and D. A. Nicewicz, *Nat. Synth.*, 2024, **4**, 97–105; (*c*) T. Miura, T. Nakamuro, Y. Nagata, D. Moriyama, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2019, **141**, 13341–13345; (*d*) R. H. Beddoe, D. C. Edwards, L. Goodman and R. M. Denton, *Chem. Commun.*, 2020, **56**, 6480–6483; (*e*) D. Chen, L. Xu, Z. Wang and C. Liu, *Chem*, 2023, **9**, 3212–3223; (*f*) Z. A. Tolchin and J. M. Smith, *J. Am. Chem. Soc.*, 2024, **146**, 2939–2943; (*g*) H. M. H. Nguyen, D. C. Thomas, M. A. Hart, K. R. Steenback, J. N. Levy and A. McNally, *J. Am. Chem. Soc.*, 2024, **146**, 2944–2949; (*h*) G. L. Bartholomew, S. L. Kraus, L. J. Karas, F. Carpaneto, R. Bennett, M. S. Sigman, C. S. Yeung and R. Sarpong, *J. Am. Chem. Soc.*, 2024, **146**, 2950–2958; (*i*) P. Xu, H.-Q. Jiang, H. Xu, S. Wang, H.-X. Jiang, S.-L. Zhu, L. Yin, D. Guo and X. Zhu, *Chem. Sci.*, 2024, **15**, 13041–13048; (*j*) X. Li, J. Zhou, W. Deng, Z. Wang, Y. Wen, Z. Li, Y. Qiu and Y. Huang, *Chem. Sci.*, 2024, **15**, 11418–11427.

8 For selected papers by using D_2O as the reactant to access D-stereogenic compounds, see: (*a*) L.-W. Zhan, C.-J. Lu, J. Feng and R.-R. Liu, *Angew. Chem., Int. Ed.*, 2023, **62**, e202312930; (*b*) Q. Shi, M. Xu, R. Chang, D. Ramanathan, B. Peñin, I. Funes-Ardoiz and J. Ye, *Nat. Commun.*, 2022, **13**, 4453; (*c*) W. Kong, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3987–3991; (*d*) Y. Yan, J. Yang, L. Wang, D. Xu, Z. Yu, X. Guo, G. P. Horsman, S. Lin, M. Tao and S.-X. Huang, *Chem. Sci.*, 2020, **11**, 3959–3964.

9 For selected papers on the synthesis of chiral isoindolinones, see: (*a*) L. Chen and Y.-X. Zou, *Adv. Synth. Catal.*, 2021, **363**, 4159–4176; (*b*) R. Savela and C. Méndez-Gálvez, *Chem.–Eur. J.*, 2021, **27**, 5344–5378; (*c*) S. Samanta, S. A. Ali, A. Bera, S. Giri and K. Samanta, *New J. Chem.*, 2022, **46**, 7780–7830; (*d*) V. Bisai, A. Suneja and V. K. Singh, *Angew. Chem., Int. Ed.*, 2014, **53**, 10737–10741; (*e*) Y. Zhang, Y.-F. Ao, Z.-T. Huang, D.-X. Wang, M.-X. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 5282–5285; (*f*) C. Min, Y. Lin and D. Seidel, *Angew. Chem., Int. Ed.*, 2017, **56**, 15353–15357; (*g*) D. Augner, D. C. Gerbino, N. Slavov, J.-M. Neudörfl and H.-G. Schmalz, *Org. Lett.*, 2011, **13**, 5374–5377; (*h*) X. Yu, A. Lu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, *Eur. J. Org Chem.*, 2011, **2011**, 892–897; (*i*) A. Suneja, V. Bisai and V. K. Singh, *J. Org. Chem.*, 2016, **81**, 4779–4788; (*j*) S. Lebrun, R. Sallio, M. Dubois, F. Agbossou-Niedercorn, E. Deniau and C. Michon, *Eur. J. Org Chem.*, 2015, **2015**, 1995–2004; (*k*) A. Di Mola, M. Tiffner, F. Scorzelli, L. Palombi, R. Filosa, P. D. Caprariis, M. Waser and A. Massa, *Beilstein J. Org. Chem.*, 2015, **11**, 2591–2599; (*l*) A. Beriša, D. Glavač, C. Zheng, S.-L. You and M. Gredičak, *Org. Chem. Front.*, 2022, **9**, 428–435; (*m*) P. Mukherjee, A. Sairaman, H. J. Deka, S. Jain, S. K. Mishra, S. Roy, P. Bhaumik and D. Maiti, *Nat. Synth.*, 2024, **3**, 835–845; (*n*) G. Yang, C. Shen and W. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 9141–9145; (*o*) M.-W. Chen, Q.-A. Chen, Y. Duan, Z.-S. Ye and Y.-G. Zhou, *Chem. Commun.*, 2012, **48**, 1698–1700; (*p*) W.-J. Cui, Z.-J. Wu, J. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2020, **142**, 7379–7385; (*q*) K. Fang, W. Huang, C. Shan, J. Qu and Y. Chen, *Org. Lett.*, 2021, **23**, 5523–5527; (*r*) M.-Y. Teng, Y.-J. Wu, J.-H. Chen, F.-R. Huang, D.-Y. Liu, Q.-J. Yao and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2024, **63**, e202318803.

