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Control of the Dual Reactivity (Iminium-Dienamine) of β-Arylmethyl α,β-Unsaturated Aldehydes in Organocatalytic 1,3-Dipolar Cycloadditions with *N*-Benzoyl *C,N*-Cyclic Azomethine Imines

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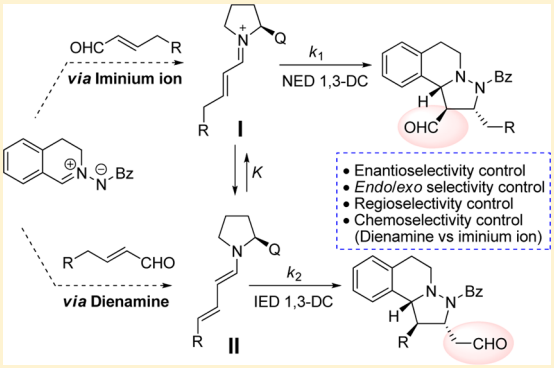
Supporting Information

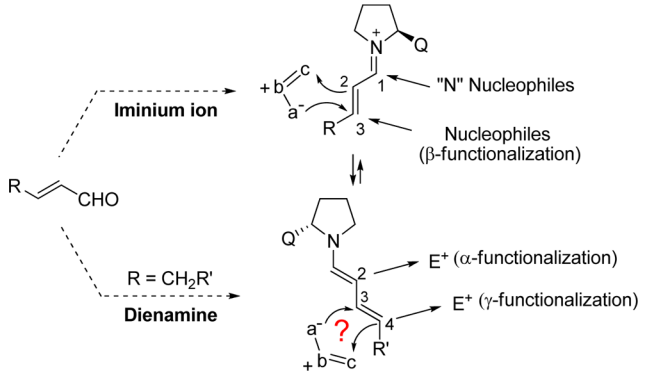
ABSTRACT: 1,3-Dipolar cycloadditions of *C,N*-cyclic azomethine imines with α,β-unsaturated aldehydes can be performed with complete control of the regio-, *exo*-, and enantioselectivity under aminocatalytic conditions. The so far never studied competence of the iminium-dienamine reactivity inherent to β-alkyl α,β-unsaturated aldehydes was studied, which was possible by allowing achievement of complete control of the chemoselectivity in reactions of the β-arylmethyl derivatives with azomethine imines by using different additives and organocatalysts, whose role has been rationalized by DFT calculations and chemical proofs. Thus, it has been possible to selectively obtain the pyrazolidines resulting from both the attack to the C2−C3 (via iminium) and the C3−C4 (via dienamine) bonds at the starting enals, which can be used as precursors of interesting tetrahydroisoquinolinic compounds.



INTRODUCTION

One of the most studied substrates in organocatalysis[1] are α,β-unsaturated aldehydes due to the versatility derived from their easy transformation into electrophilic (iminium) or nucleophilic (dienamine) species with pyrrolidine type catalysts, both of them offering two reactive positions. Iminium species are able to be attacked by nucleophiles at C-1 and C-3 whereas dienamines react with electrophiles at C-2 and C-4 (Scheme 1). As the result of this dual reactivity and the ambivalent character of the formed species, it has been possible to get the α-,[2] β-,[3] and γ-functionalization[4] of the enals, as well as the attack to their carbonyl carbons (C-1).[5] The regioselectivity control difficulties derived from the ambivalent character of the iminium species have been overcome by the well-defined tendencies of the nucleophiles to attack on C-3 or C-1,[3,5] whereas for dienamines this problem was solved modulating the steric hindrance at C-2 and C-4.[6] On the other hand, chemoselectivity control difficulties derived from the dual reactivity (iminium vs dienamine) were obviated by using reagents without dual reactivity (nucleophiles or electrophiles).

Scheme 1. Different Reactivies of α,β-Unsaturated Aldehydes under Aminocatalysis



1,3-Dipolar cycloadditions (1,3-DC) have a pre-eminent role in the construction of heterocyclic systems and heterofunctionalized acyclic molecules resulting from their reductive ring opening.[7] The simultaneous formation of iminium and dienamine species from β-alkyl α,β-unsaturated aldehydes (R = CH_2R' at Scheme 1) in the presence of pyrrolidine type organocatalysts[8] suggests that their 1,3-DC with dipoles, presumably also with ambivalent reactivity, would be an appropriate scenario for studying the chemoselectivy derived from the dual reactivity (iminium-dienamine) of the enals. However, the so far studied dipoles[9] have only exhibited reactivity with the iminium species, and therefore, these chemoselectivity studies (dienamine-iminium) could not be performed.

