



HAL
open science

Catalytic Enantioselective Allylboration and Related Reactions of Isatins Promoted by Chiral BINOLs: Scope and Mechanistic Studies

Julien Braire, Aurélie Macé, Rania Zaier, Marie Cordier, Joëlle Vidal, Claudia Lalli, Arnaud Martel, François Carreaux

► **To cite this version:**

Julien Braire, Aurélie Macé, Rania Zaier, Marie Cordier, Joëlle Vidal, et al.. Catalytic Enantioselective Allylboration and Related Reactions of Isatins Promoted by Chiral BINOLs: Scope and Mechanistic Studies. *Journal of Organic Chemistry*, 2023, 88 (3), pp.1469-1492. 10.1021/acs.joc.2c02476 . hal-03971612

HAL Id: hal-03971612

<https://hal.science/hal-03971612>

Submitted on 12 Oct 2023

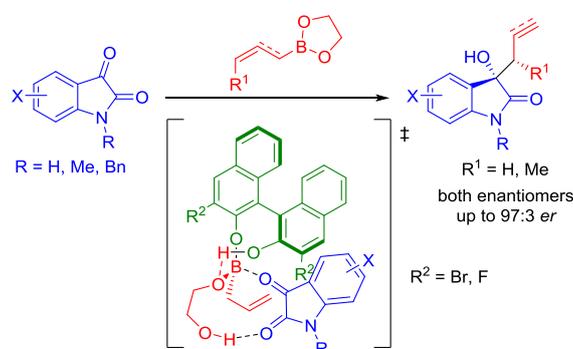
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Catalytic Enantioselective Allylboration and Related Reactions of Isatins Promoted by Chiral BINOLs: Scope and Mechanistic Studies

Julien Braire,[†] Aurélie Macé,[†] Raina Zaier,[‡] Marie Cordier,[†] Joëlle Vidal,^{†*} Claudia Lalli,^{†*} Arnaud Martel,^{‡*} and François Carreaux^{†*}

[†] Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) -UMR 6226, F-35000 Rennes, France. [‡] Institut des Molécules et Matériaux du Mans, UMR 6283 CNRS-Université du Maine, avenue Olivier Messiaen, 72085 Cedex Le Mans, France



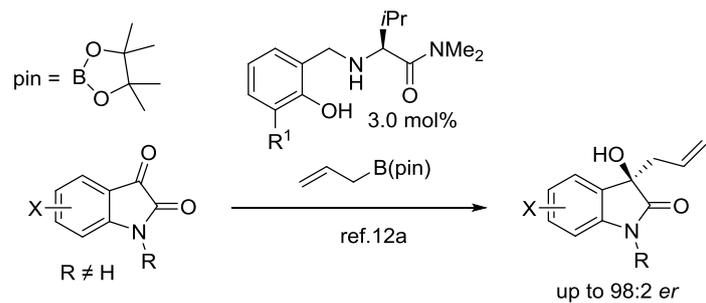
ABSTRACT: An improvement of the catalytic enantioselective allylboration of isatins with 2-allyl-1,3,2-dioxaborolane in the presence of chiral BINOL derivatives is reported offering an efficient one-step access to enantioenriched *N*-unprotected 3-allyl-3-hydroxy-2-oxindoles. This catalytic process is also effective for the crotylboration reaction with enantiomeric ratios (*er*) up to 97:3 as well as for the asymmetric synthesis of homopropargylic alcohols *via* an allenyl addition to indoline-2,3-diones. Origins of the high enantioselectivity in chiral BINOL catalyzed allylboration of isatins were examined by DFT calculations. A hypothetical scenario suggested a crucial internal hydrogen bonding between the amide group (C=O \cdots H-O) and the ethylene hydroxyl of the transient chiral mixed boronate ester generating a rigid and stabilized system that favors the addition of the allylboron species to the *Re* face of the ketone function. The key role of the alcohol additive (*t*-BuOH or *t*-AmOH) in the enantioselective allylboration reaction of isatins has also been shown on the basis of a kinetics study and computational calculations, by favoring the transesterification of the 2-allyl-1,3,2-dioxaborolane with BINOL *via* proton transfer processes.

INTRODUCTION

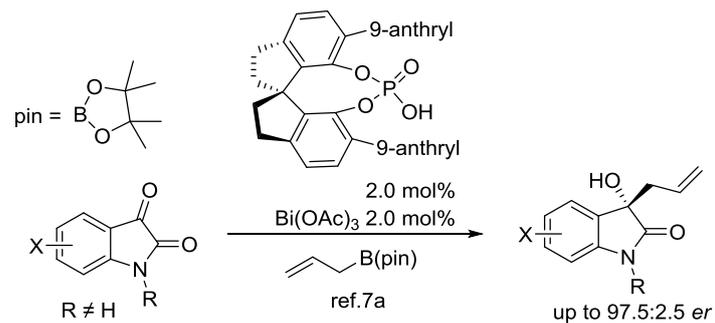
Among the existing allylation reactions of carbonyl compounds, the asymmetric allylboration constitutes probably one of the most reliable and predictable stereoselective methods for the formation of homoallylic alcohols *via* a Zimmerman-Traxler transition state.¹ Moreover, a simple implementation coupled with non-toxic and easily accessible enantioenriched allylboron reagents has made this non-metal approach very popular.² Unfortunately, this approach requires stoichiometric amounts of chiral auxiliaries for which the recovery and recycling can hardly be applied. As a response to environmental sustainability requirements, the discovery of chiral catalysts to promote the allylboration reaction became a research topic incrementally important over time.³ The pioneering results in this area have mainly been described by Miyura, and Hall based on Lewis and Brønsted acid-catalyzed allylboration.⁴ Since the seminal work of Antilla's group on the highly enantioselective TRIP catalyzed allylboration of aldehydes,⁵ a great number of work have been reported highlighting the significant interest of chiral phosphoric acids as Brønsted acid catalysts.⁶ Examples with ketones are less common, because they are less electrophilic and sterically more hindered than aldehydes.⁷ The Schaus group was one of the first to develop an efficient catalytic enantioselective synthesis of tertiary homoallylic alcohols from α -aryl ketones using allyldiisopropoxyborane as allyl reagent and in the presence of chiral diols such as BINOL derivatives.⁸ The method is based on the transient formation of a chiral allylboronate *via* reversible exchange of the boron's achiral alkoxy ligand with the chiral diol catalyst.⁹ As a result of those outcomes, several research works in this area have been disclosed employing different allylic boron reagents such as boronic acids or dioxaborinanes to non-activated ketones using chiral biphenol catalysts.¹⁰ This mode of catalysis can be extended to the enantioselective preparation of homopropargylic alcohols from ketones using allenylboronates under solvent-free microwaves conditions.¹¹ For substrates containing an activated ketone group, such as *N*-protected isatins, a chiral catalyst based on 1,3-amino alcohols incorporating an acidic phenol functionality was designed by the Hoveyda's group¹² (Figure 1a) while Li's group has reported the use of SPINOL-derived phosphoric acid with Bi(III) salt^{7a} (Figure 1b). Recently, we have shown that commercially available chiral BINOL derivatives can also catalyze an asymmetric allylboration of these substrates with 2-allyl-1,3,2-dioxaborolane under optimized conditions (Figure 1c).¹³ The choice to use a five-membered cyclic boronic ester, more stable than an acyclic boronate but more reactive than a

six-membered cyclic analog,¹⁴ was crucial to produce the expected chiral tertiary homoallylic alcohols in good yields and with excellent enantiomeric ratios. Unfortunately, an experimental limitation was observed with the *N*-unprotected isatins since these starting materials need an additional reaction time compared to their corresponding *N*-substituted compounds (6 days instead of 24 h). Due to our interest toward allylboration methodologies¹⁵ and considering the 3-allyl-3-hydroxy-2-oxindole moiety as a privileged scaffold for the synthesis of natural or biologically active products (Figure 1d),¹⁶ we planned to refine the experimental conditions of this organocatalytic method to further increase the scope. Moreover, in light of the stereochemical outcome obtained with cyclic non-activated ketones such as indan-1-one,^{8,13} we considered that a computational study of this catalytic process was crucial to rationalize the face differentiation of the carbonyl group in the case of isatins.

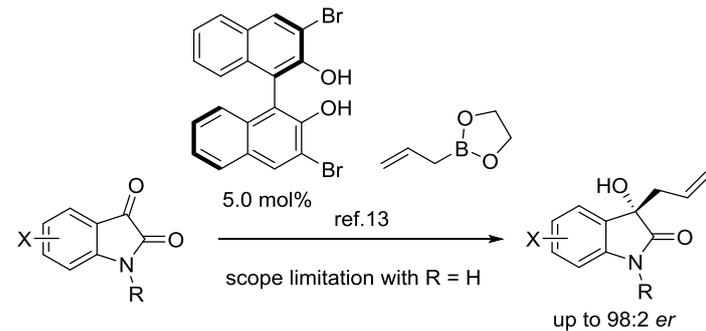
a)



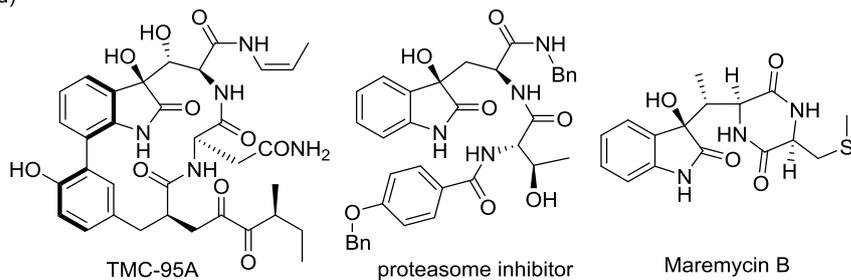
b)



c)



d)



e)

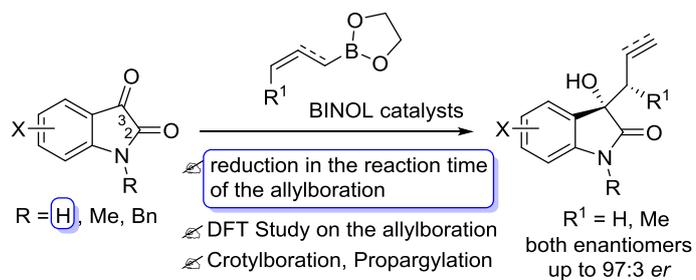


Figure 1. Catalysts for the asymmetric allylboration of isatins. a) Catalytic process developed by Hoveyda's group. b) Catalytic process developed by Li's group. c) Our previous work describing BINOL derivatives as catalysts. d) Representative bioactive compounds containing the 3-substituted-3-hydroxyindole core. e) This work: improvement/extension to the methodology using BINOL catalysts and mechanistic study.

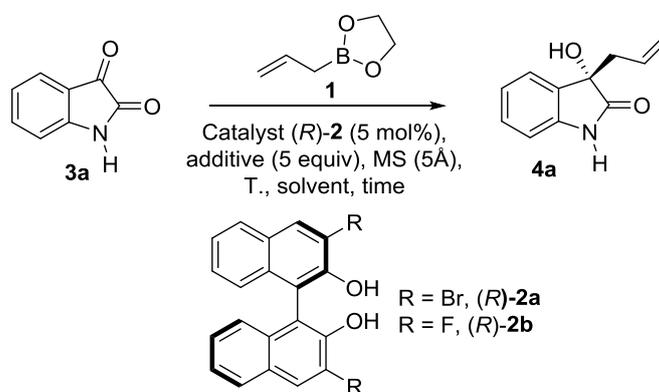
Herein, we report the improvements of BINOL derivatives-catalyzed allylboration of isatins, in particular with *N*-unprotected substrates. We also show that this catalytic process is effective for the crotylboration reaction with excellent enantiomeric ratios as well as for the asymmetric synthesis of tertiary homopropargylic alcohols through the addition of an ethylene glycol allenylboronate to isatins (Figure 1e). Results of DFT calculations of this allylboration reaction are also described and suggest the formation of a favored transition state, in agreement with the experimentally observed stereoselectivity, resulting from an internal hydrogen bonding involving the ethylene glycol of the chiral mixed boronate ester and the oxygen of the carbonyl group at position 2 of isatin. The role of the alcohol additive (*t*-BuOH or *t*-AmOH) on the reaction rate and enantioselectivity was also investigated *via* kinetic studies and computational calculations.

RESULTS AND DISCUSSION

Experimental studies. In order to find better experimental conditions for the enantioselective allylboration of *N*-unprotected isatins with 2-allyl-1,3,2-dioxaborolane **1**, indoline-2,3-dione **3a** was chosen as model substrate (Table 1). Our previous works using (*R*)-3,3'-Br₂-BINOL **2a** as catalyst (5 mol%) at -10 °C in toluene have shown that the reaction was almost completed after 6 days with an excellent enantiomeric ratio (Entry 1).¹³ In this context, the goal was to reduce the reaction time while maintaining a high enantioselectivity. Due to the negative impact on the enantiomeric ratio by increasing the temperature (Entry 2), we decided to examine the effect of the solvent.¹⁷ Inspired by Schaus findings,⁸ we first tested a mixture of toluene (PhCH₃) and α,α,α -trifluorotoluene (PhCF₃), this latter being considered as an environmentally friendly solvent.¹⁸ A 1:2 solvent ratio in favor of PhCF₃ at -10 °C gave a lower enantioselectivity (Entry 3). When PhCF₃ was used as sole solvent at the same temperature, a higher enantiomeric ratio (94.5:5.5 *er*) was obtained (Entry 4). It is interesting to note that, in both cases, the reaction time is roughly 4 times shorter than employing only toluene as solvent. At this stage, we cannot assign this positive effect to a better solubility of **3a** in PhCF₃¹⁹ but probably other physical properties of this solvent such as polarity have to be considered. Encouraged by this outcome, we evaluated (*R*)-3,3'-F₂-BINOL organocatalyst

2b which was described as efficient as **2a** in the asymmetric allylboration reaction of ketones.^{10a} After 36 h, the use of (*R*)-**2b** (5 mol%) led to a lower yield of **4a** accompanied by a significant drop in the enantioselectivity (Entry 5). Further optimizations were focused on tuning the reaction temperature as well as the nature of the alcohol additive (Entries 6-8). Using catalyst **2a**, the best conditions were found at room temperature in PhCF₃ by replacing *tert*-butyl alcohol (*t*-BuOH) with *tert*-amyl alcohol (*t*-AmOH), that has a lower melting point (Entry 7). Thanks to these easy-to-implement modifications, the 3-allyl-3-hydroxyindole **4a** was obtained after purification in 94% yield and 94.5:5.5 *er* in a shorter reaction time (5 h). Moreover, a simple recrystallization of **4a** using CH₂Cl₂ allowed to obtain the (*S*)-enantiomer in a higher optical purity and with a moderate drop in yield (73%, >99:1 *er*, Entry 7). Reaction of **3a** at a ten times greater scale provided the homoallyl alcohol **4a** with similar yield and enantioselectivity demonstrating the good reproducibility of this process (Entry 8). The enantioselective allylboration starting from 2 mmol of **3a** was repeated twice with similar results (Entry 8). Compared to the initial conditions, significant improvements in terms of reaction time and temperature have been brought offering the prospect of a convenient and large-scale access to chiral *N*-unprotected 3-allyl-3-hydroxyoxindoles.

Table 1. Optimization of the allylboration reaction with *N*-unprotected isatin **3a**



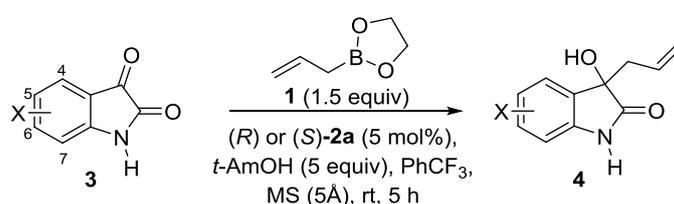
Entry ^a	Cat.	additive	Solvent	T (°C)	Time (h)	Yield (%) ^b	<i>ee</i> (%) ^c
1	2a	<i>t</i> -BuOH	PhCH ₃	-10 °C	144	87	94
2	2a	<i>t</i> -BuOH	PhCH ₃	rt	22	97	85
3	2a	<i>t</i> -BuOH	PhCH ₃ /PhCF ₃ (1:2)	-10 °C	36	93	86
4	2a	<i>t</i> -BuOH	PhCF ₃	-10 °C	36	95	89

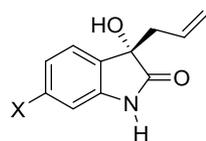
5	2b	<i>t</i> -BuOH	PhCF ₃	-10 °C	36	85	62
6	2a	<i>t</i> -BuOH	PhCF ₃	rt	5	97	85
7	2a	<i>t</i> -AmOH ^d	PhCF ₃	rt	5	94 (73) ^e	89 (>98) ^e
8 ^f	2a	<i>t</i> -AmOH ^d	PhCF ₃	rt	5	99 (86) ^e	90 (>98) ^e

^a All reactions were performed with isatin **3a** (0.2 mmol), boronate **1** (0.3 mmol), solvent (1 mL) under Ar at the indicated temperature and reaction time. ^b Isolated yield after chromatography purification on silica. ^c Determined by chiral HPLC. ^d *tert*-Amyl alcohol. ^e Obtained after a single recrystallization using CH₂Cl₂. ^f Starting from 2 mmol of isatin **3a**.

With the aim to define the substrate-scope of this asymmetric organocatalytic methodology, a set of diversely substituted NH isatins **3a-m** has been evaluated under these optimized reaction conditions (Table 2). Whatever their electronic nature, the presence of substituents at C5, C6 and/or C7 positions on the aromatic ring was not a barrier to obtain the expected products **4a-l** with excellent yields.

Table 2. Asymmetric allylboration of various *N*-unprotected isatins **3 and ORTEP diagram of compounds **4h** and **4k**^a**

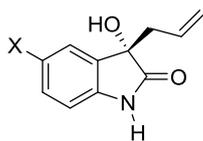




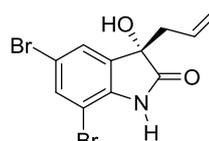
4a, X = H, 94%, 89% ee
(73%, >98% ee)^f

4b, X = Br, 87%, 89% ee

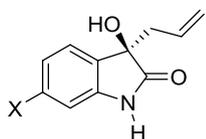
4c, X = F₃C, 82%, 83% ee



4d^c, X = F, 88%, 86% ee
4e^c, X = CF₃O, 95%, 81% ee
(60%, >98% ee)^f



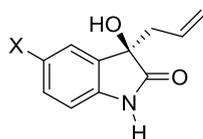
4f^d, 88%, 89% ee



4g^b, X = H, 97%, 85% ee
(69%, >98% ee)^f

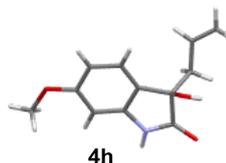
4h^{b,d}, X = MeO, 93%, 89% ee
(48%, >98% ee)^f

4i^b, X = Cl, 90%, 87% ee

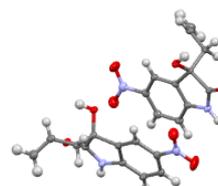


4j^b, X = MeO, 98%, 86% ee
(51%, 88% ee)^f

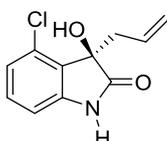
4k^{b,d}, X = NO₂, 98%, 79% ee
(60%, >98% ee)^f



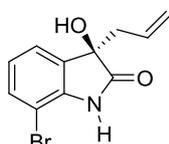
4h



4k



4m^{b,e}, 38%, 18% ee



4l^b, 98%, 85% ee
(70%, >98% ee)^f

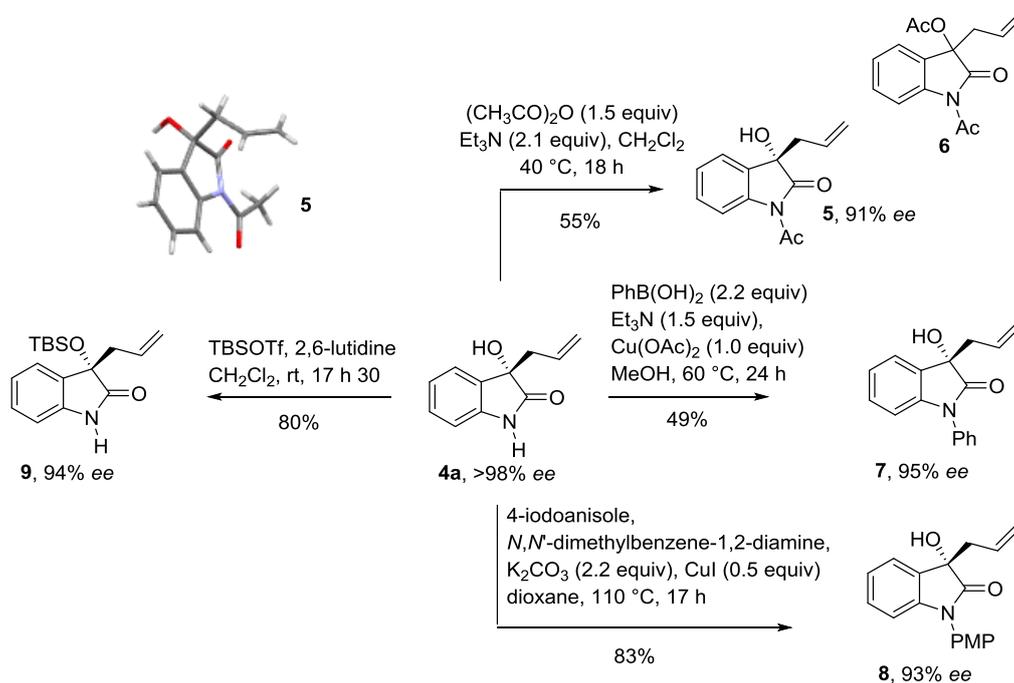
^a All reactions were performed with **3** (0.2 mmol), boronate **1** (0.3 mmol), catalyst (*R*)-**2a** (5 mol%) in PhCF₃ (1 mL) under Ar. Isolated yields are shown. Enantiomeric excess was determined by chiral HPLC. ^b Catalyst (*S*)-**2a** was used. ^c 2 h 30 instead of 5 h. ^d 12 h instead of 5 h. ^e 144 h instead of 5 h. ^f In brackets, yield and enantiomeric ratio through a single recrystallization process using CH₂Cl₂.