10 R. Appel, S. Chelli, T. Tokuyasu, K. Troshin and H. Mayr, *J. Am. Chem. Soc.*, 2013, **135**, 6579–6587.

11 For selected papers on the synthesis of N-N atropisomers bearing two chiral elements, see: (*a*) J. Feng and R.-R. Liu, *Chem.–Eur. J.*, 2024, **30**, e202303165; (*b*) X.-F. Bai, Y.-M. Cui, J. Cao and L.-W. Xu, *Acc. Chem. Res.*, 2022, **55**, 2545–2561; (*c*) H.-H. Zhang, T.-Z. Li, S.-J. Liu and F. Shi, *Angew. Chem., Int. Ed.*, 2024, **63**, e202311053; (*d*) A. Gaucherand, E. Yen-Pon, A. Domain, A. Bourhis, J. Rodriguez and D. Bonne, *Chem. Soc. Rev.*, 2024, **53**, 11165–11206; (*e*) S.-J. Wang, X. Wang, X. Xin, S. Zhang, H. Yang, M. W. Wong and S. Lu, *Nat. Commun.*, 2024, **15**, 518; (*f*) W.-T. Wang, S. Zhang, W. Lin, Z.-H. Luo, D. Hu, F. Huang, R. Bai, Y. Lan, L. Qian and J.-Y. Liao, *Org. Chem. Front.*, 2024, **11**, 3308–3319; (*g*) T.-T. Wang, J. Cao and X. Li, *Org. Lett.*, 2024, **26**, 6179–6184; (*h*) S. S. Ranganathappa, B. S. Dehury, G. K. Singh, S. Shee and A. T. Biju, *ACS Catal.*, 2024, **14**, 6965–6972; (*i*) C. Portolani, G. Centonze, S. Luciani, A. Pellegrini, P. Righi, A. Mazzanti, A. Ciogli, A. Sorato and G. Bencivenni, *Angew. Chem., Int. Ed.*, 2022, **61**, e202209895; (*j*) X. Wang, S.-J. Wang, X. Xin, H. An, Z. Tu, H. Yang, M. W. Wong and S. Lu, *Chem. Sci.*, 2024, **15**, 13240–13249; (*k*) F.-B. Ge, C.-J. Lu, X. Chen, W. Yao, M. An, Y.-K. Jiang, L.-P. Xu and R.-R. Liu, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400441; (*l*) T.-J. Han, Q.-L. Yang, J. Hu, M.-C. Wang and G.-J. Mei, *JACS Au*, 2024, **4**, 4445–4454; (*m*) Y. Wang, X. Zhu, D. Pan, J. Jing, F. Wang, R. Mi, G. Huang and X. Li, *Nat. Commun.*, 2023, **14**, 4661.

12 For selected papers on the synthesis of N–N atropisomers, see: (*a*) G. Centonze, C. Portolani, P. Righi and G. Bencivenni, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303966; (*b*) Z.-H. Chen, T.-Z. Li, N.-Y. Wang, X.-F. Ma, S.-F. Ni, Y.-C. Zhang and F. Shi, *Angew. Chem., Int. Ed.*,

2023, **62**, e202300419; (*c*) K.-W. Chen, Z.-H. Chen, S. Yang, S.-F. Wu, Y.-C. Zhang and F. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116829; (*d*) Y. Gao, L.-Y. Wang, T. Zhang, B.-M. Yang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200371; (*e*) C.-S. Wang, Q. Xiong, H. Xu, H.-R. Yang, Y. Dang, X.-Q. Dong and C.-J. Wang, *Chem. Sci.*, 2023, **14**, 12091–12097; (*f*) Q. Huang, Y. Li, C. Yang, W. Wu, J. Hai and X. Li, *Org. Chem. Front.*, 2024, **11**, 726–734; (*g*) T.-Z. Li, S.-F. Wu, N.-Y. Wang, C.-S. Hong, Y.-C. Zhang and F. Shi, *J. Org. Chem.*, 2024, **89**, 12559–12575; (*h*) Z. Huang, Y. Xu, W. Lin, R. Qian, W. Zhang and X. Li, *Org. Chem. Front.*, 2024, **11**, 5437–5442; (*i*) J. Wang, D. Pan, F. Wang, S. Yu, G. Huang and X. Li, *Sci. Adv.*, 2024, **10**, eado4489; (*j*) X.-M. Wang, P. Zhang, Q. Xu, C.-Q. Guo, D.-B. Zhang, C.-J. Lu and R.-R. Liu, *J. Am. Chem. Soc.*, 2021, **143**, 15005–15010; (*k*) G.-J. Mei, J. J. Wong, W. Zhang, A. A. Nangia, K. N. Houk and Y. Lu, *Chem*, 2021, **7**, 2743–2757; (*l*) S.-Y. Yin, Q. Zhou, C.-X. Liu, Q. Gu and S.-L. You, *Angew. Chem., Int. Ed.*, 2023, **62**, e202305067; (*m*) X. Zhu, H. Wu, Y. Wang, G. Huang, F. Wang and X. Li, *Chem. Sci.*, 2023, **14**, 8564–8569.

13 (*a*) J. E. Smyth, N. M. Butler and P. A. Keller, *Nat. Prod. Rep.*, 2015, **32**, 1562–1583; (*b*) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller and P. J. Edwards, *J. Med. Chem.*, 2011, **54**, 7005–7022; (*c*) M. Basilaia, M. H. Chen, J. Secka and J. L. Gustafson, *Acc. Chem. Res.*, 2022, **55**, 2904–2919.