Organocatalytic reactions of dipoles with iminium species, considered as normal-electron-demand (NED) cycloaddi-

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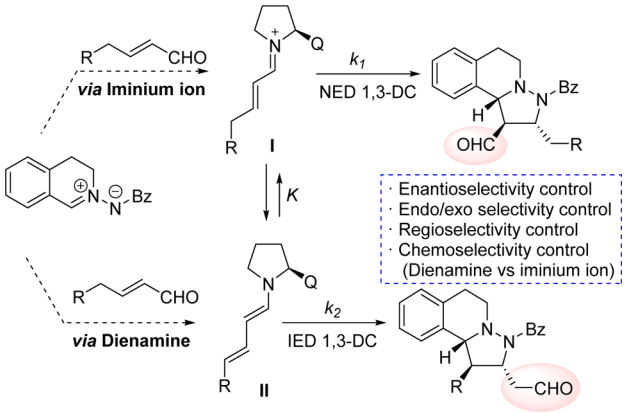
tions,[10] are well-known.[11] By contrast, the enantioselective organocatalytic inverse-electron-demand (IED)[10] 1,3-DCs are, to our knowledge, scarcely known and mainly restricted to the use of vinylethers catalyzed by Brønsted acids.[12] Interestingly, the dienamine has not been applied in IED 1,3-DCs reactions, thus remaining as a challenge. At this point we decided to investigate these reactions using the *C,N*-cyclic azomethine imines as dipoles,[13] recently incorporated in enantioselective [2 + 3]-dipolar cycloadditions.[12a,13a,b] These dipoles can be easily prepared and give access to pharmaceuticaly attractive chiral substituted tetrahydroisoquinoline skeletons.[14] Moreover, species **I** might exhibit the desired dual reactivity (NED and IED) that is not found with other dipoles. In this work we describe the 1,3-DC of the *N*-benzoyl *C,N*-cyclic azomethine imines with *β*-aryl and *β*-alkyl *α,β*-unsaturated aldehydes under different organocatalytic conditions which have demonstrated their efficiency for obtaining cycloadducts on the fragments C(2)−C(3) (NED processes via iminium **I**) and C(3)−C(4) (IED processes via dienamine **II**) in a completely chemoselective way, simultaneously controlling the regio-, enantio-, and *endo/exo*-selectivities (Scheme 2). The breaking of the N−N bonds at the cycloadducts resulting by both routes provided interesting tetrahydroisoquinoline derivatives.

Scheme 2. Dual Reactivity (Iminium-Dienamine) of *β*-Arylmethyl *α,β*-Unsaturated Aldehydes with *N*-Benzoyl *C,N*-Cyclic Azomethine Imines



During the preparation of this manuscript, the IED 1,3-DCs of the dipole **1a** with some of the dienamines studied in this paper has been published.[15] As the results reported in the aforementioned publication showed serious discrepancies with our results, we have added some comments and experiences concerning it (see addendum at the end of the Results and Discussion section).