In some instances, the reaction time was shorter (2 h 30, **4d-e**) or longer (12 h, **4f**, **4h**, **4k**) to reach a complete conversion at room temperature. In all cases, high enantioselectivities were obtained which could be sometimes enhanced by a simple recrystallization using CH₂Cl₂. As expected, yields and enantiomeric ratios in the same order of magnitude have been achieved for the synthesis of (*R*)-3-allyl-3-hydroxyoxindoles **4g-l** employing the (*S*)-**2a** catalyst. The single-crystal X-Ray diffraction of **4h** and **4k** confirmed their absolute configuration and by inference, those of all of the products of the allylboration.²⁰ Significant limitations in terms of reaction time and stereoselectivity were observed starting from the C4-substituted isatin **3m**. The expected product **4m** was isolated with a poor yield after 6 days (38%) and in an almost racemic form. This negative impact on the reaction suggests a steric hindrance between the substituent on the aromatic ring and the organocatalyst grafted on the boron atom. This point will be further discussed in the mechanistic study.

In order to demonstrate the synthetic value of chiral *N*-unprotected 3-allyl-3-hydroxyindolin-2-ones, selective *O*- and *N*-functionalizations of compound **4a** have been

carried out (Scheme 1). *N*-acetylation was performed using acetic anhydride and Et₃N at 40 °C for 18 h using an oil bath. The formation of the desired product **5** was accompanied by the presence of another compound **6** in a respective ratio 7:3, resulting from a subsequent *O*-acetylation of the tertiary hydroxyl group. Nevertheless, the *N*-acetyl-3-allyl-3-hydroxyindolin-2-one **5** was isolated with a good yield (55%) and a high enantioselectivity (95.5:4.5 *er*). Recrystallization from CH₂Cl₂ allowed to obtain single crystals of **5** which were subjected to X-ray diffraction.²¹ This strategy in two steps thus permitted to circumvent the drawback associated to the low enantioselectivity of the direct asymmetric allylboration of *N*-acetyl isatin (57.5:42.5 *er*).¹³ Copper-mediated coupling methods were used to prepare the *N*-aryl oxindoles **7** and **8**.²² Treatment of **4a** with phenyl boronic acid and cupric acetate in the presence of triethylamine afforded the *N*-phenyl compound **7** in 49% yield.²³ For the introduction of the *p*-methoxyphenyl (PMP) protecting group, an Ullmann-type reaction was chosen.

Scheme 1. Chemoselective *O*- and *N*-functionalization of (*S*)-3-allyl-3-hydroxyindolin-2-one **4a and ORTEP diagram of compound **5****



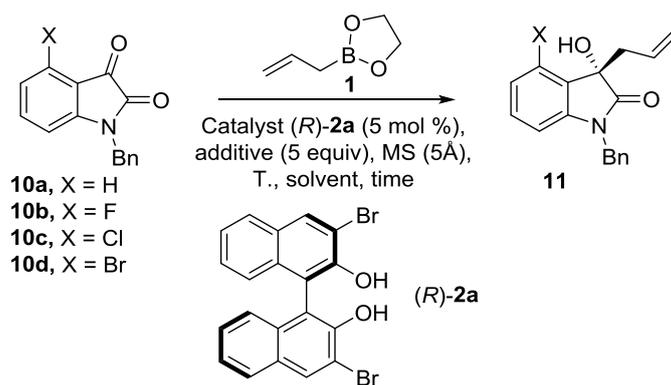
The coupling of 4-iodoanisole with **4a** using a copper iodide/*N,N'*-dimethylbenzene-1,2-diamine system provided the compound **8** in a good yield (83%). At last, silylation of **4a** with the *tert*-butyldimethylsilyl trifluoromethanesulfonate reagent (TBSOTf) at room temperature

followed by an acid work-up led to the selective formation of the TBS ether **9** in a good yield and a high enantioselectivity.

For the purpose of determining if the positive effect of solvent, PhCF₃, on the reaction time can be extended to *N*-protected isatins, some modifications (solvent, temperature, additive alcohol) of our previously described procedure related to the asymmetric allylboration of 1-benzylindoline-2,3-dione **10a** (X = H, Entry 1, Table 3) have been made.¹³ The replacement of toluene by PhCF₃ led to a shorter reaction time for the formation of **11a** at -10 °C (12 h instead of 24 h) with a slight decrease of the enantioselectivity (Entry 2). Unfortunately, this drop was significantly enhanced when the reaction was performed at room temperature rendering the use of PhCF₃ as solvent for the *N*-substituted substrates less interesting (Entries 3-4). The use of *t*-AmOH as additive in toluene at -10 °C did not bring any improvement compared to *t*-BuOH in terms of reaction time and enantioselectivity (Entry 5 compared to Entry 1). In the case of hexafluoroisopropanol (HFIP) at the same temperature (-10 °C), the complete conversion was much faster but **11a** was obtained in racemic form (Entry 6). This result can be explained by the high propensity of HFIP to form hydrogen bond (H-bond) clusters²⁴ and the mechanistic aspects derived from this experimental observation shall be discussed in the following section.

Subsequently, we examined if the presence of a substituent at C4 position on the aromatic ring could also be problematic for *N*-protected substrates (Entries 7-9, Table 3) as it was for NH isatins (**4m**, Table 2). Therefore, halogen-substituted compounds **10b-d** have been screened. In all cases, a very low conversion was observed compared to the unsubstituted compound **10a**. However, a slight difference can be noted between **10d** and **10b-c** since after 24 h at -10 °C, a lower conversion was observed (around 9%). Three days have been necessary to isolate **11d** in 30% yield (Entry 9).

Table 3. Additional information on the asymmetric allylboration of *N*-protected isatins 10



Entry ^a	Product	Solvent	Additive	T (°C)	Time (h)	Yield (%) ^b	ee (%) ^c
1	11a	PhCH ₃	<i>t</i> -BuOH	-10	24	99	94
2	11a	PhCF ₃	<i>t</i> -BuOH	-10	12	98	90
3	11a	PhCH ₃	<i>t</i> -BuOH	r.t.	16	98	88
4	11a	PhCF ₃	<i>t</i> -BuOH	r.t.	2	96	79
5	11a	PhCH ₃	<i>t</i> -AmOH	-10	24	99	88
6	11a	PhCH ₃	HFIP	-10	3	91	0
7	11b	PhCH ₃	<i>t</i> -BuOH	-10	24	15	5
8	11c	PhCH ₃	<i>t</i> -BuOH	-10	24	18	0
9	11d	PhCH ₃	<i>t</i> -BuOH	-10	72	30	19

^a All reactions were performed with isatin **10** (0.2 mmol), boronate **1** (1.5 equiv), solvent (1 mL) under Ar at the indicated temperature and reaction time. ^b Isolated yield after chromatography purification on silica. ^c Determined by HPLC analysis using a chiral column.

This difference in reactivity could be ascribed to the increased radius of halogen atoms then highlighting the argument of steric hindrance. This decrease reaction rate was also accompanied by a drastic drop of the enantioselectivity whatever halogen atom in C4 substituted isatins.

Mechanistic studies. With the aim of identifying the most probable activation mode involved in this enantioselective allylboration reaction catalyzed by (*R*)-3,3'-Br₂-BINOL **2a** (Table 3, Entry 1), several possible activation modes were considered in our DFT calculations (Figure 2). The first activation mode with (*R*)-**2a**, taken into account in this article, was based on the mechanism previously proposed by S. C. Pellegrinet and J. M. Goodman (Figure 2, pathway 2)^{9c} and applied to allenylboronates²⁵ or trifluoromethyl allylboronic acids²⁶ or with crotylboronates.²⁷ These DFT studies suggested that a macrocyclic allylboronate was formed

in situ. The authors proposed that this cyclic boronate could be responsible for the enantioselectivity of the reaction despite its higher free energy.²⁵ Then, we considered the possible activation of the allylboronate and/or isatin by the formation of H-bonds with (*R*)-**2a** (Figure 2, pathway 3). Indeed, Grayson et al. have already proposed an activation of oxygen atoms of the boronate (in green, pathway 3, Figure 2).^{6g} Simultaneously, the reactive carbonyl group of **10** would be further stimulated through a second H-bond with the amide carbonyl group of isatin (in red, pathway 3, Figure 2). Finally, a modified version of the mechanism proposed by Schaus involving the mono-transesterification of the allylboronate^{9a,b} by chiral BINOL **2a** was next studied (Figure 2, pathway 4). Based on NMR data that proved the formation of the mono-transesterification product from diisopropyl allylboronate, these authors proposed a transition state involving an intramolecular H-bond between the catalyst and the alkoxy ligand with opposite facial selectivity compared to isatin. In the present case, additional H-bonds with the amide carbonyl group will be studied (in red, pathway 4, Figure 2). As we used 2-allyl-1,3,2-dioxaborolane **1**, we speculated about the presence of an additional intramolecular H-bond which could favor the *Re* facial attack on the carbonyl group of isatin **10** (in red, pathway 4, Figure 2).

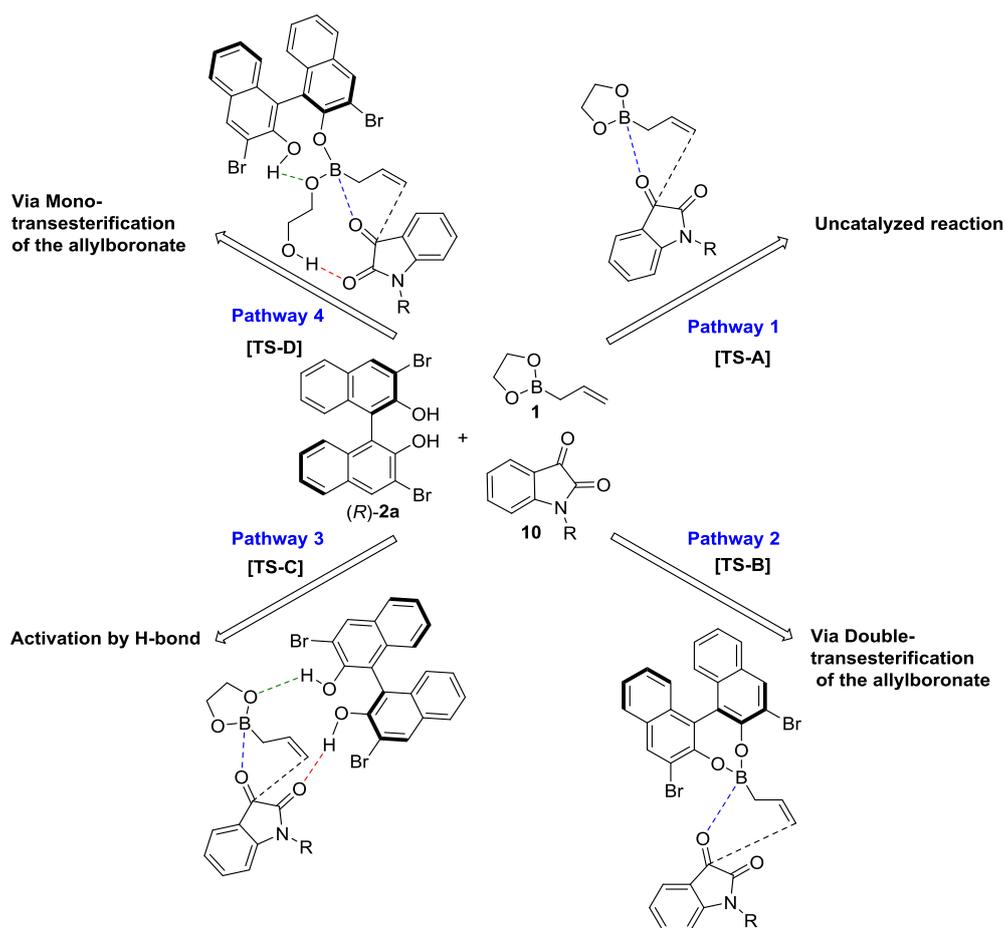


Figure 2. Different mechanistic pathways.

Considering pathways **4** and **2** that require prior formation of the allylboronates **12** and **13** resulting from the mono or double transesterification of allylboronate **1**, it was decided to calculate by DFT these intermediates and to compare their relative stability to the starting materials (Figure 3). The role played by the additive (*t*-BuOH) in these reactions was also one of the main objectives of the present study. Therefore, the intermediates **14**, **15** resulting from the possible transesterification with the additive (*t*-BuOH) were also studied (Figure 3). The DFT calculations were performed at the M06-2X/6-311+G (d,p)²⁸ using the SMD²⁹ model for the description of the solvent (toluene) at 298 K and atmospheric pressure. $\Delta\Delta E$ describes the electronic energy compared to the starting materials. $\Delta\Delta H_{298}$ and $\Delta\Delta G_{298}$ are respectively the relative enthalpies and Gibbs free energies at 298K compared to the starting materials.

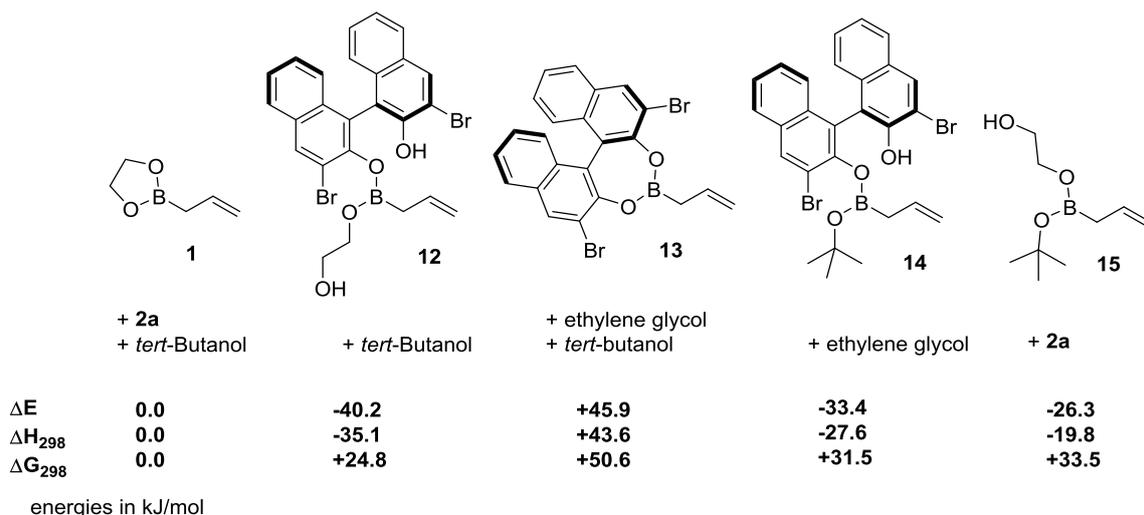


Figure 3. Relative energy compared to the starting materials of the transesterification products in kJ/mol.

If the transesterification of the boronate **1** by BINOL **2a** or even *tert*-butanol leads to the electronic stabilization of the products formed (**12**, **14** and **15**), the corresponding free Gibbs energies are higher than the starting materials. Among those species, **12** is the most stable, but the Gibbs free energy is sufficiently high to prevent its identification by NMR from the reaction mixture.³⁰ Interestingly, the cyclic boronate **13** appears significantly less stable than the starting boronate **1**, both electronic and Gibbs free energies suggesting that this mechanistic pathway 2 should be disfavored in the present case with allylboronate **1**^{9c} even if the Lewis acidity of the boron atom should be enhanced as proposed by Grayson and Goodman.²⁵ Indeed, while the torsion angle between the aromatic rings in **2a** from a crystal structures³¹ can be measured to 87.7°, the same dihedral angle is constrained to 50.7° in the calculated structure of **13**. This cycle strain contributes largely to the lower stability of **13** (+ ethylene glycol) compared to **12**.

At this stage the possible transition states corresponding to each pathway involved in the allylboration reaction were calculated (Figure 2). The *N*-Me derivative of isatin **10e** was considered as a good model to limit the computation cost compared to the benzyl derivative **10a** (similar yield and enantioselectivity).¹³ **TS-A** corresponds to the uncatalyzed allylboration reaction (pathway 1). **TS-B** involves the cyclic boronate formed by double transesterification with (*R*)-3,3'-Br₂-BINOL **2a** (pathway 2). **TS-C** corresponds to the activation of the boronate by the formation of H-bonds with the OH groups of **2a** (pathway 3). Finally, **TS-D** involves the boronate issued from the monoesterification by BINOL **2a** (pathway 4).

Being by far the most stable reaction course,³² only the chair-like transition states were calculated and are presented (Figures 4-8). Interestingly, the uncatalyzed reaction (**TS-A**) presents an energy gap similar to that of **TS-B** considering the enthalpy and even greater considering the free energy, even for the most favored approach from the *Si* face of isatin (**TS-B-Si**) (Figure 4). It should also be noted that this transition state leads to a selectivity opposite to the experimentally observed one. Hence, in the current case, contrary to the previous DFT calculations,^{9c,25-27} a mechanism involving a cyclic boronate like **13** is most likely not involved in the present reaction with the allylboronate **1** due to the enhanced reactivity of the carbonyl group of isatin compared to alkyl and aryl ketones.

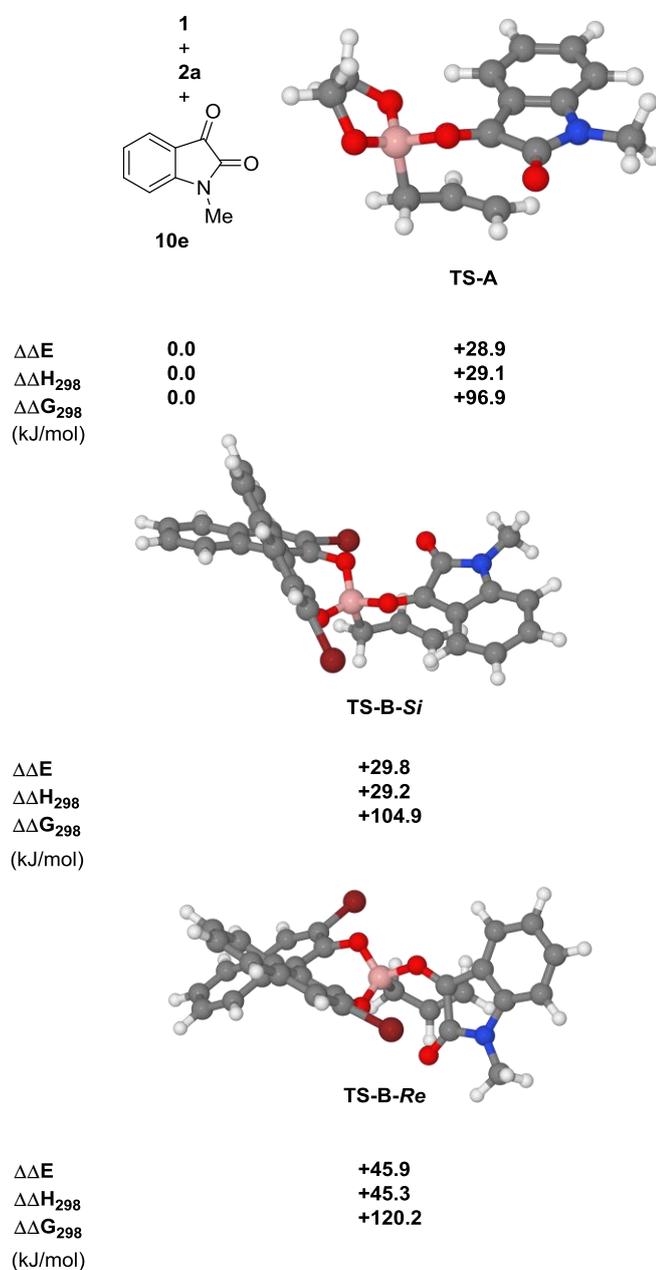


Figure 4. Representation of **TS-A** and **TS-B** (pathway 1 and 2).

The next possible mode of activation of the boronate (pathway 3) proceeds *via* the formation of H-bonds. The four most stable **TS-C** were calculated (Figures 5 and 6), and the most stable transition state found corresponds to an approach from the *Si* face of isatin to form the experimentally unfavored (*R*) product. These transition states corresponding to the two approaches on isatin (face *Re* and *Si*) reveal low energy gaps and subsequently weak expected selectivities. These reactions are almost certainly responsible of the background reaction lowering the selectivity at higher temperature and in the absence of *t*-BuOH.

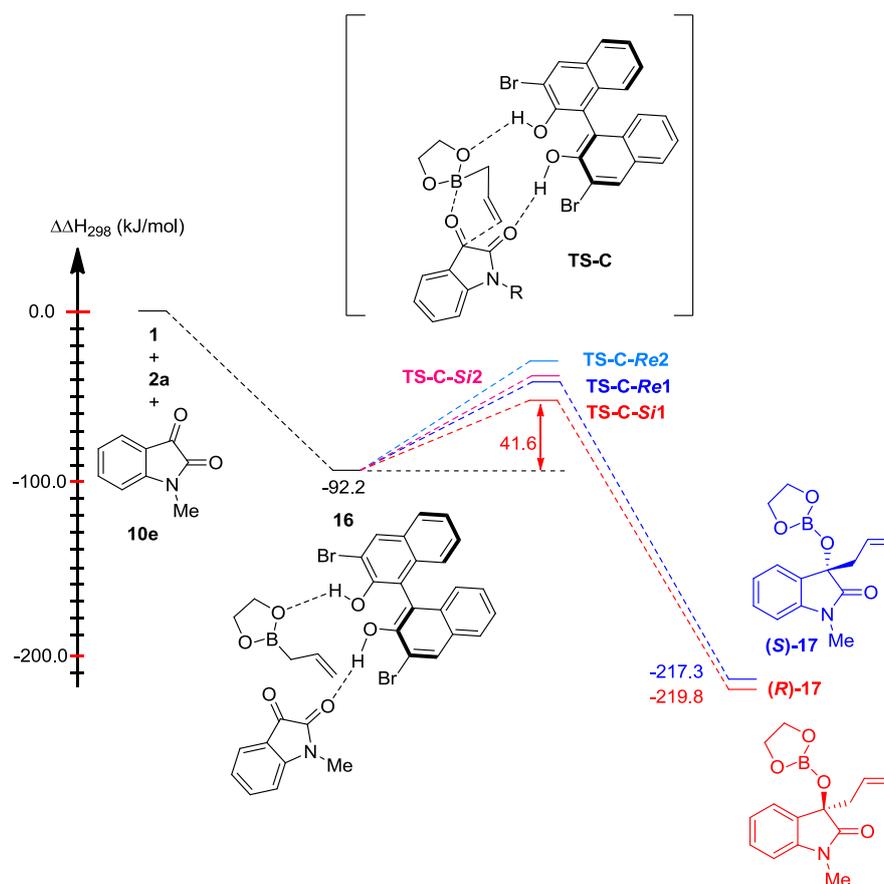


Figure 5. Energy diagram of the allylboration step for pathway 3 in kJ/mol.

In these transition states, **2a** forms H-bonds with both reagents to enhance the reactivity (Figure 6). One of the hydroxy groups of **2a** is linked to the oxygen atom of amide, and the other hydroxyl group plays a role in the activation of the boron atom *via* the formation of a H-bond with one of the oxygen atoms of the boronate. Interestingly, **TS-C-Si1** displays the lowest free energy and contribute evidently to the background reaction that reduces the selectivity of the reaction. Nevertheless, it should be considered that DFT calculations fail to

calculate accurately the real entropic contribution in a reaction mixture that contains 5 eq of *t*-BuOH due to the numerous states generated. In addition, the presence of *t*-BuOH will strongly contribute to disturb the hydrogen bonds involved in **TS-C** transition states providing a first explanation of the role played by *t*-BuOH as additive.

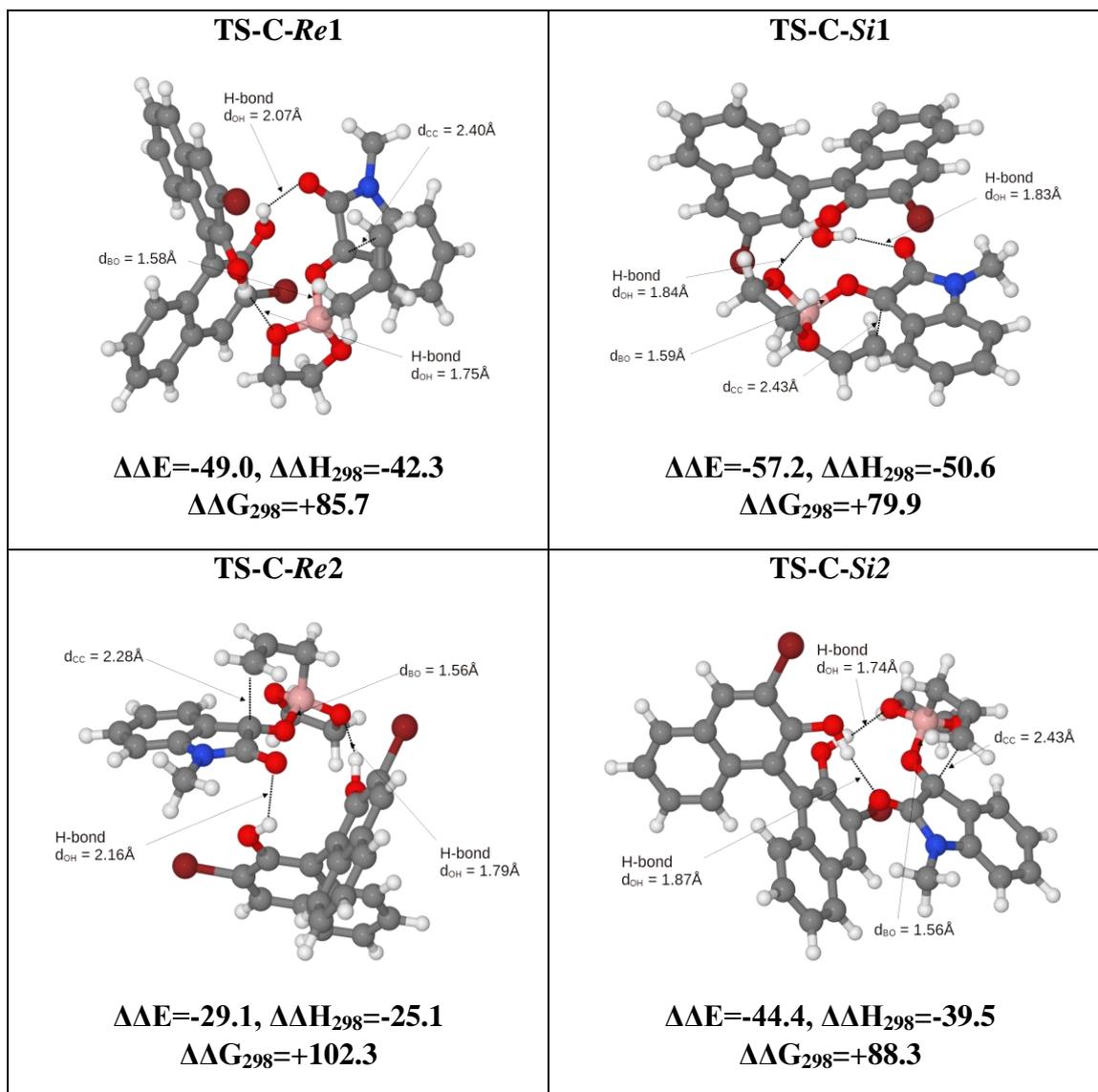


Figure 6. TS-C transition state structures (kJ/mol).

The stabilization of the partial charges in the transition states by the formation of H-bonds with BINOL **2a**, and hence the catalytic effect associated are consistent with the increase in the kinetic of the reaction described previously in the presence of HFIP (Table 3, Entry 6). These polar solvents contribute to even stabilize the transition state in the background reaction explaining the complete drop of selectivity observed in the presence of HFIP.

We tried to evaluate the role played by the H-bonds in the energy of these calculated transition states. Emamian and Lu proposed a correlation between the H-bond energy and the electron density at the critical point $\rho(r)$ for neutral complexes.³³ A single point calculation of the TSs was performed at the B3LYP-D3(BJ)/ma-TZVPP level as described by Emamian *et al.* The electron density was calculated using MultiWfn³⁴ and the equation applied to neutral complexes (bond energy in kcal/mol = $-223.08*\rho+0.7423$) was applied. Then, the energies of the two H-bonds were converted to kJ/mol and the sums are collected in Table 4. These results highlight the fact that other interactions play a crucial role in the relative energy of these transition states.

Table 4. Contribution of H-bonds in TS-C

Entry	TS	Σ H-bond stabilization energy (kJ/mol)	$\Delta\Delta E$ (kJ/mol)
1	TS-C-Re1	-48.0	-49.0
2	TS-C-Re2	-44.5	-29.1
3	TS-C-Si1	-56.5	-57.2
4	TS-C-Si2	-65.6	-39.5

The **TS-D** transition states were then calculated at the same level and the two most stable transition states corresponding to each approach could be calculated (Figure 7, pathway 4); two leading to the *S* and two to the *R* product, from the approaches of the allyl group on the *Re* and *Si* face of the isatin, respectively. In the most favored transition state **TS-D-Re1**, two H-bonds are formed (Figure 8), one between the ethylene glycol and the oxygen atom of the amide C=O group of isatin, which plays a key role in the creation of the oxygen-boron bond prior to the transition state. A second H-bond exists between the residual OH of BINOL **2a** and one of the oxygens of the boronate. Owing to its energy gap compared with the three other transition states, this approach is most likely responsible for the observed selectivity.

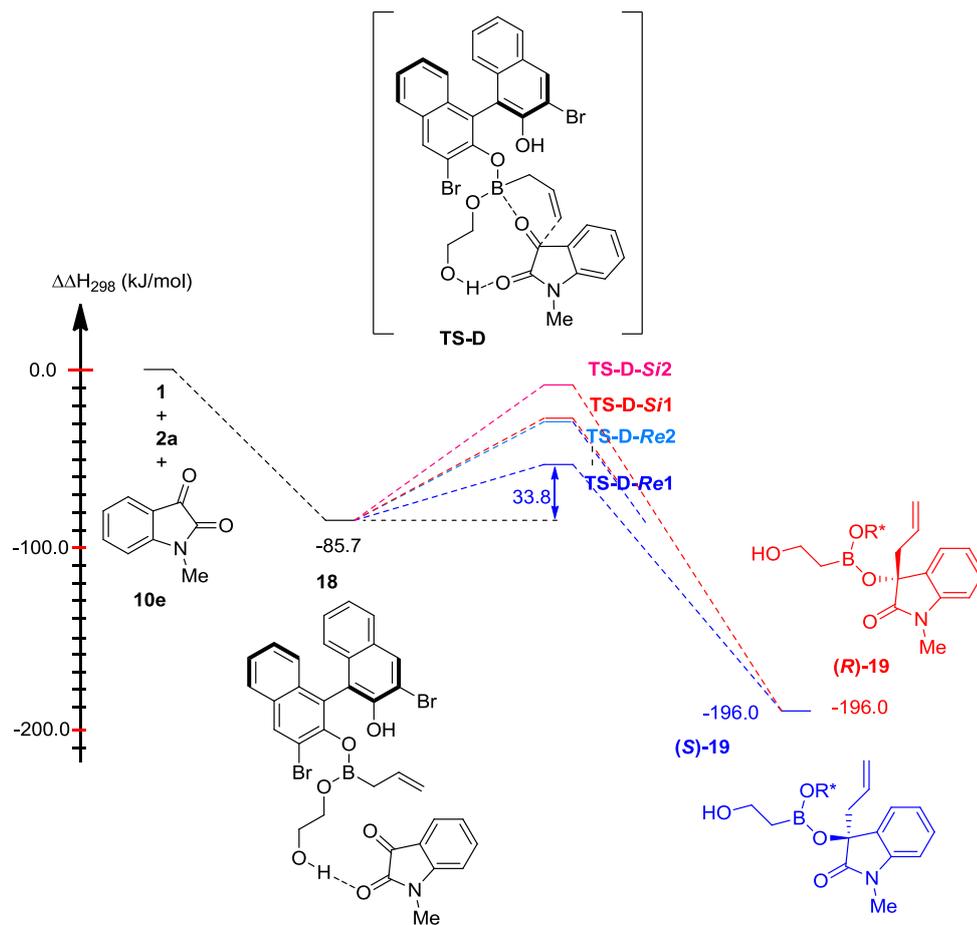


Figure 7. Energy diagram of the allylboration step for pathway 4 (kJ/mol).

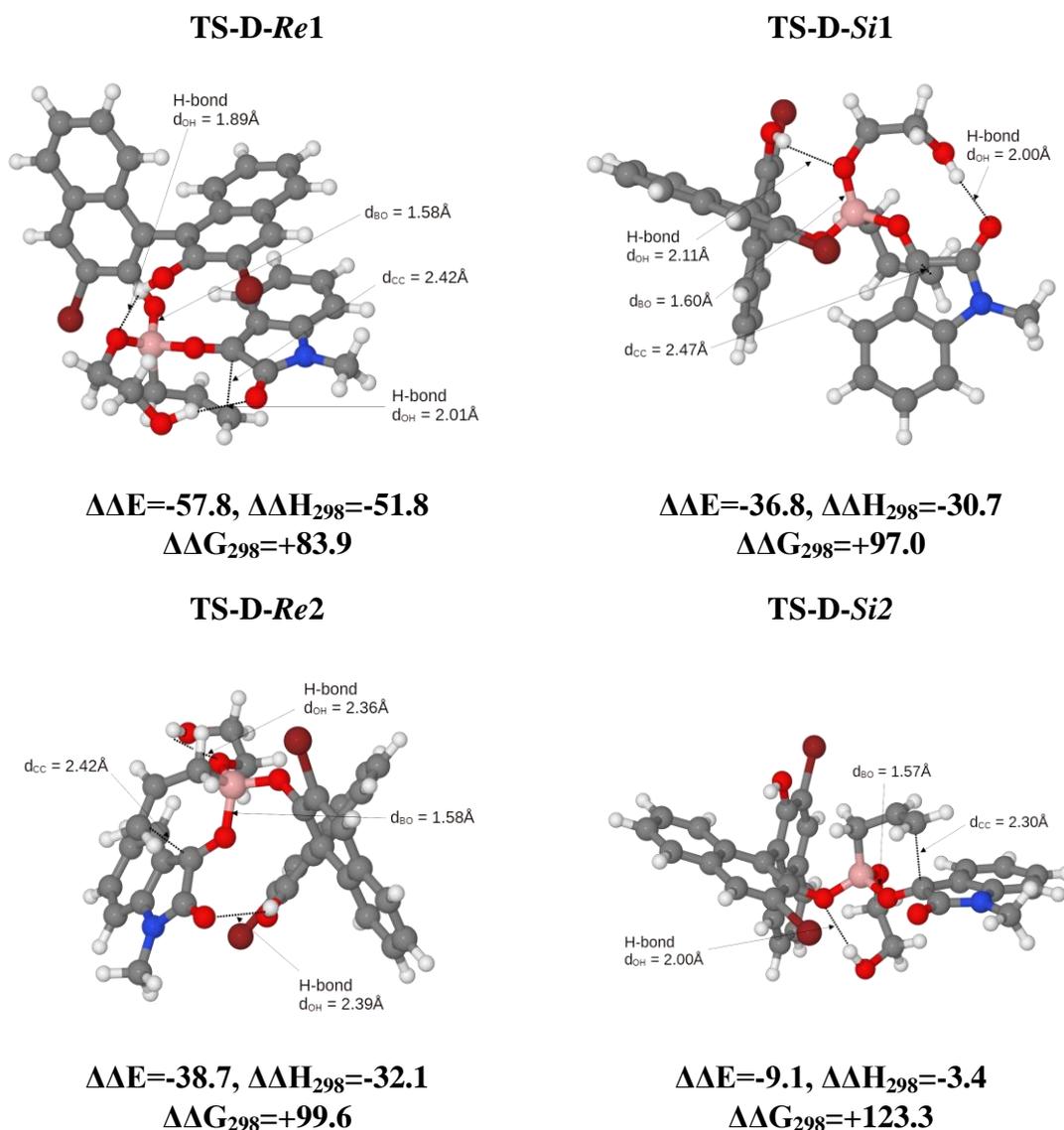


Figure 8. TS-D transition state structures (kJ/mol).

In order to identify the non-covalent interactions (NCI) occurring in **TS-D-Re1**, an NCI plot using Multiwfn³⁴ was performed (Figure 9). This representation confirms the presence of two H-bonds in this transition state. It also displays a large surface of non-covalent interactions existing between one of the naphthol moiety and isatin due to π - π interactions. Considering the importance of these interactions in the present case, this is mandatory to model the reaction with a full BINOL molecule in order to avoid to set aside some critical interactions.

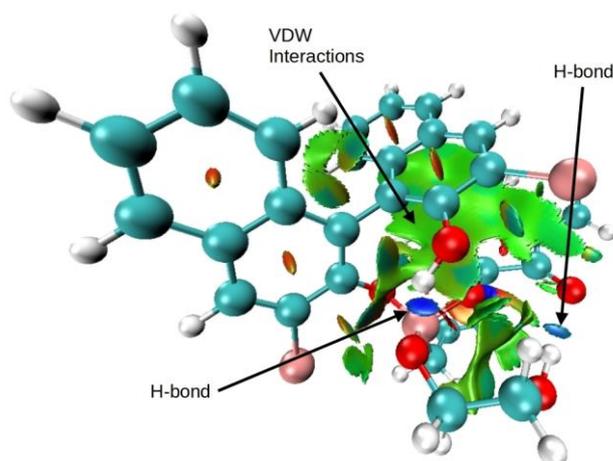


Figure 9. NCI plot of **TS-D-Re1**.

As previously described, the contribution of H-bonds in these transition states was calculated and contrary to **TS-Cs**, the stabilization of the TSs by the H-bonds follows approximately the same trend as the relative energies of the TSs (Table 5 and Figure 8). That illustrates the important role played by the ability to create intramolecular H-bonds in these transition states.

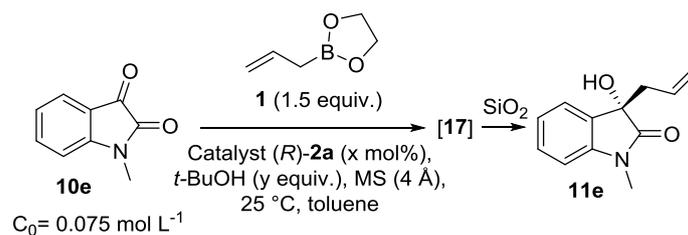
Table 5. Contribution of H-bonds in TS-D.

Entry	TS	Σ H-bond stabilization energy (kJ/mol)	$\Delta\Delta E$ (kJ/mol)
1	TS-D-Re1	-43.3	-57.8
2	TS-D-Re2	-16.4	-38.7
3	TS-D-Si1	-32.3	-36.8
4	TS-D-Si2	-18.0	-9.1

It should also be noted that the poor reactivity and selectivity observed with **10b-d** (Table 3, Entries 7-9) can easily be explained by the structure of all these calculated transition states **TS-B** and **TS-D**. Indeed, in all these structures, the atom in 4 position of the indoline-2,3-dione is pointing toward one of the oxygen atoms of the boronate. Hence, changing the hydrogen by a halogen creates an important steric bulk that contributes to dramatically decrease the reactivity of the corresponding isatin.

Kinetics study. In order to better understand the key role played by the alcohol additive, a kinetics study of the reaction of *N*-methyl isatin **10e** with 1.5 equivalent of allylboronate **1** was performed at 25 °C in toluene (Scheme 2).

Scheme 2: Reaction studied in the kinetics experiments



Because of the overlap of the IR carbonyl signals of substrate **10e** and product **11e**, IR monitoring of the reaction could not be performed. But as oxindole **11e**, the additives and allylboronate **1** are colorless, the orange color of isatin **10e** was exploited to measure the reaction progress by visible spectroscopy at 428 nm. To ensure that the initial reaction mixture is a solution, nearly saturated stock solutions in toluene of *N*-methylisatin **10e** (0.15 M) and catalyst **2a** (0.023 M) were used in the kinetics experiments. Initial velocities V_0 were determined for a consumption of isatin **10e** being lower than 10% and at an initial concentration in **10e** of 0.075 mol L^{-1} . The influence of added *t*-BuOH in the presence of catalyst *(R)*-**2a** (10 mol%) was studied at first (Figure 10A.). With 1 equivalent of *t*-BuOH, the reaction was 1.6 times faster than without *t*-BuOH. The rate steadily increased with the tertiary alcohol quantity, the initial rate V_0 in the presence of 5 equiv. *t*-BuOH being 2.2 times higher than the one without. The alcohol additive had also an effect on the enantiomeric ratio of **11e**: an important improvement was observed as soon as one equivalent was added but was nearly not dependent on the quantity of *t*-BuOH (*er* from 83:17 for 1 and 2 equiv. to 86:14 for 3 to 5 equiv., Figure 10A). The additive *t*-BuOH favored only the rate of the catalyzed reaction, since the initial rate of the uncatalyzed reaction with 5 equivalents of added *t*-BuOH ($V_0 = 0.9 \cdot 10^{-4} \text{ mol L}^{-1} \text{ min}^{-1}$) was identical to that of the uncatalyzed one without *t*-BuOH.