RESULTS AND DISCUSSION

Screening Conditions and First Experiments. We started our study with *β*-aryl (or heteroaryl) *α,β*-unsaturated aldehydes, unable to form dienamine species, with the aim of knowing the possibilities of the *C,N*-cyclic azomethine imines in the asymmetric 1,3-DC under organocatalytic conditions, despite the synthetic problem having been elegantly solved by Maruoka by using titanium-BINOLate complexes as catalysts.[13a] After optimizing the conditions in the reaction of dipole **1a** with the aldehyde **2a** (see Supporting Information), we found that the use of the Jørgensen−Hayashi's catalyst **3A** (5 mol %) in toluene at room temperature afforded the expected aldehyde that was *in situ* transformed into the alcohol **4a** (84% yield, two steps) for determining its enantiomeric excess (98% ee, entry 1 at Table 1).[16] Similar conditions were applied to other *α,β*-unsaturated aldehydes, and the results are collected in Table 1. The presence of electron-donating (**2b** and **2c**, entries 2 and 3) or electron-withdrawing (**2d**, **2e**, and **2f**, entries 4−6) groups did not significantly modify the efficiency of these reactions. Similar behavior was observed for the *α*-furyl derivative **2g** (entry 7), but the pyridyl derivative **2h** (entry 8) exhibited a lower reactivity, with longer reaction times (80% conversion after 5 days) being necessary and a higher catalytic loading (20 mol %). Finally, reactions of the *β*-alkyl enals **2i** and **2j** were also studied (entries 10 and 12). They gave less satisfactory results with catalyst **3A**,[17] but we found that the use of **3B** cleanly provided **4i** and **4j** in high yields after longer reaction times (3 days). The higher efficiency of **3B** was also checked for the reaction of the *β*-pyridyl enal **2h** (compare entries 8 and 9), which was completely transformed into the aldehyde in only 16 h. As **4i** was obtained in 85% ee under conditions of entry 10, we repeat the reaction at 0 °C increasing the amount of catalyst to 20 mol %, thus being able to obtain **4i** enantiomerically pure (>99% ee) after 12 h in 61% yield (entry 11).

Remarkably, both regioselectivity and *endo/exo*-selectivity of all these reactions were complete, only yielding the *exo*-adducts **4**, and the enantiomeric excesses of the obtained alcohols were excellent (96−99% ee, Table 1). Configurational assignment of compounds **4** indicated in Table 1 was performed by comparison of the spectroscopic parameters and specific rotations of **4a** and **4i** with those of the same compounds described by Maruoka[13a] (see Supporting Information).[18]

As conclusion, we can state that asymmetric [3 + 2]-cycloaddition of the dipole **1a** with conjugated enals, previously reported under titanium-BINOLate complexes,[13a] can be alternatively performed with similar efficiency under organocatalytic conditions using a low catalytic loading (5 mol %). The reaction can be performed with aldehydes containing coordinating substituents, which presumably could present some incompatibilities with metallic catalysts. Moreover, the absence of cycloadducts resulting in the 1,3-DC of the dipole **1a** to the dienamine species (*β*-alkyl enals) was also interesting, whose formation would be possible for these substrates.

β-Arylmethyl *α,β*-unsaturated aldehydes (**2k−2q**) were chosen as dipolarophiles to study the 1,3-dipolar reactions with species **II** (Scheme 2), because the formation of the dienamine would be favored by aryl groups as it was previously postulated.[4e,f] The reaction of the dipole **1a** with **2k** in toluene, catalyzed by **3A** (20 mol %) at rt, afforded a 30:70 mixture of two compounds **5k** and **6k** (Scheme 3), that were identified as the adducts resulting in the 1,3-DC of **1a** to the fragments C(2)−C(3) (via iminium ion **I**) and C(3)−C(4) (via dienamine **II**). These results suggested the existence of the two species in equilibrium, dienamine **II** and iminium ion **I**, with both being able to react under the organocatalytic conditions used. Remarkably, the exclusive formation of **6k** as the only adduct resulting via dienamine indicated that the 1,3-DC of **II** is completely regio- and *exo*-selective.

Despite these promising results, both chemoselectivity (**5k**/**6k** ratio) and enantioselectivity (75% ee for **6k**) were moderate and should be improved. It prompted us to investigate the influence of the reaction parameters on both types of selectivities, with the aim of finding conditions allowing the exclusive evolution through the iminium or dienamine species, with the highest possible ee. A selection of the most significant

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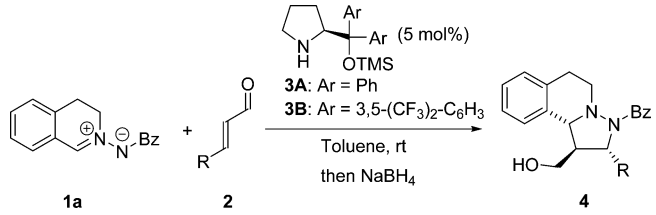
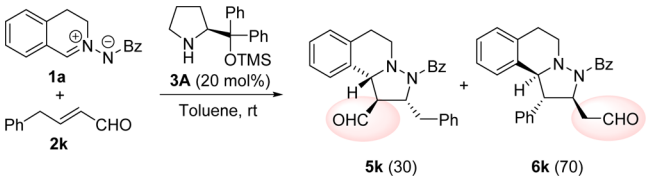
Table 1. Results Obtained in Reactions of the Dipole 1a with the Aldehydes 2a−2j Catalyzed by 3



entry	aldehyde (R)	catalyst	time (h)	product[a] (ee, %)	yield (%)
1[b]	**2a** (Ph)	**3A**	24	**4a** (98)	84
2[b]	**2b** (4-MeOC$_6$H$_4$)	**3A**	24	**4b** (96)	85
3[b]	**2c** (2-MeOC$_6$H$_4$)	**3A**	48	**4c** (98)	88
4[b]	**2d** (4-ClC$_6$H$_4$)	**3A**	36	**4d** (>99)	78
5[b]	**2e** (4-MeO$_2$CC$_6$H$_4$)	**3A**	36	**4e** (98)	91
6[b]	**2f** (4-CF$_3$C$_6$H$_4$)	**3A**	30	**4f** (96)	78
7[b]	**2g** (2-Furyl)	**3A**	24	**4g** (98)	91
8[b,c,d]	**2h** (2-Py)	**3A**	120	**4h** (96)	62
9[b,c]	**2h** (2-Py)	**3B**	16	**4h** (98)	77
10[e]	**2i** (Me)	**3B**	72	**4i** (85)	76
11[c,e,f]	**2i** (Me)	**3B**	12	**4i** (>99)	61
12[e]	**2j** (Et)	**3B**	72	**4j** (98)	78

[a]Determined by supercritical fluid chromatography (SFC). [b]Conditions: 0.2 mmol of **2** (0.4 mL of toluene), 0.3 mmol of **1a.** [c]Catalytic loading 20 mol %. [d]Conversion 80%. [e]Conditions: 0.4 mmol of **2** (0.4 mL of CH_2Cl_2), 0.2 mmol of **1a**. [f]0 °C.

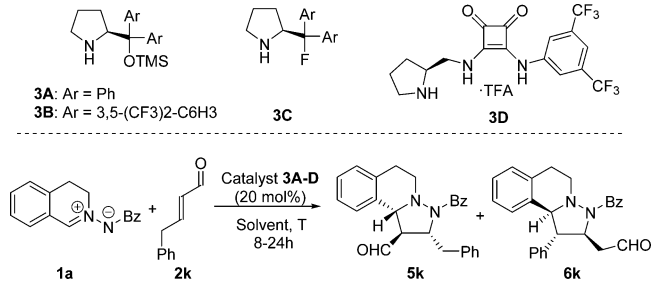
Scheme 3. Reactions of 1a with 2k Catalyzed by 3A



results obtained in this optimization with **2k** was collected in Table 2 (see Supporting Information for full screening).

Initially we explore the influence of different catalysts (**3A**−**3D**) in CH_2Cl_2 by using 20 mol % of catalytic loading (entries 6−9). Mixtures of two products **5k** and **6k** were obtained in all the cases. The use of the catalysts **3A** and **3B** provided the best results, with the first one giving the highest amount of **6k**

Table 2. Chemoselectivity Optimization for the 1,3-DC of 1a and 2k[a]



entry	cat.	solvent	additive	*T*	**5k**:**6k**[b]	yield (%)[c]	ee (%)[d]
1	(*S*)-**3B**[e]	toluene	TBAB[g]	0 °C	>98:2	70	98
2	(*S*)-**3B**[e]	toluene	TBAB[g]	rt	>98:2	70	96
3	(*S*)-**3B**	toluene	TBAB[g]	rt	>98:2	73	98
4	(*S*)-**3B**	toluene	BzOH[h]	rt	50:50	*f*	*f* /*f*
5	(*S*)-**3B**	toluene		rt	71:29	(96)	92/90
6	(*S*)-**3B**	CH_2Cl_2		rt	72:28	(85)	92/88
7	(*S*)-**3D**	CH_2Cl_2		rt	66:34	(66)	5/2
8	(*S*)-**3C**	CH_2Cl_2		rt	27:73	(51)	68/51
9	(*S*)-**3A**	CH_2Cl_2		rt	26:74	55	90/*f*
10	(*S*)-**3A**	CH_2Cl_2	OFBA[i]	rt	23:77	58	90/*f*
11	(*S*)-**3A**	CH_2Cl_2		0 °C	20:80	58	90/*f*
12[j]	(*S*)-**3A**	CH_2Cl_2		0 °C	2:>98	68	94