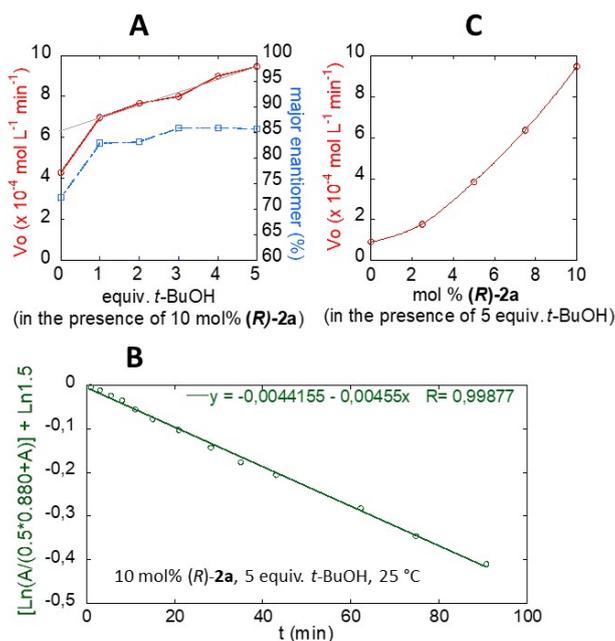


Figure 10. Initial velocity V_0 (○) at 25 °C of the reaction between *N*-methyl isatin **10e** and 1.5 equiv. of allylboronate **1** in the presence of different additives and % of the major enantiomer **11e** (□) (A and C). Second order mechanism (B). See data in supporting information.

The reaction in the presence of 5 equiv. *t*-BuOH and 10 mol% catalyst was monitored at 25 °C until conversion of **10e** reached 65% by recording absorbance (A) at 428 nm as a function of time (t). Fitting of the data according to equation 1 (Eq. 1)³⁵ proved a second order mechanism (Figure 10B), with an apparent rate constant $k_{app} = 0.12 \text{ mol}^{-1} \text{ L min}^{-1}$ (25 °C, 10 mol% (R)-**2a**, 5 eq *t*-BuOH, toluene).

(Eq. 1)

$$-0.5 c_0 k_{app} t = \ln 1.5 + \ln \frac{A}{0.5 A_0 + A}$$

This result is consistent with the hypothesis that the formation of the carbon-carbon bond between **10e** and **1** is the rate-limiting step in all mechanisms or catalytic cycles involved in these reaction conditions.

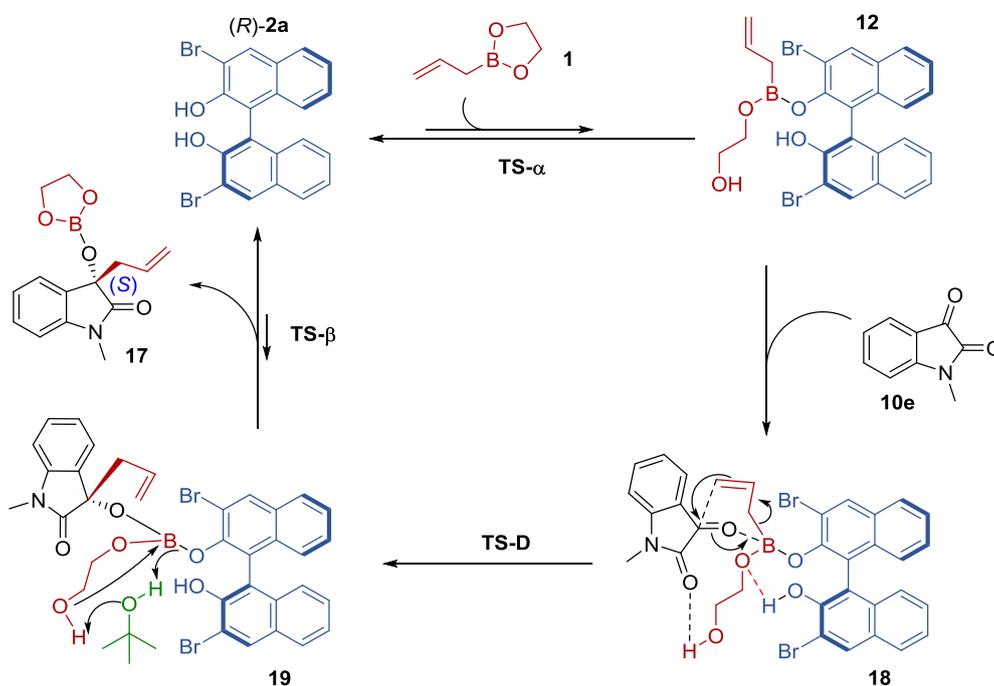
The effect of the catalyst on initial rate V_0 was also measured in the presence of 5 equivalent of *t*-BuOH (Figure 10C). At 25 °C, the uncatalyzed reaction was 10.5 times slower than the reaction in the presence of 10 mol% of (R)-**2a**. Data treatment furnished a first order of the reaction related to the catalyst (see supporting information). If we assume that the

catalyzed reaction only gives enantiopure product (*S*)-**11e** and is 10.5 times faster than the uncatalyzed reaction at 25 °C, then the proportion of enantiopure (*S*)-**11e** and racemic **11e** formed under kinetic control would be 91.3:8.7 (95.6:4.4 *er*). We can conclude that in the studied catalytic conditions at 25 °C (86:14 *er*), the minor enantiomer is also produced by the catalyzed reaction. So, it is mandatory to work at lower temperature in order to obtain **11e** in higher *er*.¹³

The influence of added hexafluoropropanol (5 equiv.) on the initial rate of the reaction in the presence of 10 mol% (*R*)-**2a** was also measured and was 1.2 times higher than the one observed with added *t*-BuOH (5 equiv.). As already observed (entries 6 and 1, Table 3) this faster reaction unfortunately led to a quasi-racemic mixture of **11e** (53.3:46.7 *er*).

Role of the alcohol additive. *Tert*-butanol is assumed to play a key role in the turn-over of the catalyst by favoring the transesterification of the allylboronate **1** by (*R*)-3,3'-Br₂-BINOL **2a**. Indeed, the mechanism proposed previously (pathway 4) requires, in the first instance, the mono-transesterification of the cyclic boronate by BINOL **2a** to furnish **12** that reacts more rapidly to form the expected allylation product **19** (Scheme 3). Then, 2-alkoxy-1,3,2-dioxaborolane **17** has to be formed to release BINOL catalyst **2a** that will continue to promote the allylation reaction.

Scheme 3. Catalytic cycle according to pathway 4



However, these reactions are not as fast as expected due to the required prototropy in these steps. It is often assumed in organic chemistry that steps involving prototropy occur easily and quickly. Nevertheless, in the absence of additive, the prototropy has to proceed *via* a 4-membered ring transition state (**TS-α-4**, Figures 11a and 12). This type of transition state is located quite high compared to the energy of the starting materials and the energy gap (ΔH_{298}) to overcome is significant (102.9 kJ/mol) compared to that of the allylboration step (Figure 11a). **TS-α-4** (Figure 12) corresponds exactly to the transfer of the hydrogen from one of the hydroxyl groups of **2a** to one of the oxygens of the boronate. The IRC calculations then highlight that the formation and cleavage of the B-O bonds occur along the path without any additional transition state.

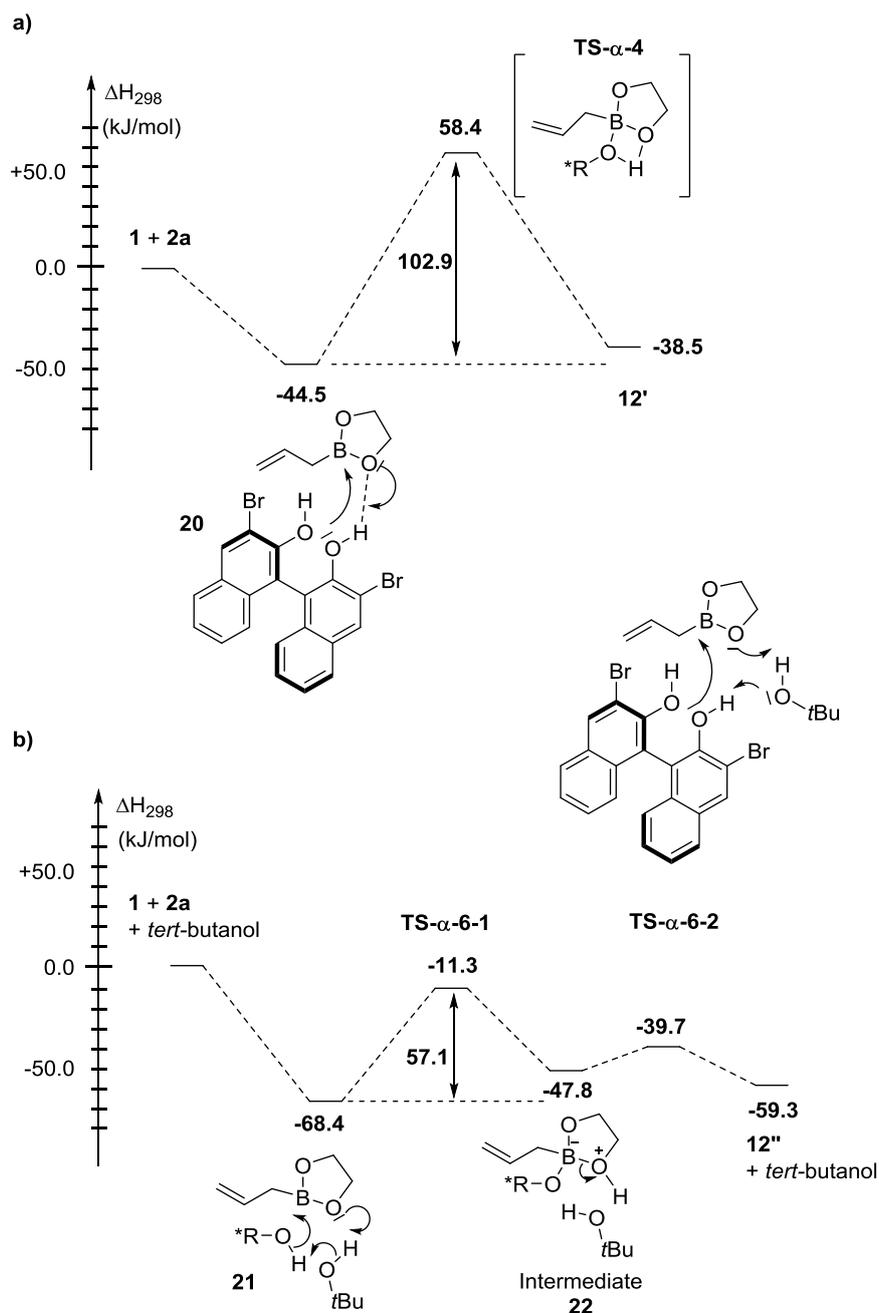
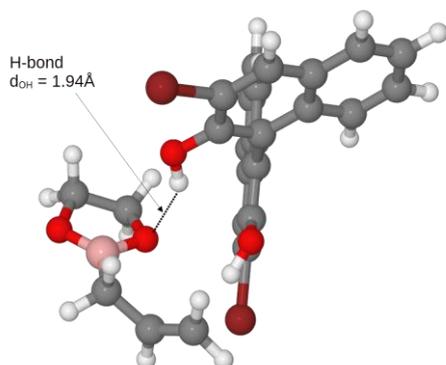


Figure 11. Reaction path for the formation of **12** (TS- α). a) 4-Membered ring mechanism. **12'** correspond to the conformations of **12** obtained from the IRC calculations. b) 6-Membered ring mechanism assisted by the additive. **12''** correspond to the conformations of **12** obtained from the IRC calculations.

The presence of a few equivalents of a protic solvent such as *t*-BuOH promotes the prototropic step to proceed *via* a six-membered ring transition state (TS- α -6, Figures 11b and 12). Obviously, this role can also be played by catalyst **2a** or **12**, but considering the small amounts of these compounds in solutions, the kinetic of the catalytic cycle is significantly

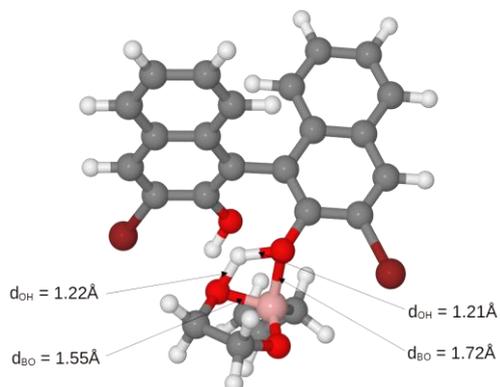
hampered in the absence of *t*-BuOH. In the presence of *t*-BuOH, the transesterification of the allylboronate proceeds *via* a two steps mechanism and *via* an intermediate revealing a tetrahedral boron atom (Figure 11b). The first step (**TS- α -6-1**, Figure 12) corresponds to the attack of the oxygen of BINOL on the boron atom with simultaneous transfer of the OH hydrogen from BINOL to the oxygen of *t*-BuOH, and the transfer of the *tert*-butanol hydrogen to the boronate oxygen to form intermediate **22**. The representation of **TS- α -6-1** (Figure 12) exhibits the key role played by *tert*-butanol to assist the attack of the oxygen atom of **2a** onto the boron atom of **1**. Indeed, the proton from BINOL **2a** is almost totally transferred to *t*-BuOH ($d_{\text{OH}} = 1.15\text{\AA}$ vs 1.28 with **2a**) to enhance the reactivity of the oxygen with the boron atom of the cyclic boronate. This concerted transfer of the proton with the formation of the B-O bond is related to the weak Lewis acidity of the boronate. Then, the second step (**TS- α -6-2**, Figure 12) figures the opening of the cyclic boronate to form **12**. In this last transition state, the B-O bond is almost broken displaying a B-O distance of 2.16 \AA (Figure 12). The calculated energy gap ($\Delta\Delta H_{298}$) for **TS- α -6-1** appears significantly lower (57.1 kJ/mol) than **TS- α -4** for the 4-membered ring mechanism.

20



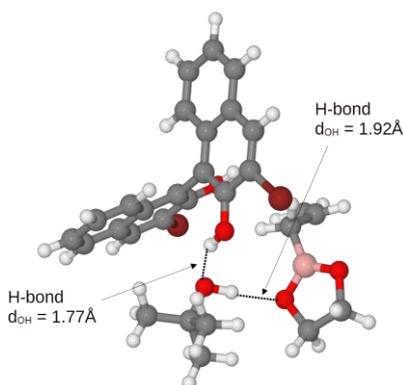
$$\Delta\Delta E = -50.4^a, \Delta\Delta H_{298} = -44.5^a$$
$$\Delta\Delta G_{298} = +12.3$$

TS- α -4



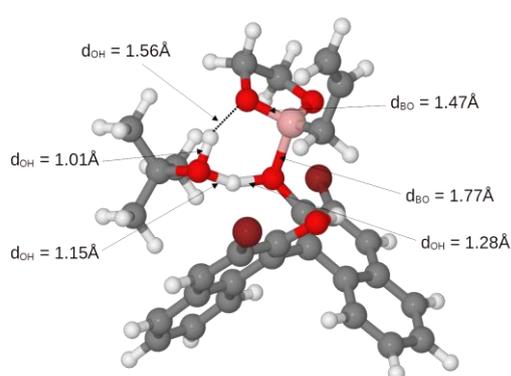
$$\Delta\Delta E = 67.3^a, \Delta\Delta H_{298} = 58.4^a$$
$$\Delta\Delta G_{298} = +127.4$$

21



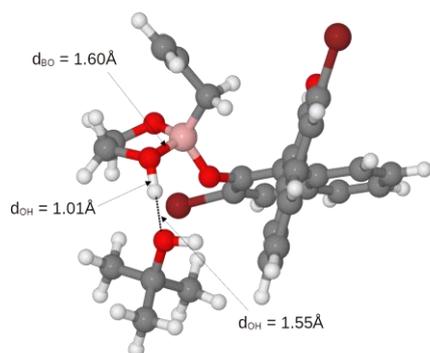
$$\Delta\Delta E = -81.3^b, \Delta\Delta H_{298} = -68.4^b$$
$$\Delta\Delta G_{298} = +32.6$$

TS- α -6-1



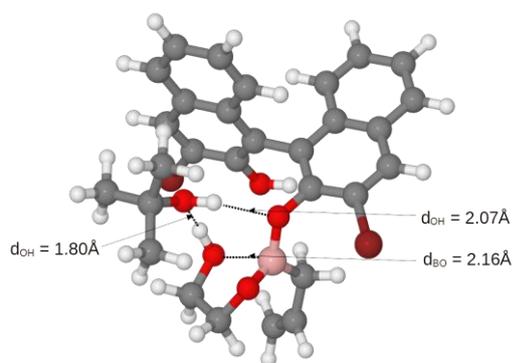
$$\Delta\Delta E = -8.0^b, \Delta\Delta H_{298} = -11.3^b$$
$$\Delta\Delta G_{298} = +113.9$$

22



$$\Delta\Delta E = -57.8^b, \Delta\Delta H_{298} = -47.8^b$$
$$\Delta\Delta G_{298} = +68.5$$

TS- α -6-2



$$\Delta\Delta E = -49.0^b, \Delta\Delta H_{298} = -39.7^b$$
$$\Delta\Delta G_{298} = +78.9$$

Figure 12. TS- α structures and energy (kJ/mol). ^a Energy relative to **1+2a**. ^b Energy relative **1+2a+tert-butanol**.

Hence, *t*-BuOH was also expected to play a similar role in the release of the catalyst at the end of the allylboration reaction. It was therefore decided to proceed to a similar study on the transesterifications occurring after the allylboration reaction. The energy gap ($\Delta\Delta H_{298}$) calculated (105.6 kJ/mol) for the 4-membered ring mechanism stands even higher than for the previous transesterification (TS- β -4, Figures 13a and 14). Like with TS- α -4, this transition state corresponds to the transfer of the proton between the oxygen of the ethylene glycol moiety and **2a**, and the cleavage and formation of the B-O bonds proceeds along the path.