[a]Conditions: 0.2 mmol of **2** (0.2 mL of the indicated solvent), 0.1 mmol of **1a**, and 20 mol % of catalyst. [b]Determined by ^{1}H NMR analysis. [c]Major isomer after derivatization (see text) and flash chromatography. Combined yields in brackets. [d]Determined by supercritical fluid chromatography (SFC) after derivatization. [e]10 mol % of the catalyst **3B** was used. [f]Not determined. [g]200 mol % of additive. [h]Benzoic acid (20 mol %). [i]*o*-Fluorobenzoic acid (20 mol %). [j]Hydrated dipole **1a**′ was used.

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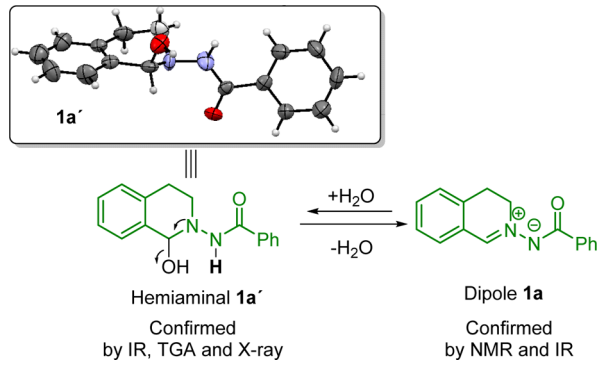
(entry 9), resulting in the evolution via dienamine, whereas **3B** mainly yielded the product via iminium **5k** (entry 6). As it occurred in reactions at Table 1, the enantiomeric excesses could not be established directly by supercritical fluid chromatography (SFC).[19] The influence of the solvent on the course of these reactions was moderate or low, with the improvement of the yield observed in toluene for reactions catalyzed by **3B** (compare entries 5 and 6) being the only aspect of significance. The use of benzoic acid (20 mol %) as additive increased the proportion of **6k**, providing almost equimolecular mixtures of **5k** and **6k** in reactions catalyzed by **3B** (entry 4), which were scarcely dependent on the pK_a of the used acid (see the influence of other acids in Supporting Information). Similarly, the addition of *o*-fluorobenzoic acid to reactions catalyzed by **3A** also increased slightly the ratio **5k**:**6k** up to 23:77 (entry 10). Much more important was the influence of the tetrabutylamonium bromide (TBAB) as additive in reactions catalyzed by **3B**, which produced a significant improvement of the proportion of **5k** that was exclusively obtained in very high enantiomeric excess (entry 3). These reactions were additionally optimized by decreasing the catalytic loading to 10 mol % (entry 2) and the temperature to 0 °C (entry 1), and these conditions were used in the scope. Less successful were the trials to optimize chemoselectivity of the reactions modifying the reaction parameters in order to favor the evolution through dienamines. In this sense, moreover, with the small effect of the acidic additives (entry 10), the slight improvement in the proportion of **6k** observed by decreasing the temperature to 0 °C (compare entries 9 and 11) was the only remarkable aspect.

At this point, some erratic results were obtained by repeating the experiments under the conditions of entry 9, which provided slightly different **5k**:**6k** ratios working under identical conditions. After performing extensive experimentation, we realized that these differences were due to the amount of water contained in the highly hygroscopic dipole, which was related to the time from its preparation and to the storing conditions. The preparation of dipoles **1**, according to the procedure reported by Maruoka,[13a] involved a final step of drying over Na_2SO_4 before evaporating the solvent (see Supporting Information). The composition of the so-obtained fresh sample (**1a**) differed from that resulting before this step (**1a′**) in one molecule of H_2O, as it was established by thermogravimetric studies (see Supporting Information). After crystallization of **1a′**, it was unequivocally demonstrated, by X-ray diffraction studies,[20] that it was the hemiaminal corresponding to the incorporation of a molecule of water to the dipole **1a** (Scheme 4). According to this, the IR spectra of both samples mainly differ in the absorption of the OH group in **1a′** (see Supporting Information). The ^{1}H NMR spectra of **1a** and **1a′** were identical, but the second one had an additional signal (δ = 1.6 ppm) which would belong to a water molecule. This experiment suggested that the hemiaminal **1a′** was highly unstable in solution and was quickly transformed into **1a** (only detected by NMR), losing a water molecule. Nevertheless, this transformation is likely not so simple (see later) because the use of the hemiaminal **1a′** (instead of the dipole **1a**) in 1,3-DC had a large influence on their chemoselectivity, increasing substantially the proportion of **6k**, which becomes exclusively obtained when the reactions were conducted under the conditions of entry 12 (**3A**, CH_2Cl_2, and 0 °C). Thus, conditions at entries 1 and 12 were, respectively, considered as the optimal ones for obtaining the best results concerning

Scheme 4. Structural Differences between 1a and 1a′



chemoselectivity (in both cases a very high enantioselectivity was observed), and they were used for evaluating the scope of the 1,3-DC of the dipole **1** to the iminium **I** and dienamine **II** species generated from unsaturated aldehydes.

Scope of the 1,3-DC via Iminum and Dienamine Species. We first studied the reactions of the hemiaminal **1a′** with different *β*-arylmethyl *α*,*β*-unsaturated aldehydes under the conditions of entry 12 in Table 2. Resulting aldehydes could be isolated, but in order to determine their enantiomeric purity by chiral supercritical fluid chromatography (SFC), their *in situ* $NaBH_4$ reduction into the alcohols **7** were performed. Results are depicted in Table 3.

Only one alcohol **7** was obtained (>98:2 in all the cases), demonstrating that the chemoselectivity control was almost complete under these conditions. We have evaluated the influence on the reaction course exerted by the presence of electron-donating (**2l**, **2n**, and **2o**, entries 2, 4, and 5) and electron-withdrawing (**2p** and **2q**, entries 6 and 7) groups at the *para* position of the aryl group. The enantioselectivity was not significatively altered by the electronic effects of the substituents, with the ee of the obtained alcohols **7** ranging between 87% and 92% (Table 3). The yields were good, ranging between 61% and 76%. The presence of an *ortho*-substituent at the aryl group (**2m**, entry 3) significantly decreased the yield of **7m** (40%). The hemiaminals **1b′** and **1c′** derived from other *C*,*N*-cyclic azomethine imines, bearing substituents at C-6 of the tetrahydroisoquinoline ring, also reacted in a completely chemoselective way, yielding **7r** and **7s** in high enantiomeric excesses, respectively (entries 8 and 9). We have also studied the reactions of other *β*-alkyl *α*,*β*-unsaturated aldehydes, like **2i** and **2j** (see Table 1), under the conditions of Table 3. Unfortunately, complex mixtures were found by ^{1}H NMR analysis which contained the signals of compounds **4i** and **4j**, whereas those of **7i** and **7j** were not easily recognizable.

On the other hand, we have studied the reactions of the dipoles **1** (freshly dried) with **2k**−**2q** under the conditions of entry 1 in Table 2 (see Table 4). Derivatization of the resulting aldehydes **5k**−**5s** was now performed by Wittig reaction with Ph_3PCHCO_2Et,[19] exclusively yielding esters **8**. The chemoselectivity control was also complete under these conditions (>98:2), which determined the exclusive evolution via iminium species. The introduction of electron-donating (**2l**, **2n**, and **2o**, entries 2, 4, and 5) and electron-withdrawing (**2p** and **2q**, entries 6 and 7) groups did not significantly modify the obtained results, and the ee of compounds **8** ranged between 94% and 99%. The aldehyde **2m**, with a methyl group at the *ortho* position, exhibited a similar behavior (entry 3). Other

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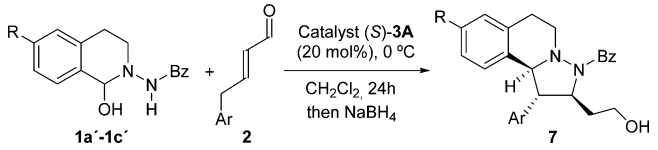
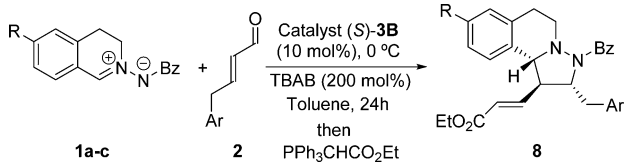
Table 3. Results Obtained in Reactions of the Aldehydes 2 with the Hemiaminals 1a′−1c′ under the Conditions of Entry 12 in Table 2