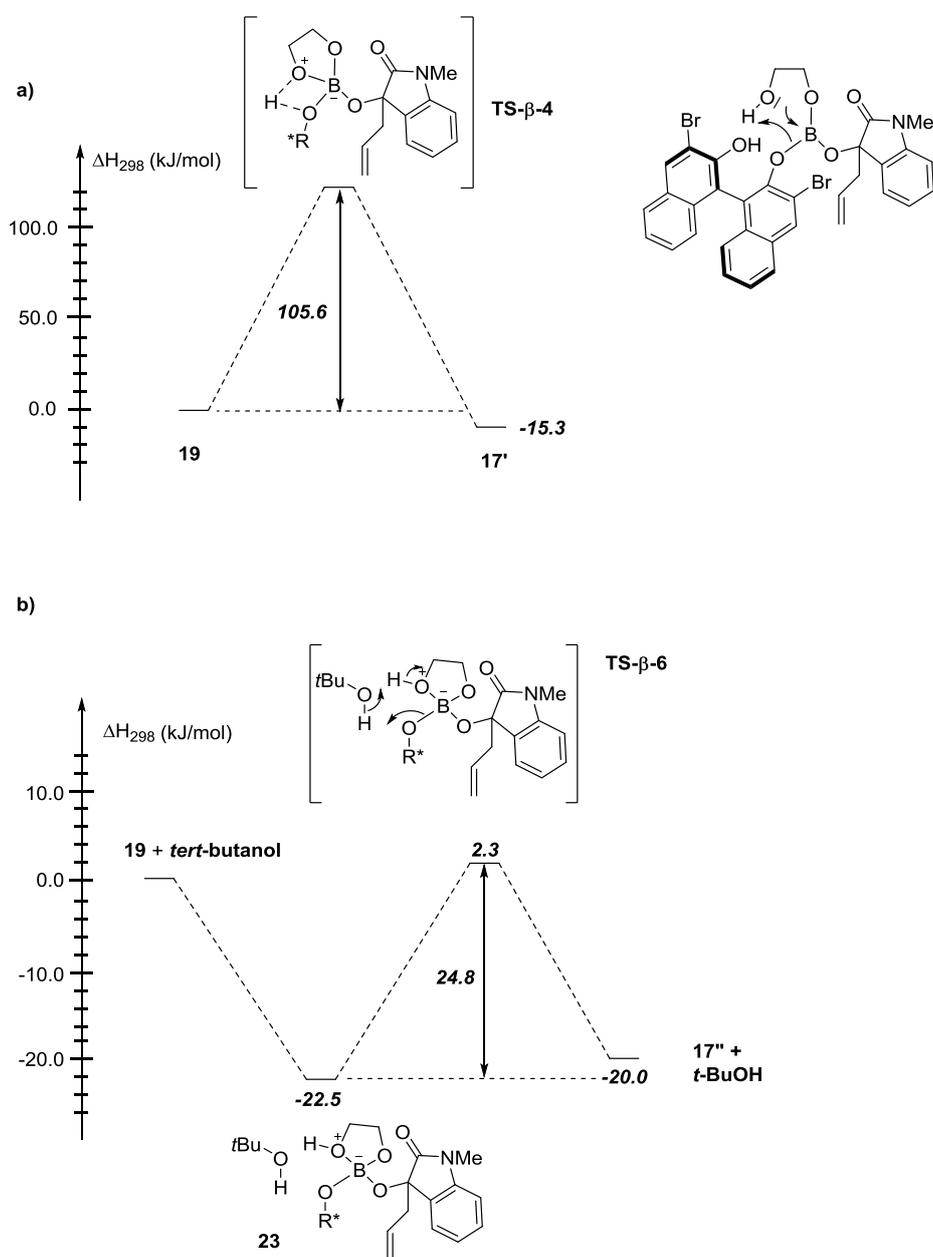
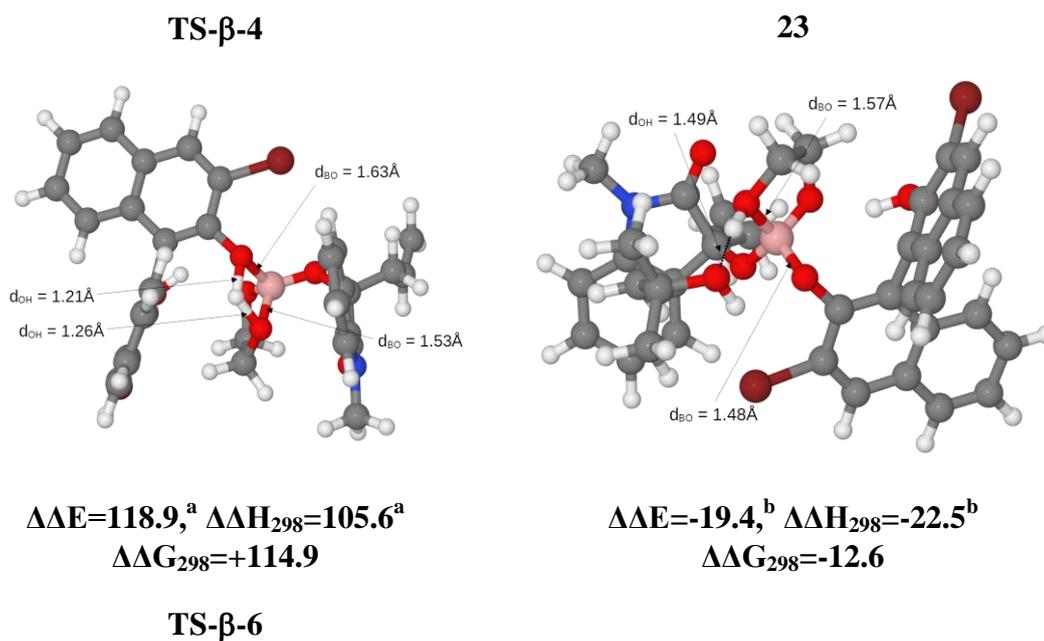
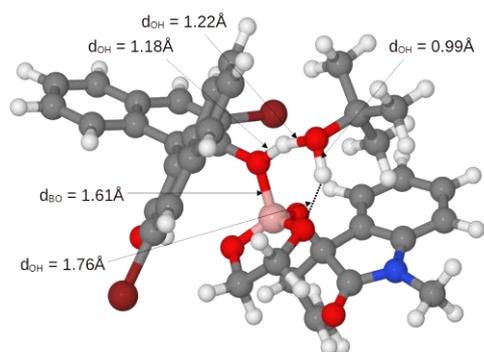


Figure 13. Reaction path for the release of the catalyst **2a** (TS- β). a) 4-Membered ring mechanism **17'** correspond to the conformations of **17** obtained from the IRC calculations. b) 6-Membered ring mechanism assisted by the additive. **17''** correspond to the conformations of **17** obtained from the IRC calculations.

Then, as previously, the 6-membered ring mechanism involving the presence of *tert*-butanol proceeds with a significantly lower energy barrier (24.8 kJ/mol, Figure 13b). The presence of *tert*-butanol facilitates greatly the transfer of the hydrogen from the CH₂OH to the BINOL **2a** (TS- β -6, Figure 14). In this case, the sequence proceeds with only one located transition state [TS- β -6] and one intermediate **23** with a tetrahedral boron atom. The first transition state corresponding to the cyclization of the boronate stands too low to be located. Interestingly, in TS- β -6 (Figure 14), the hydrogen from the boronate is already transferred to *tert*-butanol and the OH group of *tert*-butanol plays a key role in breaking down the B-O bond with BINOL **2a**.





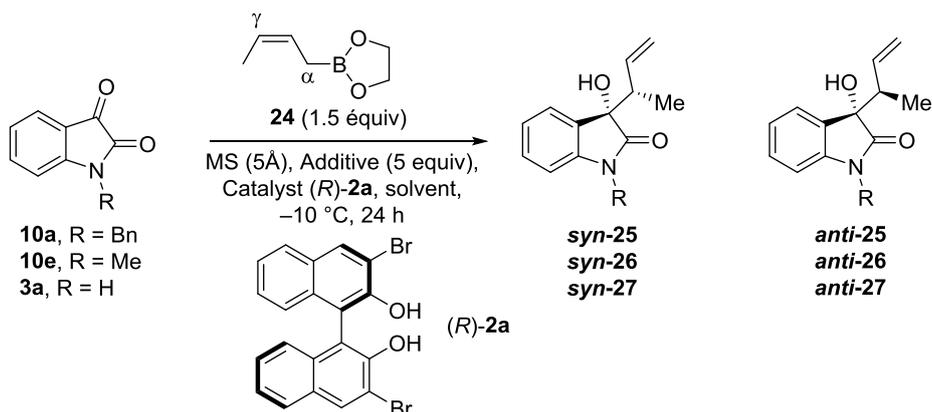
$$\Delta\Delta E=17.6,^b \Delta\Delta H_{298}=2.3^b$$

$$\Delta\Delta G_{298}=+18.2$$

Figure 14. TS- β structures and energy (kJ/mol). ^a Energy relative to **19**. ^b Energy relative to **19**+*tert*-butanol.

Asymmetric crotylboration and propargylation of isatins. With the aim to demonstrate that chiral (*R*)-3,3'-Br₂-BINOL **2a** can be a suitable organocatalyst for the enantioselective crotylboration of isatins, we selected the *Z*-2-(but-2-en-1-yl)-1,3,2-dioxoborolane **24** as reference reagent to evaluate this reaction (Table 6). We first examined the addition of **24** to *N*-benzyl isatin **10a** in the absence of chiral catalyst in order to evaluate the reaction time and determine the diastereoselectivity. A complete conversion of **10a** into the expected γ -adducts **25** was observed at room temperature in toluene after 24 h. No α -adducts resulting from a 1,3-borotropic shift was detected in the crude reaction mixture.³⁶ **25** was isolated in 95% yield with a corresponding diastereomeric ratio of 81:19 (Entry 1). As expected due to the isomeric purity of crotyl boron reagent **24** ($\geq 95\%$ (*Z*), see Supporting information), the relative configuration of the predominantly diastereomer formed was confirmed to be the *syn* isomer by a single crystal X-Ray analysis of **25** (see supporting information).³⁷ When the catalyzed reaction was performed at -10 °C in the presence of (*R*)-**2a** (5 mol%) and *tert*-butanol additive (5 equiv), the diastereoselectivity was improved and **25** was isolated in 92% yield and 97.5:2.5 *er* (Entry 2). An increased loading of catalyst to 10 mol% led to a better enantioselectivity (Entry 3).

Table 6. Asymmetric crotylboration of isatins



Entry ^a	Compound	Cat. (mol%)	Additive	Solvent	Yield (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^d
1 ^e	10a	-	-	PhCH ₃	95	81:19	-
2	10a	(R)-2a (5)	<i>t</i> -BuOH	PhCH ₃	92	91:9	95
3	10a	(R)-2a (10)	<i>t</i> -BuOH	PhCH ₃	95	92:8	98
4	10e	(R)-2a (10)	<i>t</i> -BuOH	PhCH ₃	94	94:6	96
5 ^f	3a	-	-	PhCH ₃	80	90.5:9.5	-
6 ^e	3a	(R)-2a (10)	<i>t</i> -AmOH	PhCF ₃	82 (61) ^g	82:18 (97:3) ^g	92 (>98) ^g

^a Reactions were performed with isatin **10a**, **10e** or **3a** (0.2 mmol), boronate **23** (1.5 equiv), solvent (1 mL) under Ar. ^b Isolated yield after chromatography purification on silica. ^c Ratio syn/anti was determined by ¹H NMR of the crude product. ^d Determined by HPLC analysis using a chiral column. ^e Reaction was performed at room temperature. ^f Reaction was performed at 50 °C using an oil bath for 36 h. ^g Obtained after a single recrystallization using CH₂Cl₂.

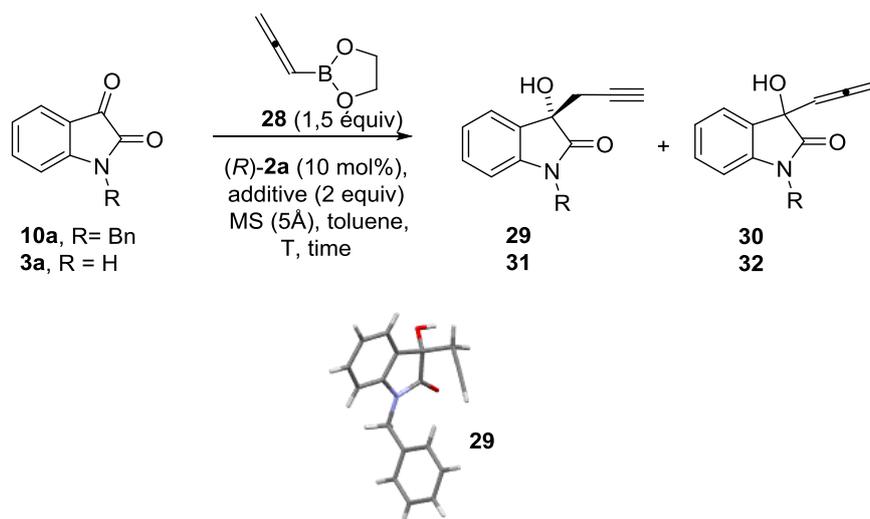
These optimized conditions were applied to *N*-methyl isatin **10e** to furnish solely the γ -addition product with an excellent diastereoselectivity (94:6 *dr*) in favor of *syn* isomer **26** and a high enantioselectivity (98:2 *er*) (Entry 4). As expected, the uncatalyzed crotylboration of *N*-unprotected isatin **3a** was more sluggish (Entry 5 relative to Entry 1). The completion of the reaction required to heat at 50 °C in toluene for 36 h compared to 24 h at room temperature for **10a**. In contrast, a higher level of diastereoselectivity was determined by ¹H NMR analysis and compound **27** was isolated in 80% yield (Entry 5). Using previously optimized conditions for the catalyzed allylboration of NH isatins (*t*-AmOH, PhCF₃, Table 2), the crotylboration of **3a** at -10 °C proved to be much slower than anticipated since the reaction was incomplete after 6 days. Fortunately, by working at room temperature, the reaction time was greatly reduced (24 h) and compound **27** was isolated in 82% yield with a good diastereoselectivity and high enantioselectivity (Entry 6). A simple recrystallization in

CH₂Cl₂ allowed to enhance significantly stereoselectivity (97:3 *dr*, >99:1 *er*) with a relatively limited impact on the yield.

Eventually, as an obvious extension of asymmetric allylboration of isatins, we studied the reactivity of allenylboronate reagent **28** in our organocatalytic method in view of the importance of homopropargylic alcohols in synthesis (Table 7).³⁸ To the best of our knowledge, only one example of asymmetric propargylation of isatins using allenylboronates was reported in the literature to date.³⁹ This metal-mediated method needed copper as a Lewis acid catalyst and chiral ligands to afford the corresponding homopropargylic alcohols with excellent yields but moderate to good enantioselectivity (*er* up to 88:12). Based on the reactivity of allenylboronates towards ketones,¹¹ our study began with the addition of **28** to isatin **10a** in toluene at 50 °C in the absence of catalyst. Under these conditions, the conversion was completed after 24 h and compound **29** was isolated in 90% yield (Entry 1). No formation of the allenyl alcohol **30** was detected by ¹H NMR analysis of the crude reaction mixture.⁴⁰ In the presence of catalyst (*R*)-**2a** (10 mol%) at the same temperature (50 °C), the reaction time was significantly reduced (1 h instead of 24 h) giving the homopropargyl alcohol **29** in 92% yield and 94:6 *er* (Entry 2). The (*S*) absolute configuration of the new stereocenter created was ascertained by the single crystal X-Ray diffraction analysis of **29**.⁴¹ The use of an alcohol additive such as *t*-BuOH (2 equiv) in the procedure had a negative impact on reaction time, selectivity (propargylation vs allenylation) and enantioselectivity (Entry 3). This outcome can be explained by the fact that the origins of stereoselectivities for the addition of allenyl- and allylboronates to carbonyl compounds could be different due to a different transition state involved in this specific case. Finally, the best results were obtained working at room temperature (Entry 4). Despite a longer reaction time, the reaction occurred with a complete selectivity in favor of propargylation adduct providing **29** with an excellent yield and in high enantiomeric ratio (95.5:4.5). Concerning propargylation of the *N*-unprotected isatin **3a**, the reaction in the absence of catalyst is drastically much slower than could have been expected if we compare with the corresponding *N*-substituted substrate **10a** (Entries 1 and 5). After 7 days at 50 °C in toluene, the conversion of the reaction into the expected product **31** was only 25%. In view of this result, the catalytic enantioselective allylboration was performed at the same temperature. Under these conditions, the reaction was completed after 24 h and **31** was isolated in 96% yield (Entry 6). Unfortunately, the enantiomeric ratio obtained was modest. In this case, the drop of enantioselectivity cannot be attributed to a negative effect of the temperature (if we compare

with entries 2-4) since when the reaction was performed at room temperature, in spite of a low conversion after 7 days, a similar enantiomeric ratio was obtained (75:25) (Entry 7). An additional study for the propargylation of *N*-unprotected isatins should be necessary to improve these results.

Table 7. Asymmetric propargylation of isatins and ORTEP diagram of compound 29



Entry ^a	Compound	Catalyst	Additive	T (°C) ^b	t (h)	Yield (%) ^c	Ratio 29/30 or 31/32	ee (%) ^d
1	10a	-	-	50	24	90	>99:1	-
2	10a	<i>(R)</i> - 2a	-	50	1	92	>99:1	88
3	10a	<i>(R)</i> - 2a	<i>t</i> -BuOH	50	18	90	96:4	80
4	10a	<i>(R)</i> - 2a	-	rt	18	94	>99:1	91
5	3a	-	-	50	168	19	>99:1	-
6	3a	<i>(R)</i> - 2a	-	50	24	96	>99:1	53
7	3a	<i>(R)</i> - 2a	-	rt	168	11	>99:1	50

^a All reactions were performed with isatin **10a** (0.2 mmol), allenylboronate **28** (1.5 equiv), 1 mL solvent under Ar at the indicated temperature and reaction time. ^b Reactions at 50 °C were performed using an oil bath. ^c Isolated yield after chromatographic purification on silica. ^d Determined by HPLC analysis using a chiral column.

CONCLUSIONS

We have developed an efficient protocol at room temperature for BINOL derivatives-catalyzed allylboration of *N*-unprotected isatins, subsequently enhancing the scope of the reaction. This approach also opens the way towards *N*-substituted-3-allyl-3-hydroxyindolin-2-ones which cannot be prepared with a high enantioselectivity by direct allylboration of the

corresponding *N*-protected isatins such as *N*-acetyl substrates. The reaction catalyzed by (*R*)-3,3'-Br₂-BINOL **2a** follows a specific stereochemical course induced by the presence of the amide function. A complete DFT study of the possible mechanisms involved in these reactions proved the crucial role played by the H-bonds and the π - π interactions existing between the substrate and the catalyst. Kinetics experiments confirmed the key role played by *tert*-butanol as additive. Then, the DFT study explained how it increases the catalyst turn-over by enhancing prototropy in the transesterification steps of the catalytic cycle. This activation reduces significantly the energy barrier for the formation of the reactive species **12** and facilitates even more the release of the catalyst. This organocatalytic process can also be extended to other 1,3,2-dioxaborane reagents such as crotylboronates and allenylboronates with high stereoselectivities. Based on this mechanistic study, we speculate that other substrates such as acyclic α -ketoamides and esters could be used efficiently with this methodology. The work is underway in our laboratory.

EXPERIMENTAL SECTION

General Information and Materials. Toluene was distilled over sodium and *tert*-butyl alcohol (*t*-BuOH), *tert*-amylalcohol (*t*-AmOH) were distilled over CaH₂. Molecular sieve was activated by flame heating under Ar and vacuum. All other solvents and commercially available chemicals were used without further purification. TLC analyses were performed using precoated Merck TLC Silica Gel 60 F254 plates. Column chromatography purifications were performed over silica gel (Merck Geduran 60, 0.063–0.200 mm). Flash chromatography purifications were performed on a Grace Reveleris with packed columns (40 μm granulometry). NMR spectra were recorded at 300 or 400 MHz for ¹H, 75 or 101 MHz for ¹³C, 282 or 471 MHz for ¹⁹F. Data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant *J* (Hz) and integration. High-resolution mass spectra (HRMS) were recorded on a Micro-Tof-Q II or on a Q-Tof 2 using positive ion electrospray. X-ray crystallographic data were collected on a D8 VENTURE Bruker AXS diffractometer. Infrared spectra were recorded on a FT-IR spectrometer equipped with a diamond detection and an ATR unit or a single reflection ATR module; wavenumbers are given in cm⁻¹. Optical rotations were measured using 10-cm cell at 22 °C (sodium D-line: 589 nm), and the concentration is expressed in g/dL. UV-visible spectra were recorded on a JASCO-V570 spectrometer. Melting points were measured without correction on a digital melting point apparatus. All analytical high-performance liquid chromatography (HPLC) were performed, using Daicel Chiralpak IA, IB and IC columns. Isatins **3** and chiral catalysts **2** are commercially available compounds. Isatins **3** were purified before reaction. The known isatins **10a**,⁴² **10b**,⁴³ **10c**,⁴³ **10d**⁴⁴ and **10e**⁴⁵ were prepared according to literature procedures. The known boron reagents, crotylboronate **24**⁴⁶ and 2-(Propa-1,2-dien-1-yl)-1,3,2-dioxaborolane **28**¹¹ were prepared according to modified literature procedure (see supporting information).

General procedure for the synthesis of homoallylic alcohols 4. To a dried 20 mL Schlenk flushed with Ar, were successively added activated 5 Å molecular sieve (100 mg), isatin **3** (0.2 mmol), α,α,α-trifluorotoluene (0.7 mL), catalyst (*R*) or (*S*)-**2a** (4.5 mg, 0.01 mmol, 0.05 equiv), *t*-AmOH (110 μL, 5 equiv) and allylboronate **1** (1 M solution in trifluorotoluene, 0.3 mL, 0.3 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature until discoloration, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding enantioenriched 3-allyl-3-hydroxy-2-oxindole **4**.

(*S*)-3-Allyl-3-hydroxyindolin-2-one (**4a**).¹³ Prepared from isatin **3a** and using (*R*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (90/10, *R_f* 0.15) as eluent. The product was isolated as a white solid (33 mg) in 94% yield. After recrystallization from CH₂Cl₂, yield was 73% (26 mg). Mp 164–166 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 17.10 min. (minor), *t*_(*S*) = 18.98 min. (major), 5.5:94.5 *er*, 89% *ee*. After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 17.11 min. (minor), *t*_(*S*) = 18.95 min. (major), >1:99 *er*, >98% *ee* ([α]_D = –55.6 (*c* 0.45, CHCl₃)). ¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.94 (br s, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.08 (dd, *J* = 7.8, 7.4 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.80 – 5.58 (m, 1H), 5.19 – 5.08 (m, 2H), 2.75 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.62 (dd, *J* = 13.4, 8.3 Hz, 1H). The reaction was also performed starting from 2

mmol of **3a** and (*R*)-**2a** catalyst (0,1 mmol) to give, after purification, the desired product **4a** (374 mg) in 99% yield and with a high enantioselectivity (5:95 *er*, 90% *ee*).

(*S*)-3-Allyl-6-bromo-3-hydroxyindolin-2-one (**4b**).⁴⁷ Prepared from isatin **3b** and using (*R*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (90/10, *R_f* 0.20) as eluent. The product was isolated as a white solid (47 mg) in 87% yield. Mp: 209-211 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 80/20, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 7.23 min. (minor), *t*_(*S*) = 8.64 min. (major), 5.5:94.5 *er*, 89% *ee* ($[\alpha]_{\text{D}} = +3.0$ (*c* 2.0, MeOH)). ¹H NMR (400 MHz, Acetone-*d*₆) δ 9.43 – 9.33 (br s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 5.69 – 5.49 (m, 1H), 5.10 – 4.90 (m, 3H), 2.73 (ddd, *J* = 13.2, 6.6, 1.4 Hz, 1H), 2.58 (ddd, *J* = 13.2, 7.6, 1.1 Hz, 1H).