Entry	Aldehyde (Ar)	Pro-Dipole (R)	Product (*ee*, %)[a]	Yield (%)
1	**2k** (C_6H_5)	**1a'** (H)	**7k** (94)	68
2	**2l** (*p*-MeC_6H_4)	**1a'** (H)	**7l** (90)	75
3	**2m** (*o*-MeC_6H_4)	**1a'** (H)	**7m** (87)	40
4	**2n** (*p*-$OMeC_6H_4$)	**1a'** (H)	**7n** (87)	73
5	**2o**()	**1a'** (H)	**7o** (89)	76
6	**2p** (*p*-FC_6H_4)	**1a'** (H)	**7p** (92)	63
7	**2q** (*p*-$CF_3C_6H_4$)	**1a'** (H)	**7q** (92)	61
8	**2k** (C_6H_5)	**1b'** (F)	**7r** (88)	69
9	**2k** (C_6H_5)	**1c'** (OMe)	**7s** (92)	51

[a]Determined by supercritical fluid chromatography (SFC) after derivatization.

Table 4. Results Obtained in Reactions of Aldehydes 2 with the Dipoles 1a−c under Conditions of Entry 1 in Table 2



Entry	Aldehyde (Ar)	Dipole (R)	Product (*ee*, %)[a]	Yield (%)
1	**2k** (C_6H_5)	**1a** (H)	**8k** (98)	70
2	**2l** (*p*-MeC_6H_4)	**1a** (H)	**8l** (94)	75
3	**2m** (*o*-MeC_6H_4)	**1a** (H)	**8m** (99)	71
4	**2n** (*p*-$OMeC_6H_4$)	**1a** (H)	**8n** (98)	85
5	**2o**()	**1a** (H)	**8o** (98)	78
6	**2p** (*p*-FC_6H_4)	**1a** (H)	**8p** (99)	72
7	**2q** (*p*-$CF_3C_6H_4$)	**1a** (H)	**8q** (96)	75
8	**2k** (C_6H_5)	**1b** (F)	**8r** (>99)	78
9	**2k** (C_6H_5)	**1c** (OMe)	**8s** (96)	41

[a]Determined by supercritical fluid chromatography (SFC) after derivatization.

dipoles, derived from *C,N*-cyclic azomethine imines with substituents at the tetrahydroisoquinoline ring (**1b** and **1c**), also evolved in a completely chemoselective way, exclusively yielding **8r** and **8s** in high ee (entries 8 and 9). The yield was good for **8r** (78%) but only moderate for **8s** (41%), which evidenced a negative influence of the electron-donating group at dipole, also detectable in the formation of **7s** (51%, entry 9 at Table 3).

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The absolute configurations of the adducts resulting in the cycloaddition via dienamine (Table 3) or iminium (Table 4) species were unequivocally assigned by X-ray analysis, from the hydrochlorides **10·HCl** (1*S*, 2*S*, 10b*S*) and **9·HCl** (1*R*, 2*R*, 10b*R*), obtained in the reductive amination of the corresponding aldehydes (see Figure 1 and Supporting Information).[21] As