(*S*)-3-Allyl-3-hydroxy-6-(trifluoromethyl)indolin-2-one (**4c**). Prepared from isatin **3c** and using (*R*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (90/10, *R_f* 0.15) as eluent. The product was isolated as a white solid (42 mg) in 82% yield. Mp: 191-193 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 7.72 min. (minor), *t*_(*S*) = 12.31 min. (major), 8.5:91.5 *er*, 83% *ee* ($[\alpha]_{\text{D}} = -32.5$ (*c* 2.0, MeOH)). ¹H NMR (400 MHz, Acetone-*d*₆) δ 9.63 – 9.55 (br s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 1.7 Hz, 1H), 5.68 – 5.50 (m, 1H), 5.26 (s, 1H), 5.06 – 4.93 (m, 2H), 2.78 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.62 (dd, *J* = 13.3, 8.0 Hz, 1H). ¹³C {¹H} NMR (101 MHz, Acetone-*d*₆) δ 179.0, 143.4, 136.4, 131.9, 131.4 (q, *J* = 31.9 Hz), 125.8, 125.1 (q, *J* = 271.3 Hz), 119.8, 119.6 (q, *J* = 4.3 Hz), 106.9 (q, *J* = 3.3 Hz), 76.4, 43.1. ¹⁹F NMR (282 MHz, Acetone-*d*₆) δ -63.1. IR (cm⁻¹) 3325, 3160, 1718, 1673, 1640, 1514, 1465, 1436, 1404, 1362, 1320, 1273, 1255, 1218, 1191, 1159, 1125, 1099, 1058, 999, 973, 925, 879, 838, 830, 784, 767, 728. HRMS (ESI): *m/z* calcd. for C₁₂H₁₂NO₂F₃Na [M+Na]⁺ 280.0556; found 280.0559.

(*S*)-3-Allyl-5-fluoro-3-hydroxyindolin-2-one (**4d**).⁴⁷ Prepared from isatin **3d** and using (*R*)-**2a** catalyst (2 h 30). Purified using a CH₂Cl₂/acetone mixture (90/10, *R_f* 0.15) as eluent. The product was isolated as a white solid (36 mg) in 88% yield. Mp: 134-136 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IA-3, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*S*) = 9.90 min. (major), *t*_(*R*) = 12.62 min. (minor), 93:7 *er*, 86% *ee* ($[\alpha]_{\text{D}} = -10.1$ (*c* 1.55, MeOH)). ¹H NMR (500 MHz, CDCl₃) δ 7.81 – 7.73 (br s, 1H), 7.12 (dd, *J* = 7.7, 2.7 Hz, 1H), 6.97 (ddd, *J* = 8.8, 8.8, 2.6 Hz, 1H), 6.80 (dd, *J* = 8.5, 4.1 Hz, 1H), 5.69 (dddd, *J* = 15.6, 11.9, 8.3, 6.5 Hz, 1H), 5.18 – 5.11 (m, 2H), 3.05 – 3.00 (br s, 1H), 2.72 (ddt, *J* = 13.5, 6.5, 1.2 Hz, 1H), 2.60 (ddt, *J* = 13.5, 8.3, 1.0 Hz, 1H). ¹⁹F NMR (471 MHz, CDCl₃) δ -119.41.

(*S*)-3-Allyl-3-hydroxy-5-(trifluoromethoxy)indolin-2-one (**4e**).⁴⁸ Prepared from isatin **3e** and using (*R*)-**2a** catalyst (2 h 30). Purified using a CH₂Cl₂/acetone mixture (80/20, *R_f* 0.40) as eluent. The product was isolated as a white solid (52 mg) in 95% yield. After recrystallization from CH₂Cl₂, yield was 60% (33 mg). Mp: 115-117 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IA-3, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*S*) = 7.45 min. (major), *t*_(*R*) = 10.17 min. (minor), 90.5:9.5 *er*, 81% *ee*; After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IA-3, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*S*) = 6.92 min. (major), *t*_(*R*) = 9.33 min. (minor), >99:1 *er*, >98% *ee* ($[\alpha]_{\text{D}} = -6.0$ (*c* 0.95, MeOH)). ¹H NMR (300 MHz, CD₃OD/CDCl₃ (1:4)) δ 7.04 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.92 (ddd, *J* = 8.5, 2.5, 1.1 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.47 – 5.31 (m, 1H), 4.89 – 4.80 (m, 2H), 2.53 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.38 (dd, *J* = 13.3, 8.2 Hz, 1H). ¹⁹F NMR (282 MHz, CD₃OD/CDCl₃ (1:4)) δ -54.95.

(*S*)-3-Allyl-5,7-dibromo-3-hydroxyindolin-2-one (**4f**).⁴⁹ Prepared from isatin **3f** and using (*R*)-**2a** catalyst (12 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R_f* 0.65) as eluent. The product was isolated as a white solid (61 mg) in 88% yield. Mp: 122–124 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*S*) = 9.03 min. (major), *t*_(*R*) = 11.01 min. (minor), 94.5:5.5 *er*, 89% *ee* ([α]_D = +15.4 (*c* 2.6, MeOH)). ¹H NMR (500 MHz, CDCl₃) δ 7.60 – 7.56 (br s, 1H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 5.69 (dddd, *J* = 16.8, 10.2, 8.4, 6.5 Hz, 1H), 5.23 – 5.14 (m, 2H), 2.99 – 2.96 (br s, 1H), 2.71 (ddt, *J* = 13.6, 6.5, 1.4 Hz, 1H), 2.60 (ddt, *J* = 13.6, 8.4, 0.9 Hz, 1H).

(*R*)-3-Allyl-3-hydroxyindolin-2-one (**4g**).^{12a} Prepared from isatin **3a** and using (*S*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (90/10, *R_f* 0.15) as eluent. The product was isolated as a white solid (34 mg) in 97% yield. After recrystallization from CH₂Cl₂, yield was 69% (24 mg). Mp 164–166 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 17.22 min. (major), *t*_(*S*) = 19.10 min. (minor), 92.5:7.5 *er*, 85% *ee*; After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IA-3, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*S*) = 10.54 min. (minor), *t*_(*R*) = 15.39 min. (major), >1:99 *er*, >98% *ee* ([α]_D = +56.0 (*c* 0.54, CHCl₃)). ¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.94 (br s, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.08 (dd, *J* = 7.8, 7.4 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.80 – 5.58 (m, 1H), 5.19 – 5.08 (m, 2H), 2.75 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.62 (dd, *J* = 13.4, 8.3 Hz, 1H).

(*R*)-3-Allyl-3-hydroxy-6-methoxyindolin-2-one (**4h**). Prepared from isatin **3h** and using (*S*)-**2a** catalyst (12 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R_f* 0.30) as eluent. The product was isolated as a white solid (41 mg) in 93% yield. After recrystallization from CH₂Cl₂, yield was 48% (21 mg). Mp 163–165 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 26.57 min. (major), *t*_(*S*) = 39.29 min. (minor), *er* 94.5:5.5, *ee* 89%; After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-3, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 37.44 min. (major), *t*_(*S*) = 53.46 min. (minor), >99:1 *er*, >98% *ee* ([α]_D = +10.5 (*c* 0.90, MeOH)). ¹H NMR (500 MHz, Acetone-*d*₆) δ 9.24 – 9.18 (br s, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 6.54 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 5.58 (dddd, *J* = 16.9, 10.2, 8.1, 6.5 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.81 – 4.79 (br s, 1H), 3.77 (s, 3H), 2.70 (ddt, *J* = 13.3, 6.5, 1.5 Hz, 1H), 2.56 (ddt, *J* = 13.3, 8.1, 1.1 Hz, 1H). ¹³C {¹H} NMR (126 MHz, Acetone-*d*₆) δ 179.9, 161.8, 143.9, 132.8, 126.0, 124.0, 119.1, 107.1, 97.6, 76.3, 55.6, 43.4. IR (cm⁻¹): 3340, 3169, 1699, 1666, 1628, 1603, 1509, 1452, 1403, 1345, 1319, 1281, 1249, 1192, 1159, 1133, 1090, 1025, 995, 952, 930, 886, 834, 824, 789, 766, 719 cm⁻¹. HRMS (ESI): *m/z* calcd. for C₁₂H₁₃NO₃Na [M+Na]⁺ 242.0788; found 242.0788.

(*R*)-3-Allyl-6-chloro-3-hydroxyindolin-2-one (**4i**).⁵⁰ Prepared from isatin **3i** and using (*S*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R_f* 0.45) as eluent. The product was isolated as a white solid (40 mg) in 90% yield. Mp 196–198 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(*R*) = 13.47 min. (major), *t*_(*S*) = 17.56 min. (minor), 93.5:6.5 *er*, 87% *ee* ([α]_D = +1.44 (*c* 2.0, MeOH)). ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.46 (br s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 5.68 (dddd, *J* = 15.0, 11.5, 8.4, 6.4 Hz, 1H), 5.18 – 5.11 (m, 2H), 2.72 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.59 (dd, *J* = 13.5, 8.4 Hz, 1H).

(*R*)-3-Allyl-3-hydroxy-5-methoxyindolin-2-one (**4j**).⁴⁸ Prepared from isatin **3j** and using (*S*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R_f* 0.30) as eluent. The product was isolated as a beige

solid (43 mg) in 98% yield. After recrystallization from CH₂Cl₂, yield was 51% (22 mg). Mp 162–164 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(R) = 21.74 min. (major), *t*_(S) = 28.47 min. (minor), 93:7 *er*, 86% *ee*. After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-3, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, 254 nm, *t*_(R) = 26.96 min. (major), *t*_(S) = 33.78 min. (minor), 94:6 *er*, 88% *ee* ($[\alpha]_D = -17.5$ (*c* 1.10, MeOH)). ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.07 – 10.00 (br s, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.76 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.98 – 5.96 (br s, 1H), 5.52 – 5.36 (m, 1H), 4.99 – 4.88 (m, 2H), 3.70 (s, 3H), 2.59 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.43 (dd, *J* = 13.1, 7.9 Hz, 1H).

(*R*)-3-Allyl-3-hydroxy-5-nitroindolin-2-one (**4k**).⁴⁹ Prepared from isatin **3k** and using (*S*)-**2a** catalyst (12 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R*_f 0.35) as eluent. The product was isolated as a yellow solid (46 mg) in 98% yield. After recrystallization from CH₂Cl₂, yield was 60% (28 mg). Mp 114–116 °C. Before recrystallisation, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, 254 nm, *t*_(S) = 14.69 min. (minor), *t*_(R) = 16.93 min. (major), 10.5:89.5 *er*, 79% *ee*. After recrystallisation, the enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, 254 nm, *t*_(S) = 14.38 min. (minor), *t*_(R) = 16.11 min. (major), >1:99 *er*, >98% *ee* ($[\alpha]_D = -65.8$ (*c* 1.00, MeOH)). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.02 – 10.94 (br s, 1H), 8.19 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.36 – 6.34 (br s, 1H), 5.54 – 5.41 (m, 1H), 5.01 – 4.94 (m, 2H), 2.71 (ddt, *J* = 13.2, 6.5, 1.3 Hz, 1H), 2.53 – 2.45 (m, 1H).

(*R*)-3-Allyl-7-bromo-3-hydroxyindolin-2-one (**4l**). Prepared from isatin **3l** and using (*S*)-**2a** catalyst (5 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R*_f 0.60) as eluent. The product was isolated as a beige solid (53 mg) in 98% yield. After recrystallization from CH₂Cl₂, yield was 70% (38 mg). Mp 144–146 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, 254 nm, *t*_(S) = 15.41 min. (minor), *t*_(R) = 23.95 min. (major), 7.5:92.5 *er*, 85% *ee*. After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IC-3, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, 254 nm, *t*_(S) = 18.71 min. (minor), *t*_(R) = 31.43 min. (major), >1:99 *er*, >98% *ee* ($[\alpha]_D = +30.8$ (*c* 1.30, MeOH)). ¹H NMR (300 MHz, CDCl₃) δ 8.19 – 8.15 (br s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.96 (dd, *J* = 8.2, 7.4 Hz, 1H), 5.75 – 5.55 (m, 1H), 5.17 – 5.05 (m, 2H), 3.60 – 3.40 (br s, 1H), 2.74 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.61 (dd, *J* = 13.5, 8.2 Hz, 1H). ¹³C {¹H} NMR (75 MHz, CDCl₃) δ 179.0, 139.8, 132.5, 131.8, 130.0, 124.4, 123.5, 121.1, 103.5, 77.6, 43.0. IR (cm⁻¹): 3335, 3240, 1705, 1622, 1472, 1454, 1426, 1331, 1277, 1230, 1210, 1172, 1139, 1122, 1096, 994, 980, 932, 918, 879, 846, 795, 778, 737, 757. HRMS (ESI): *m/z* calcd. for C₁₁H₁₀NO₂BrNa [M+Na]⁺ 289.9787; found 289.9790.

(*R*)-3-Allyl-4-chloro-3-hydroxyindolin-2-one (**4m**).⁴⁸ Prepared from isatin **3m** and using (*S*)-**2a** catalyst (144 h). Purified using a CH₂Cl₂/acetone mixture (80/20, *R*_f 0.35) as eluent. The product was isolated as a white solid (17 mg) in 38% yield. Mp 208–210 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, 254 nm, *t*_(S) = 13.92 min. (minor), *t*_(R) = 15.88 min. (major), 41.0:59.0 *er*, 18% *ee*, ($[\alpha]_D = +4.30$ (*c* 0.80, MeOH)). ¹H NMR (300 MHz, CD₃OD/CDCl₃ (1:4)) δ 6.98 (dd, *J* = 8.2, 7.7 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 5.23 – 5.06 (m, 1H), 4.87 (d, *J* = 17.0 Hz, 1H), 4.72 (d, *J* = 10.2 Hz, 1H), 3.00 (dd, *J* = 12.8, 7.3 Hz, 1H), 2.58 (dd, *J* = 12.8, 7.6 Hz, 1H).

(S)-1-acetyl-3-allyl-3-hydroxyindolin-2-one (5).¹³ (S)-3-Allyl-3-hydroxyindolin-2-one (**4a**) (50 mg, 0.26 mmol, 1.0 equiv) was dissolved in DCM (3 mL). Triethylamine (77 μ L, 0.56 mmol, 2.1 equiv) was introduced, followed by acetic anhydride (37 μ L, 0.40 mmol, 1.5 equiv). The reaction mixture was stirred at 40 °C using an oil bath for 39 h, diluted with DCM and washed with water. The combined organic phases were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (100% DCM to 98/2 DCM/Acetone as eluent) to give the (S)-1-acetyl-3-allyl-3-hydroxyindolin-2-one (**5**) (33 mg, 55% yield) as a white solid. R_f = 0.70 (DCM/Acetone = 9:1). Mp: 108–110 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, heptane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_{(R)}$ = 6.38 min. (minor), $t_{(S)}$ = 6.94 min. (major), 4.5:95.5 *er*, 91% *ee* ($[\alpha]_D^{20}$ = –46.9 (c 1.5, CHCl₃)). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (ddd, J = 8.2, 1.1, 0.6 Hz, 1H), 7.44 (ddd, J = 7.5, 1.5, 0.6 Hz, 1H), 7.39 (ddd, J = 8.2, 8.0, 1.5 Hz, 1H), 7.26 (ddd, J = 8.0, 7.5, 1.1 Hz, 1H), 5.57 (dddd, J = 16.2, 10.7, 8.6, 6.2 Hz, 1H), 5.19 – 5.11 (m, 2H), 2.75 (ddt, J = 13.4, 6.2, 1.3 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.66 (s, 3H).

(S)-3-allyl-3-hydroxy-1-phenylindolin-2-one (7).¹³ (S)-3-Allyl-3-hydroxyindolin-2-one (**4a**) (50 mg, 0.26 mmol, 1.0 equiv) was dissolved in methanol (1.2 mL). Phenylboronic acid (70 mg, 0.58 mmol, 2.2 equiv) was introduced, followed by triethylamine (55 μ L, 0.40 mmol, 1.5 equiv) and copper (II) acetate (47 mg, 0.26 mmol, 1.0 equiv). The reaction mixture was stirred at 60 °C using an oil bath for 24 h, diluted with DCM and washed with water. The combined organic phases were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Eluent 100% DCM to 95/5 DCM/Acetone) to afford the (S)-3-allyl-3-hydroxy-1-phenylindolin-2-one (**7**) (34 mg, 49% yield) as a brown syrup. R_f = 0.40 (DCM/Acetone 95/5). The enantiomeric ratio was determined using a Daicel Chiralpak OD-H, hexane/*i*-PrOH = 95/5, 0.7 mL/min, 254 nm, $t_{(R)}$ = 19.52 min. (minor), $t_{(S)}$ = 24.82 min. (major), 2.5:97.5 *er*, 95% *ee* ($[\alpha]_D^{20}$ = –32.5 (c 1.35, CHCl₃)). ¹H NMR (300 MHz, CDCl₃) δ 7.58 – 7.33 (m, 6H), 7.26 (td, J = 7.8, 1.4 Hz, 1H), 7.14 (td, J = 7.5, 1.1 Hz, 1H), 6.80 (dd, J = 7.7, 1.0 Hz, 1H), 5.67 (dddd, J = 16.6, 10.1, 8.4, 6.3 Hz, 1H), 5.22 – 5.10 (m, 1H), 3.25 – 3.21 (br s, 1H), 2.85 (ddt, J = 13.2, 6.3, 1.2 Hz, 1H), 2.75 (dd, J = 13.2, 8.4 Hz, 1H).

(S)-3-allyl-3-hydroxy-1-(4-methoxyphenyl)indolin-2-one (8). (S)-3-Allyl-3-hydroxyindolin-2-one (**4a**) (50 mg, 0.26 mmol, 1.0 equiv), 4-iodoanisole (91 mg, 0.39 mmol, 1.5 eq.), copper (I) iodide (25 mg, 0.13 mmol, 0.5 equiv) and potassium carbonate (79 mg, 0.57 mmol, 2.2 equiv) were placed in a two-necked flask equipped with a condenser. After degassing with argon, repeated three times, the mixture was dissolved in degazed dioxane (1.75 mL) and *N,N'*-dimethylbenzene-1,2-diamine (41 μ L, 0.26 mmol, 1.0 equiv). The reaction mixture was stirred at 110 °C using an oil bath for 17 h, cooled to room temperature, filtered through a pad of Celite with AcOEt and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (Eluent 100% DCM to 95/5 DCM/Acetone) to give (S)-3-allyl-3-hydroxy-1-(4-methoxyphenyl)indolin-2-one (**8**) (64 mg, 83% yield) as a brown solid. R_f = 0.35 (DCM/Acetone = 95:5). Mp: 72–74 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC, heptane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_{(S)}$ = 21.31 min. (major), $t_{(R)}$ = 27.84 min. (minor), 96.5:3.5 *er*, 93% *ee* ($[\alpha]_D^{20}$ = –34.2 (c 2.95, CHCl₃)). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (dd, J = 7.3, 1.4 Hz, 1H), 7.31 – 7.21 (m, 3H), 7.12 (ddd, J = 7.5, 7.3, 1.1 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 7.5 Hz, 1H), 5.66 (dddd, J = 16.6, 10.1, 8.4, 6.3 Hz, 1H), 5.21 – 5.08 (m, 2H), 3.85 (s, 3H), 3.33 – 3.24 (br s, 1H), 2.84 (ddt, J = 13.2, 6.3, 1.2 Hz, 1H), 2.73 (dd, J = 13.2,

8.9 Hz, 1H). ^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 177.5, 159.4, 143.9, 130.6, 129.7, 129.4, 128.0, 126.7, 124.4, 123.5, 120.7, 115.1, 109.7, 76.1, 55.7, 43.6. IR (cm^{-1}): 3344, 2919, 2849, 1697, 1612, 1513, 1485, 1463, 1443, 1433, 1383, 1330, 1282, 1248, 1192, 1165, 1107, 1091, 1022, 997, 983, 925, 881, 836, 812, 778, 755. HRMS (ESI): m/z calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 318.1101; found 318.1100.

(S)-3-allyl-3-((tert-butyldimethylsilyl)oxy)indolin-2-one (9).⁵¹ 2,6-Lutidine (0.14 mL, 1.19 mmol, 2.85 equiv) was added to a stirred solution of (S)-3-Allyl-3-hydroxyindolin-2-one (**4a**) (80 mg, 0.42 mmol, 1 equiv) in DCM (1 mL) at 0 °C under argon, followed by addition of tert-butyldimethylsilyl trifluoromethanesulfonate (0.26 mL, 1.12 mmol, 2.7 equiv). The reaction mixture was stirred at room temperature for 17 h 30. The reaction was quenched with brine at 0 °C. The aqueous layer was extracted with DCM, and the combined organic layers were washed with brine, and concentrated. The crude material was then dissolved in a mixture of THF (0.2 mL), H_2O (0.2 mL) and acetic acid (0.2 mL), and was heated to 70 °C using an oil bath and stirred for 5 h 30. The excess THF was removed under reduced pressure, and the remaining mixture was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (95/5 to 90/10 Cyclohexane/AcOEt as eluent) to afford (S)-3-allyl-3-((tert-butyldimethylsilyl)oxy)indolin-2-one (**9**) (102 mg, 80% yield) as a white solid. R_f = 0.45 (Cyclohexane/AcOEt = 8:2). Mp: 116–118 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-3, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, $t_{(S)}$ = 3.27 min. (major), $t_{(R)}$ = 3.77 min. (minor), 97:3 *er*, 94% *ee* ($[\alpha]_{\text{D}}^{20}$ = +17.6 (c 3.35, CHCl_3)). ^1H NMR (300 MHz, CDCl_3) δ 7.57 – 7.52 (br s, 1H), 7.32 – 7.20 (m, 2H), 7.03 (td, J = 7.5, 1.0 Hz, 1H), 6.81 (dt, J = 7.7, 0.9 Hz, 1H), 5.74 – 5.58 (m, 1H), 5.07 – 4.98 (m, 2H), 2.73 (ddt, J = 13.3, 6.3, 1.4 Hz, 1H), 2.53 (ddt, J = 13.3, 8.2, 0.9 Hz, 1H), 0.88 (s, 7H), -0.04 (s, 3H), -0.24 (s, 3H).

General procedure for the synthesis of homoallylic alcohols 11. To a dried 20 mL Schlenk flushed with Ar, were successively added activated 5 Å molecular sieve (100 mg), *N*-protected isatin derivative **10** (0.2 mmol, 1 equiv), toluene (0.7 mL), (*R*)-**2a** catalyst (4.5 mg, 0.01 mmol, 0.05 equiv), *t*-BuOH (93 μL , 5 equiv) and allylboronate **1** (1 M solution in trifluorotoluene, 0.3 mL, 0.3 mmol, 1.5 equiv). The resulting mixture was stirred at -10 °C for 24 h (72 h for **10d**), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (100 % DCM to 80/20 DCM/ acetone as eluent) to afford product **11**.

(S)-3-allyl-1-benzyl-3-hydroxyindolin-2-one (**11a**).¹³ Prepared from isatin **10a** (24 h). The product was isolated as a white solid (56 mg) in 99% yield. Mp 64–66 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, 254 nm, $t_{(R)}$ = 7.15 min. (minor), $t_{(S)}$ = 11.48 min. (major), 3:97 *er*, 94% *ee* ($[\alpha]_{\text{D}}^{20}$ = -15.2 (c 1.00, CHCl_3)). ^1H NMR (300 MHz, CDCl_3) δ 7.45 – 7.36 (m, 1H), 7.35 – 7.24 (m, 5H), 7.24 – 7.16 (m, 1H), 7.11 – 7.00 (m, 1H), 6.73 – 6.65 (m, 1H), 5.73 – 5.54 (m, 1H), 5.22 – 5.06 (m, 2H), 5.02 (d, J = 15.7 Hz, 1H), 4.72 (d, J = 15.7 Hz, 1H), 3.18 – 3.05 (br s, 1H), 2.88 – 2.61 (m, 2H).

(S)-3-allyl-1-benzyl-4-fluoro-3-hydroxyindolin-2-one (**11b**). Prepared from isatin **10b** (24 h). The product was isolated as a white solid (9 mg) in 15% yield. Mp 135–137 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, 254 nm, $t_{(S)}$ = 5.47 min.

(major), $t_{(R)}$ = 6.19 min. (minor), 52.5:47.5 *er*, 5% *ee*; ^1H NMR (300 MHz, CDCl_3) δ 7.37 – 7.23 (m, 5H), 7.21 – 7.13 (m, 1H), 6.74 (dd, J = 8.6, 7.9 Hz, 1H), 6.49 (dd, J = 7.9, 0.7 Hz, 1H), 5.61 – 5.45 (m, 1H), 5.17 (dd, J = 17.1, 1.7 Hz, 1H), 5.06 (dd, J = 10.1, 2.0 Hz, 1H), 5.00 (d, J = 15.7 Hz, 1H), 4.73 (d, J = 15.7 Hz, 1H), 3.12 – 3.05 (br s, 1H), 3.00 (ddd, J = 13.0, 6.7, 1.2 Hz, 1H), 2.87 (dd, J = 13.0, 8.1 Hz, 1H). ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 176.9, 159.7 (d, J = 250.8 Hz), 144.7 (d, J = 8.9 Hz), 135.2, 131.7 (d, J = 8.8 Hz), 130.4, 129.0, 128.0, 127.4, 121.0, 115.1 (d, J = 19.6 Hz), 111.1 (d, J = 20.8 Hz), 105.8 (d, J = 3.2 Hz), 76.4 (d, J = 1.6 Hz), 44.3, 41.8. HRMS (ESI): m/z calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_2\text{FNa}$ $[\text{M}+\text{Na}]^+$ 320.1057; found 320.1062.

(*S*)-3-allyl-1-benzyl-4-chloro-3-hydroxyindolin-2-one (**11c**).⁵² Prepared from isatin **10c** (24 h). The product was isolated as a white solid (11 mg) in 18% yield. Mp 141–143 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, 254 nm, $t_{(S)}$ = 5.72 min., $t_{(R)}$ = 6.28 min., 50:50 *er*, 0% *ee*. ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.22 (m, 5H), 7.17–7.08 (m, 1H), 7.02–6.96 (m, 1H), 6.61–6.55 (m, 1H), 5.50–5.32 (m, 1H), 5.21–5.09 (m, 1H), 5.07–4.93 (m, 2H), 4.72 (d, J = 15.8 Hz, 1H), 3.29–3.18 (m, 1H), 3.11–3.09 (br s, 1H), 3.00–2.87 (m, 1H). ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 176.8, 144.6, 135.1, 131.7, 131.0, 130.2, 129.0, 128.0, 127.4, 125.9, 124.3, 120.7, 108.1, 77.4, 44.2, 40.5.

(*S*)-3-allyl-1-benzyl-4-bromo-3-hydroxyindolin-2-one (**11d**).⁵³ Prepared from isatin **10d** (72 h). The product was isolated as a white solid (22 mg) in 30% yield. Mp 148–150 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC, hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, 254 nm, $t_{(S)}$ = 7.86 min. (major), $t_{(R)}$ = 10.06 min. (minor), 59.5:40.5 *er*, 19% *ee* ($[\alpha]_{\text{D}}^{20}$ = –3.4 (c 1.00, CHCl_3)). ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.22 (m, 5H), 7.19–7.14 (m, 1H), 7.10–7.00 (m, 1H), 6.67–6.54 (m, 1H), 5.48–5.32 (m, 1H), 5.20–5.11 (m, 1H), 5.08–4.93 (m, 2H), 4.71 (d, J = 15.8 Hz, 1H), 3.35–3.24 (m, 1H), 3.00–2.83 (m, 2H). ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 176.6, 144.8, 135.0, 131.1, 130.1, 129.0, 128.0, 127.5, 127.4, 127.3, 120.8, 119.5, 108.7, 77.9, 44.1, 40.4.

General procedure for the asymmetric crotylboration. To a dried 5 mL tube flushed with Ar were successively added activated 5 Å molecular sieve (400 mg/mmol), toluene (0.7 mL), catalyst (*R*)-**2a** (9.0 mg, 0.02 mmol, 0.1 equiv), *t*-BuOH (93 μL , 5 equiv) and *Z*-crotyl boronate **24** (1 M solution in toluene, 0.3 mL, 0.3 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 5 minutes, then cooled to –10 °C and stirred for 15 min before addition of the isatin derivative **10a**, **10e** or **3a** (0.2 mmol, 1 equiv). After complete starting material consumption, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (100% DCM to 80% DCM, 20% acetone) to afford the expected enantio-enriched 3-allyl-3-hydroxy-2-oxindole.

(*S*)-1-benzyl-3-((*S*)-but-3-en-2-yl)-3-hydroxyindolin-2-one (**syn-25**).⁵⁴ Prepared from isatin **10a** (–10 °C, 24h). The product was isolated as a white solid (56 mg) in 95% yield (92:8 *dr* (*syn:anti*)). R_f = 0.70 (DCM/Acetone = 9:1). Mp 58–60 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 1 mL/min, 254 nm, $t_{(\text{syn } R,R)}$ = 48.89 min., $t_{(\text{anti } S,R)}$ = 58.74 min., $t_{(\text{anti } R,S)}$ = 86.74 min., $t_{(\text{syn } S,S)}$ = 91.42 min., 1:99 *er*, 98% *ee* ($[\alpha]_{\text{D}}^{20}$ = –61.8 (c 1.00, CHCl_3)). ^1H NMR (300 MHz, CDCl_3) δ 7.39 (ddd, J = 7.4, 1.4, 0.6 Hz, 1H), 7.33 – 7.25 (m, 5H), 7.21 (td, J = 7.8, 1.4 Hz, 1H), 7.06 (td, J = 7.6, 1.1 Hz, 1H), 6.69 (dt, J = 7.7, 0.8 Hz, 1H), 6.10 (ddd, J = 17.7, 10.5, 7.3 Hz, 0.08H (*anti*)), 5.71 (ddd, J = 17.1, 10.1, 9.3 Hz, 0.92H (*syn*)), 5.25 (ddd, J = 17.1, 1.9, 0.8 Hz, 1H), 5.14 (dd, J = 10.1, 1.9 Hz, 1H), 5.02 (d, J = 15.8 Hz, 1H), 4.69 (d, J = 15.8 Hz, 1H), 3.00 (s, 1H), 2.82 (dq, J = 9.3, 6.9 Hz, 1H), 1.06 (d, J = 6.9 Hz, 2.76H (*syn*)),

0.86 (d, $J = 6.9$ Hz, 0.24H (*anti*)). ^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 177.8, 143.4, 137.2, 135.7, 129.8, 128.9, 128.8, 127.8, 127.5, 124.3, 123.1, 119.2, 109.5, 78.0, 47.2, 44.0, 14.4.

(*S*)-3-((*S*)-but-3-en-2-yl)-3-hydroxy-1-methylindolin-2-one (**syn-26**).⁵⁵ Prepared from isatin **10e** (-10 °C, 24h). The product was isolated as a white solid (41 mg) in 94% yield (94:6 *dr* (*syn:anti*)). $R_f = 0.50$ (DCM/Acetone = 9:1). Mp 106–108 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IB, heptane/*i*-PrOH = 98/2, 1.0 mL/min, 254 nm, $t_{(\text{syn } R,R)} = 81.47$ min., $t_{(\text{anti } S,R)} = 92.92$ min., $t_{(\text{syn } S,S)} = 121.01$ min., $t_{(\text{anti } R,S)} = 133.92$ min., 2:98 *er*, 96% *ee* ($[\alpha]_D^{20} = -94.8$ (c 1.0, CHCl_3)). ^1H NMR (300 MHz, CDCl_3) δ 7.37 (ddd, $J = 7.3, 1.3, 0.6$ Hz, 1H), 7.32 (ddd, $J = 7.8, 7.5, 1.3$ Hz, 1H), 7.08 (ddd, $J = 7.5, 7.3, 1.0$ Hz, 1H), 6.80 (ddd, $J = 7.8, 1.0, 0.6$ Hz, 1H), 6.08 (ddd, $J = 17.3, 10.5, 7.2$ Hz, 0.06H (*anti*)), 5.61 (ddd, $J = 17.1, 10.1, 9.1$ Hz, 0.94H (*syn*)), 5.18 (ddd, $J = 17.1, 1.9, 0.8$ Hz, 1H), 5.08 (dd, $J = 10.1, 1.9$ Hz, 1H), 3.14 (s, 3H), 2.76 (dq, $J = 9.1, 6.9$ Hz, 1H), 1.02 (d, $J = 6.9$ Hz, 0.82H (*syn*)), 0.74 (d, $J = 6.7$ Hz, 0.18H (*anti*)). ^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 177.7, 144.1, 137.2, 129.8, 128.8, 124.3, 123.0, 118.7, 108.3, 78.2, 47.0, 26.1, 14.1. IR (cm^{-1}): 3315, 2977, 1692, 1616, 1498, 1468, 1425, 1384, 1357, 1302, 1273, 1260, 1203, 1163, 1122, 1101, 1059, 1022, 995, 967, 945, 933, 864, 838, 760, 709, 693. HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 240.0995; found 240.0996.

(*S*)-3-((*S*)-but-3-en-2-yl)-3-hydroxyindolin-2-one (**syn-27**).⁵⁶ Prepared from isatin **3a** (50 °C using an oil bath, 36h). The product was isolated as a white solid (33 mg) in 82% yield (82:18 *dr* (*syn:anti*)). $R_f = 0.10$ (DCM/Acetone = 9:1). After recrystallization, yield was 61% (25 mg) (97:3 *dr* (*syn:anti*)). Mp 155–157 °C. Before recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IA-3, heptane/*i*-PrOH = 98/2, 0.8 mL/min, 220 nm, $t_{(\text{syn } S,S)} = 107.68$ min., $t_{(\text{anti } R,S)} = 124.92$ min., $t_{(\text{syn } R,R)} = 151.65$ min., $t_{(\text{anti } S,R)} = 188.37$ min., 96:4 *er*, 92% *ee*. After recrystallization, the enantiomeric ratio was determined using a Daicel Chiralpak IA-3, hexane/*i*-PrOH = 98:2, flow rate = 0.8 mL/min, 220 nm, $t_{(\text{syn } S,S)} = 107.66$ min., $t_{(\text{anti } R,S)} = 125.40$ min., $t_{(\text{syn } R,R)} = 152.46$ min., $t_{(\text{anti } S,R)} = 190.04$ min., >99:1 *er*, >98% *ee* ($[\alpha]_D^{20} = -119.2$ (c 0.6, CHCl_3)). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 7.3$ Hz, 1H), 7.27 (ddd, $J = 7.8, 7.6, 1.3$ Hz, 1H), 7.08 (ddd, $J = 7.8, 7.6, 1.1$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.07 (ddd, $J = 17.1, 10.4, 7.4$ Hz, 0.03H (*anti*)), 5.73 (ddd, $J = 17.1, 10.1, 9.1$ Hz, 0.97H (*syn*)), 5.24 (ddd, $J = 17.1, 1.9, 0.8$ Hz, 1H), 5.17 (dd, $J = 10.1, 1.9$ Hz, 1H), 3.00-2.84 (br s, 1H), 2.74 (dq, $J = 9.3, 6.9$ Hz, 0.97H), 1.04 (d, $J = 6.9$ Hz, 2.91H (*syn*)), 0.87 (d, $J = 6.8$ Hz, 0.09H (*anti*)). ^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 179.7, 141.1, 137.1, 129.8, 129.4, 124.7, 123.3, 119.0, 110.1, 78.5, 47.1, 14.1.

General procedure for the asymmetric propargylation. To a dried 5 mL tube flushed with Ar, were successively added activated 5 Å molecular sieve (400 mg/mmol), toluene (0.7 mL), catalyst (*R*)-**2a** (9.0 mg, 0.02 mmol, 0.1 equiv), and allenylboronate **28** (1 M solution in toluene, 0.3 mL, 0.3 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 15 minutes before addition of **10a** or **3a** (0.2 mmol, 1 equiv) was added. After complete starting material consumption, the reaction mixture was directly deposited on silica gel and a purification was performed *via* preparative liquid chromatography (100% DCM to 80% DCM, 20% acetone). The pure fractions were collected and the solvent was evaporated to give the expected enantio-enriched homopropargylic alcohol.

(*S*)-1-benzyl-3-hydroxy-3-(prop-2-yn-1-yl)indolin-2-one (**29**).³⁹ Prepared from **10a** (rt, 18h). The product was isolated as a white solid (52 mg) in 94% yield. $R_f = 0.65$ (DCM/Acetone = 9:1). Mp 132–134 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IC-5, heptane/*i*-PrOH = 80:20, 1.0 mL/min, 254

nm, $t_{(R)}$ = 8.44 min. (minor), $t_{(S)}$ = 10.76 min. (major), 4.5:95.5 *er*, 91% *ee* ($[\alpha]_D^{20} = -55.5$ (c 1.0, CHCl₃)). ¹H NMR (300 MHz, CDCl₃): δ 7.56 (ddd, $J = 7.3, 1.4, 0.6$ Hz, 1H), 7.38 – 7.18 (m, 6H), 7.09 (ddd, $J = 7.6, 7.3, 1.0$ Hz, 1H), 6.73 (ddd, $J = 7.9, 1.0, 0.6$ Hz, 1H), 5.04 (d, $J = 15.7$ Hz, 1H), 4.75 (d, $J = 15.7$ Hz, 1H), 3.42 (s, 1H), 2.99 (dd, $J = 16.4, 2.7$ Hz, 1H), 2.85 (dd, $J = 16.4, 2.7$ Hz, 1H), 1.94 (t, $J = 2.7$ Hz, 1H). ¹³C {¹H} NMR (75 MHz, CDCl₃) δ 176.9, 142.7, 135.3, 130.2, 129.1, 128.9, 127.9, 127.5, 124.3, 123.4, 109.7, 77.8, 74.6, 71.7, 44.1, 29.0.

(*S*)-3-hydroxy-3-(prop-2-yn-1-yl)indolin-2-one (**31**).³⁹ Prepared from **3a** (50 °C using an oil bath, 24h). The product was isolated as a white solid (36 mg) in 96% yield. $R_f = 0.40$ (DCM/Acetone = 8:2). Mp 164-166 °C. The enantiomeric ratio was determined using a Daicel Chiralpak IA-3, heptane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, $t_{(S)}$ = 6.32 min. (major), $t_{(R)}$ = 9.91 min. (minor), 76.5:23.5 *er*, 53% *ee* ($[\alpha]_D^{20} = -26.8$ (c 1.1, MeOH)). ¹H NMR (300 MHz, CD₃OD): δ 7.46 (d, $J = 7.6$ Hz, 1H), 7.36 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.05 (td, $J = 7.6, 0.8$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 2.85 (dd, $J = 16.0, 2.7$ Hz, 1H), 2.78 (dd, $J = 16.0, 2.7$ Hz, 1H), 1.94 (t, $J = 2.7$ Hz, 1H).

Kinetics experimental section. To a 3 mL test tube under argon and in a thermostat at 25.0 °C, were added molecular sieves (4 Å, 35 mg), anhydrous toluene (v_1 μ L), (*R*)-3,3'-dibromoBINOL (0.0235 mol/L in toluene, v_2 μ L), *B*-allyl-1,3,2-dioxaborolane (1.00 M in toluene, 100 μ L, 0.100 mmol, 1.5 eq) and *tert*-butanol (8.36 mol/L in toluene, v_3 μ L). Variable volumes v_1 , v_2 , and v_3 were chosen in order to set a constant total volume ($v_1 + v_2 + v_3 = 340$ μ L). The resulting solution was stirred before *N*-methyl isatin **10e** was added (0.150 mol/L in toluene, 440 μ L, 0.066 mmol). The reaction was followed by quenching aliquots (50 μ L) in toluene (2.80 mL) every minute. The absorbance of the resulting solution was measured in a 10 mm light path glass cuvette at 428 nm. The initial rate V_0 was then determined by measuring the slope of the *N*-methylisatin concentration curve versus time, the consumption of *N*-methylisatin being lower than 10 %. After overnight reaction and purification on a TLC silica plate, the enantiomeric excess of *N*-methyl 3-allyl-3-hydroxy-2-oxindole **11e**¹³ was measured by HPLC using a Daicel Chiralpak IC3 column, hexane/*i*-PrOH = 80/20, flow rate = 1 mL/min, 254 nm, $t_{(R)}$ = 9.10 min., $t_{(S)}$ = 11.52 min (major).

Computational Methods. Considering the numerous possible conformations for TS-C and the numerous possible orientations of the BINOL and the ethylene glycol moieties in TS-D, the most stable transition states were found from a conformational analysis performed with Spartan 10. For TS-Cs, the structure of TS-A was used as the starting geometry and a molecule of **2a** was added. The B-O and C-C bonds formed during the reaction were then frozen, and it was submitted to a conformational analysis with MMFF molecular mechanics. For TS-D, a first transition state based on pathway 4 was found and optimized to B3LYP/6-31+G(d) level using Spartan 10.⁵⁷ Then, the B-O and C-C bonds formed during the reaction were frozen, and the structure was submitted to a conformational analysis with MMFF molecular mechanics. For both TS-C and TS-D, all the conformers were then optimized under the same constraint to the B3LYP/3-21G level. The two most stable transition states for each approach (*Re* and *Si*) were then optimized using Gaussian 16⁵⁸ to B3LYP/6-31+G(d) level, then with M062X/6-31+G(d) and finally with M062X/6-311+G (d,p) using the SMD solvent model for the

description of toluene as the solvent. Frequency calculations were used to characterize stationary points by the number of negative eigenvalues of their analytic Hessian matrix. The imaginary frequencies were checked to exhibit the expected motion and transition states were verified using IRC calculation.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its supporting information

Supporting Information statement. This material is available free of charge via the Internet at <http://pubs.acs.org>.

- Copies of ^1H , $^{13}\text{C}\{^1\text{H}\}$, ^{19}F NMR spectra of all compounds as well as their corresponding HPLC chromatograms (PDF)
- Crystal data, CCDC 2127790 for **4h**, CCDC 2127791 for **4k**, CCDC 2127792 for **5**, CCDC 2155726 for *syn-25*, CCDC 2127789 for **29** (CIF)
- DFT calculation data and IR spectra of **10e** and **11e**, visible spectrum of **10e**, table of kinetics data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mails: joelle.vidal@univ-rennes1.fr; claudia.lalli@univ-rennes1.fr; arnaud.martel@univ-lemans.fr; francois.carreaux@univ-rennes1.fr.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

This work was supported by the University of Rennes 1 and the Centre National de la Recherche Scientifique (CNRS). One of us (J.B.) thanks “Ecole doctorale 3M” and University of Rennes 1 for a research fellowship. The authors would like to thank Marielle Blot for her technical assistance.

REFERENCES

- (1) For some reviews, see: (a) Hoffmann, R. W. Diastereogenic Addition of crotylmetal compounds to Aldehydes. *Angew. Chem. Int. Ed.* **1982**, *21*, 555-642. (b) Stereodirected Synthesis with Organoboranes, Ed. D. S. Matteson, Springer, Berlin, 1995. (c) Hall, D. G.; Lachance, H. *Allylboration of Carbonyl Compounds*; Wiley: Hoboken, NJ, 2012. (d) Yus, M.; González-Gómez, J. C.; Foubelo, F. Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, 5595-5698.
- (2) Representative chiral auxiliaries used, see: (a) Brown, H. C.; Jadhav, P. K. Asymmetric Carbon-Carbon Bond Formation via B-Allyldiisopinocampheylborane. Simple Synthesis of secondary Homoallylic Alcohols with Excellent Enantiomeric Purities. *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093. (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. Diastereo- and Enantioselective Aldehyde Addition Reactions of 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylic Esters, a Useful Class of Tartarate Ester Modified Allylboronates. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190. (c) Short, R. P.; Masamune, S. Asymmetric Allylboration with B-Allyl-2-(trimethylsilyl)borolane. *J. Am. Chem. Soc.* **1989**, *111*, 1892-1894. (d) Corey, E. J.; Yu, C.-M.; Kim, S. S.; A practical and Efficient Method for Enantioselective Allylation of Aldehydes. *J. Am. Chem. Soc.* **1989**, *111*, 5496-5498.
- (3) For some reviews, see: (a) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem. Rev.* **2003**, *103*, 2763-2793. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines. *Chem. Rev.* **2011**, *111*, 12, 7774-7854. For metal-mediated allylboration, see: (c) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. Catalytic Asymmetric Allylation of Carbonyl Compounds and Imines with Allylic Boronates. *Org. Chem. Front.* **2014**, *1*, 303-320.
- (4) For chiral Lewis acids, see: (a) Ishiyama, T.; Ahiko, T.-A.; Miyura, N. Acceleration Effect of Lewis Acid in Allylboration of Aldehydes: Catalytic, Regiospecific, Diastereospecific and Enantioselective Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415. For chiral Brønsted acids, see: (b) Rauniyar, V.; Hall, D. G. Catalytic Enantioselective and Catalyst-Controlled Diastereofacial Additions of Allyl- and Crotylboronates to Aldehydes Using Chiral Brønsted Acids. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426-2428. (c) Rauniyar, V.; Zhai, H.; Hall, D.G. Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol·SnCl₄ Complexes. Optimization, Substrate Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490.
- (5) Jain, P.; Antilla, J. C. Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886.
- (6) For a review, see: (a) Sedgwick, D. M.; Grayson, M. N.; Fustero, S.; Barrio, P. Recent Developments and Applications of the Chiral Brønsted Acid Catalyzed Allylboration of Carbonyl Compounds. *Synthesis* **2018**, 1935-1957. For some recent papers, see: (b) Farrar, E. H. E.; Grayson, M. N. Computational Studies of Chiral Hydroxyl Carboxylic Acids: The Allylboration of Aldehydes. *J. Org. Chem.* **2020**, *85*, 15449-15456. (c) Gao, S.; Liu, J.; Chen, M. Catalytic Asymmetric Transformations of Racemic α -Borylmethyl-(E)-Crotylboronate via Kinetic Resolution or Enantioconvergent Reaction. *Chem. Sci.*, **2021**, *12*, 13398-13403 and references cited therein. (d) Yuan, J.; Jain, P.; Antilla, J. C. Chiral Phosphoric Acid-Catalyzed Enantio- and Diastereoselective Allylboration of Aldehydes with β,γ -Substituted Allylboronates. *J. Org. Chem.* **2022**, *87*, 8256-8266 and references cited therein.
- (7) Recent publications using metal complex mediated asymmetric allylations of isatins with allylboronates have been reported, see: (a) Wang, J.; Zhang, Q.; Li, Y.; Liu, X.; Li, X.; Cheng, J.-P. Bi(OAc)₃/chiral phosphoric acid

catalyzed enantioselective allylation of isatins. *Chem. Commun.* **2020**, *56*, 261-264. (b) Li, K.; Sun, X.; Zhao, S.; Li, T.; Zha, Z.; Wang, Z. Zn-Catalyzed enantioselective allylation and allenylation of isatins by virtue of a proline-derived chiral ligand. *Chem. Commun.* **2022**, *58*, 2156-2159.

(8) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2006**, *128*, 12660-12661.

(9) For mechanistic experiments, see: (a) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Acyl Imines Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2007**, *129*, 15398-15404. (b) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. The Mechanism and an Improved Asymmetric Allylboration of Ketones Catalyzed by Chiral Biphenols. *Angew. Chem. Int. Ed.* **2009**, *48*, 8679-8682. For DFT calculations, see: (c) Paton, R.S.; Goodman, J. M.; Pellegrinet, S. C. Mechanistic Insights into the Catalytic Asymmetric Allylboration of Ketones: Brønsted or Lewis Acid Activation? *Org. Lett.* **2009**, *11*, 37-40.

(10) (a) Zhang, Y.; Li, N.; Qu, B.; Ma, S.; Lee, H.; Gonnellá, N. C.; Gao, J.; Li, W.; Tan, Z.; Reeves, J. T.; Wang, J.; Lorenz, J. C.; Li, G.; Reeves, D. C.; Premasini, A.; Grinberg, N.; Haddad, N.; Lu, B. Z.; Song, J. J.; Senanayake, C. H. Asymmetric Methallylation of Ketones Catalyzed by a Highly active Organocatalyst. *Org. Lett.* **2013**, *15*, 1710-1713. (b) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration. *J. Am. Chem. Soc.* **2015**, *137*, 11262-11265. (c) Chai, G.-L.; Zhu, B.; Chang, J. Synthesis and Application of Substituted 1,16-Dihydroxytetraphenylenes in Catalytic Asymmetric Allylboration of Ketones. *J. Org. Chem.* **2019**, *84*, 120-127. (d) Liu, J.; Tong, X.; Chen, M. Allylboration of Ketones and Imines with a Highly reactive Bifunctional Allyl Pinacolatoboronate Reagent. *J. Org. Chem.* **2020**, *85*, 5193-5202.

(11) Barnett, D. S.; Schaus, S. E. Asymmetric Propargylation of Ketones Using Allenylboronates Catalyzed by Chiral Biphenols. *Org. Lett.* **2011**, *13*, 4020-4023.

(12) (a) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. Simple Organic Molecules as catalysts for Enantioselective Synthesis of Amines and Alcohols. *Nature* **2013**, *494*, 216-221. (b) Robbins, D. W.; Lee, K.; Silverio, D. L.; Volkov, A.; Torker, S.; Hoveyda, A. H. Practically and Broadly Applicable Catalytic Enantioselective Additions of Allyl-B(pin) Compounds to Ketones and α -Ketoesters. *Angew. Chem. Int. Ed.* **2016**, *55*, 9610-9614. (c) Mszar, N. W.; Mikus, M. S.; Torker, S.; Haeffner, F.; Hoveyda, A. H. Electronically Activated Organoboron Catalysts for Enantioselective Propargyl Addition to trifluoromethyl Ketones. *Angew. Chem. Int. Ed.* **2017**, *56*, 8736-8741. (d) Van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. Practical, Broadly Applicable, α -selective, Z-selective, Diastereoselective, and Enantioselective Addition of Allylboron Compounds to Mono, Di, Tri, and Polyfluoroalkyl Ketones. *J. Am. Chem. Soc.* **2017**, *139*, 9053-9065.

(13) Braire, J.; Dorcet, V.; Vidal, J.; Lalli, C.; Carreaux, F. BINOL Derivatives-Catalysed Enantioselective Allylboration of Isatins: Application to the Synthesis of (R)-Chimonamidine. *Org. Biomol. Chem.* **2020**, *18*, 6042-6046.

(14) Concerning the reactivity of allylboron reagents in allylboration, see: (a) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. Organoboranes 53. A High-Field Variable-Temperature ^1H and ^{11}B NMR Study of the effects of Solvent and Structure on Reactivity in Allylboration. *J. Org. Chem.* **1990**, *55*, 1868-1874. Concerning the relative rates of transesterification of boronates, see: (b) Roy, C. D.; Brown, H. C. Stability of Boronic Esters-

Structural effects on the relative rates of transesterification of 2-(phenyl)-1,3,2-dioxaborolane. *J. Organomet. Chem.* **2007**, *692*, 784-790.

(15) (a) Hemelaere, R.; Carreaux, F.; Carboni, B. A Diastereoselective Route to *trans*-2-Aryl-2,3-dihydrobenzofurans through Sequential Cross-Metathesis/Isomerization/Allylboration Reactions: Synthesis of Bioactive Neolignans. *Eur. J. Org. Chem.* **2015**, 2470-2481. (b) Macé, A.; Touchet, S.; Andres, P.; Cossio, F.; Dorcet, V.; Carreaux, F.; Carboni, B. [3,3]-Sigmatropic Rearrangement/Allylboration/Cyclisation Sequence: Enantioenriched Seven-Membered-Ring Carbamates and Ring Contraction to Pyrrolidines. *Angew. Chem. Int. Ed.*, **2016**, *55*, 1025-1029. (c) Henrion, S.; Macé, A.; Vallejos, M. M.; Roisnel, T.; Carboni, B.; Villalgorido, J. M.; Carreaux, F. Asymmetric Synthesis of *trans*-4,5-Disubstituted γ -Butyrolactones Involving a Key Allylboration Step. First Access to (-)-Nicotlactone B and (-)-Galbacin. *Org. Biomol. Chem.* **2018**, *16*, 1672-1678.

(16) (a) Peddibhotla, S. 3-Substituted 3-hydroxy-2-Indole, an Emerging New Scaffold for Drug Discovery with Potential Anti-Cancer and Other Biological Activities. *Curr. Bioact. Compd.* **2009**, *5*, 20-38. (b) Zhou, F.; Liu, Y.-L.; Zhou, J. Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 position. *Adv. Synth. Catal.* **2010**, *352*, 1381-1407. (c) Richey, N.; Sarraf, D.; Maréchal, X.; Janmamode, N.; Le Guével, R.; Genin, E.; Reboud-Ravaux, M.; Vidal, J. Structure-based design of human immuno- and constitutive proteasomes inhibitors. *Eur. J. Med. Chem.* **2018**, *145*, 570-587.

(17) In our precedent works with *N*-substituted isatins (ref. 13), we observed that using solvents such as CH₂Cl₂ and cyclohexane led to lower enantioselectivity.

(18) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. Benzotrifluoride and Derivatives: Useful Solvents for Organic Synthesis and Fluorous Synthesis. *Top. Curr. Chem.* **1999**, *206*, 79-105.

(19) Solubility of **3a** in PhCF₃ at room temperature was estimated at 0.23 g/L (0.0016 M). For PhCH₃, the value was estimated at 0.19 g/L (0.0013 M). At 24 °C, solubility of **3a** was estimated at 3.3 g/L in solution of *t*-BuOH (1 M) in PhCF₃ and at 2.9 g/L for *t*-BuOH (1 M) in PhCH₃.

(20) CCDC 2127790 and 2127791 contain the supplementary crystallographic data for respectively compounds **4h** and **4k**.

(21) CCDC 2127792 contains the supplementary crystallographic data for compound **5**.

(22) For some examples, see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New *N*- and *O*-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39*, 2933-2936. (b) Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J.-H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. Copper-Catalyzed *N*-Arylation of Oxindoles. *Tetrahedron Lett.* **2006**, *47*, 7137-7138.

(23) Direct allylboration of *N*-phenyl isatin lead to compound **7** with a lower enantioselectivity (95.5:4.5 *er*), see ref.13.

(24) Yu, C.; Sanjosé-Orduna, J.; Patureau, F. W.; Pérez-Temprano, M. H. Emerging unconventional organic solvents for C-H bond and related functionalization reactions. *Chem. Soc. Rev.* **2020**, *49*, 1643-1652.

(25) Grayson, M. N.; Goodman, J. M. Lewis Acid Catalysis and Ligand Exchange in the Asymmetric Binaphthol-Catalyzed Propargylation of Ketones *J. Org. Chem.* **2013**, *78*, 8796-8801.

(26) Jonker, S. J. T.; Jayarajan, R.; Kireilis, T.; Deliaival, M.; Eriksson, L.; Szabó, K. J. Organocatalytic Synthesis of α -Trifluoromethyl Allylboronic Acids by Enantioselective 1,2-Borotropic Migration. *J. Am. Chem. Soc.* **2020**, *142*, 21254-21259.

- (27) Huang, G.; Diner, C.; Szabó, K. J.; Himo, F. Mechanism and Stereoselectivity of the BINOL-Catalyzed Allylboration of Skatoles. *Org. Lett.* **2017**, *19*, 5904–5907.
- (28) Zhao, Y.; Truhlar, D. G.; Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Accounts* **2007**, *120*, 215–241.
- (29) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- (30) The ¹H NMR reaction monitoring of **1** with (*R*)-3,3'-Br₂-BINOL **2a** at -78 °C did not allow to observe the formation of **12**.
- (31) Kuroda, R.; Imai, Y.; Sato, T. Chirality Recognition in Solvent-Free Solid-State Crystallization: Chiral Adduct Formation by Bis- β -naphthol Derivatives and Benzoquinone Crystals. *Chirality* **2001**, *13*, 588-594.
- (32) (a) Li, Y.; Houk, K. N. Transition Structures for the Allylboration reactions of formaldehyde by Allylborane and Allylboronic Acid. *J. Am. Chem. Soc.* **1989**, *111*, 1236-1240. (b) Sakata, K.; Fujimoto, H. Quantum Chemical Study of Lewis Acid Catalyzed Allylboration of Aldehydes *J. Am. Chem. Soc.* **2008**, *130*, 12519-12526.
- (33) Emamian, S.; Lu, T.; Kruse, H.; Emamian, H. Exploring Nature and Predicting Strength of Hydrogen Bonds: A Correlation Analysis Between Atoms-in-Molecules Descriptors, Binding Energies, and Energy Components of Symmetry-Adapted Perturbation Theory. *J. Comput. Chem.* **2019**, *40*, 2868–2881.
- (34) Lu, T.; Chen, F. Multiwfn: A Multifunctional Wavefunction Analyzer, *J. Comput. Chem.* **2012**, *33*, 580-592.
- (35) Laidler, K. J. *Chemical Kinetics (3rd Ed.)*; Prentice Hall, 1997.
- (36) α -adducts are mainly formed using crotylboronates as reagents when the reaction is performed in the presence of transition metal-based Lewis acids, see: ref 3c.
- (37) CCDC 2155726 contains the supplementary crystallographic data for compound **syn-25**.
- (38) For some reviews, see: (a) Ding, C.-H.; Hou, X.-L. Catalytic Asymmetric Propargylation. *Chem. Rev.* **2011**, *111*, 1914-1937. (b) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074-3112. (c) Wisniewska, H. M.; Jarvo, E. R. Enantioselective Propargylation and Allenylation Reactions of Ketones and Imines. *J. Org. Chem.* **2013**, *78*, 11629-11636.
- (39) Gupta, N.; Tak, R.; Nazish, M.; Jakhar, A.; Khan, N. H.; Kureshy, R. I. Copper (II) triflate Catalyzed Regioselective and Enantioselective Propargylation of Isatins Derivatives by using Allenylboronic Acid Pinacol Ester. *Eur. J. Org. Chem.* **2018**, 1384-1392.
- (40) Compounds **30** and **32** have been described in the reference 7b.
- (41) CCDC 2127789 contains the supplementary crystallographic data for compound **29**.
- (42) Ellis, J. M.; Overman, L. E.; Tanner, H. R.; Wang, J. A Versatile Synthesis of Unsymmetrical 3,3'-Bioxindoles: Stereoselective Mukaiyama Aldol Reactions of 2-Siloxyindoles with Isatins. *J. Org. Chem.* **2008**, *73*, 9151-9154.
- (43) Buxton, C. S.; Blakemore, D. C.; Bower, J. F. Reductive Coupling of Acrylates with Ketones and Ketimines by a Nickel-Catalyzed Transfer-Hydrogenative Strategy. *Angew. Chem. Int. Ed.* **2017**, *56*, 13824-13828.

- (44) Vyas, D. J.; Fröhlich, R.; Oestreich, M. Stereochemical Surprises in the Lewis Acid-Mediated Allylation of Isatins. *J. Org. Chem.* **2010**, *75*, 6720-6723.
- (45) Ošek, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles. *Org. Lett.* **2016**, *18*, 1358-1361.
- (46) (a) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. Enantioselective Synthesis using Diisopropyl Tartrate Modified (*E*)-and (*Z*)-Crotylboronates: Reactions with Achiral Aldehydes. *Tetrahedron Lett.* **1988**, *29*, 5579-5582. (b) Hoffmann, R. W.; Endesfelder, A. Diastereoselective Addition of Crotylboronates to oximes. *Liebigs Ann. Chem.* **1987**, 215-219.
- (47) Cao, Z.-Y.; Jiang, J.-S.; Zhou, J. A Highly Enantioselective Hg(II)-Catalyzed Sakurai-Hosomi Reaction of Isatins with Allyltrimethylsilanes. *Org. Biomol. Chem.* **2016**, *14*, 5500-5504.
- (48) Hanhan, N. V.; Tang, Y. C.; Tran, N. T.; Franz, A. K. Scandium (III)-Catalyzed Enantioselective Allylation of Isatins using Allylsilanes. *Org. Lett.* **2012**, *14*, 2218-2221.
- (49) Cao, Z.-Y.; Zhang, Y.; Ji, C.-B.; Zhou, J. A Hg(ClO₄)₃H₂O Catalyzed Sakurai-Hosomi Allylation of Isatins and Isatin Ketoimines using Allyltrimethylsilane. *Org. Lett.* **2011**, *13*, 6398-6401.
- (50) Chen, J.; Yuan, T.; Liu, L. A Synthesis of 3-Substituted-3-Hydroxyoxindoles via an Indium-Mediated Barbier-type Allylation of Isatins in PEG-400. *J. Chem. Research* **2011**, 390-393.
- (51) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. Total Synthesis of (+)-Perophoramidine and Determination of the Absolute Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 14052-14054.
- (52) Ghosh, D.; Gupta, N.; Abdi, S. H. R.; Nandi, S.; Khan, N. H.; Kureshy, R.; Bajaj, H. C. Organocatalyzed Enantioselective Allylation of Isatins by using a chiral Amino Alcohol Derived Squaramide as Catalyst. *Eur. J. Org. Chem.* **2015**, 2801-2806.
- (53) Wang, T.; Hao, X.-Q.; Huang, J.-J.; Wang, K.; Gong, J.-F.; Song, M.-P. Chiral CNN Pincer Palladium (II) Complexes with 2-Aryl-6-(oxazolonyl)pyridine Ligands: Synthesis, Characterization and Application to Enantioselective Allylation of Isatins and Suzuki-Miyaura Coupling Reaction. *Organometallics* **2014**, *33*, 194-205.
- (54) Itoh, J.; Han, S. B.; Krische, M. J. Enantioselective Allylation, Crotylation and Reverse Prenylation of Substituted Isatins: Iridium-Catalyzed C-C Bond-Forming Transfer Hydrogenation. *Angew. Chem. Int. Ed.* **2009**, *48*, 6313-6316.
- (55) Tang, X.; Su, Z.; Yan, L.; Tang, Q.; Dong, S.; Lin, L.; Feng, X. Diastereo- and Enantioselective Synthesis of 3-Allyl-3-hydroxyindoles via Allylation of Isatins. *Org. Lett.* **2021**, *23*, 8419-8423.
- (56) Higushi, K.; Saito, K.; Hirayama, T.; Watanabe, Y.; Kobayashi, E.; Kawasaki, T. Claisen Rearrangement through Enolization of 2-Allyloxyindolin-3-ones: Construction of Adjacent Carbon Stereocenters in 3-Hydroxyindolin-2-ones. *Synthesis* **2010**, 3609-3614.
- (57) SPARTAN, Wavefunction, Inc., 18401, Von Karman Avenue, Suite 370, Irvine CA 92612 USA.
- (58) Gaussian 16, Revision B.01, Frisch, M. J. et al Gaussian, Inc., Wallingford CT, 2016.