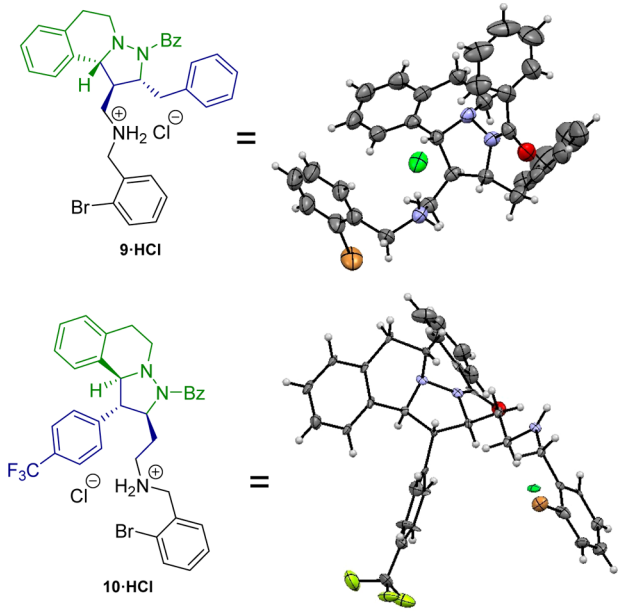


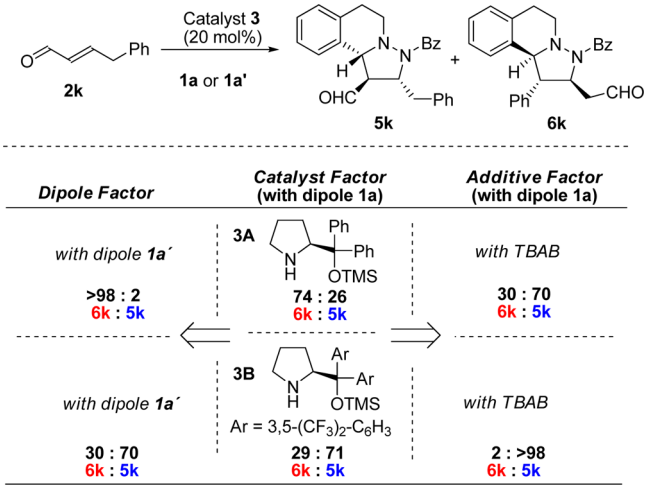
Figure 1. Determining the absolute configuration of **9** and **10**.

expected, the configurations assigned to compounds of Tables 1 and 4 (both resulting in the evolution of the reactions via iminium species) were identical, as could be anticipated by assuming a similar stereochemical course.

Synthetic Applications. Compounds at Tables 3 and 4 can be used as intermediates for preparing interesting enantiomerically pure products containing tetrahydroisoquinoline skeletons. As the key step of many of these transformations is the breaking of their N–N bonds, we have studied these reactions on the cycloadducts **6q** (92% ee) and **5k** (98% ee) as representatives of compounds from Tables 3 and 4 (see Scheme 5). The cleavage of the N–N bond could be easily performed with SmI_2. However, this reagent affects the CHO group, and therefore, it could not be directly used on aldehydes **5k** and **6q**, unless they were previously modified. The simple formation of the acetal from **6q** allowed a solution to the problem, and the hydrogenolysis of the N–N bond provided enantiopure 2-substituted tetrahydroisoquinolines that can be used as intermediates of many other transformations.[14] On the other hand, the breaking of the N–N after homologation of the CHO group into the $(CH_2)_2$–CO_2Me from **5k** opened the access to benzoquinolizidine derivatives **14**.

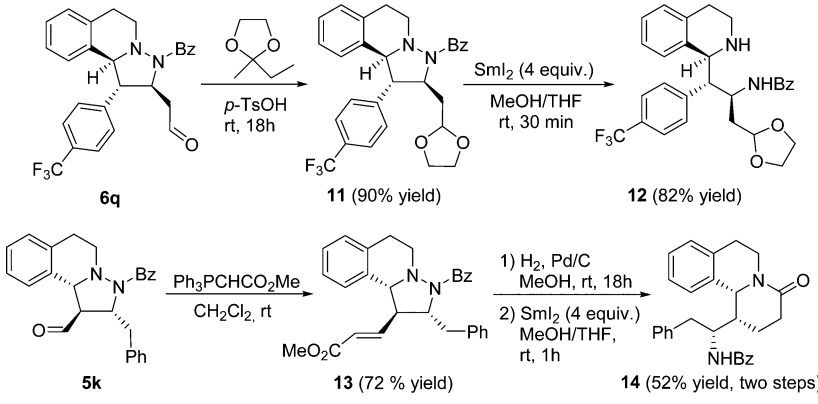
Mechanistic Considerations: Chemoselectivity. When the experimental conditions had been found, allowing the exclusive formation of the isomeric aldehydes **5** and **6**, we tried to understand the influence of the different factors on the chemoselectivity of these reactions. There were three variables provoking strong changes in the chemoselectivity (dienamine:iminium, **6**:**5** ratio): catalyst, dipole, and additive. Their influence is summarized in Scheme 6. Other factors like solvent and the electronic density of the aryl ring at **2** had a less marked influence (see above).

Scheme 6. Different Factors Affecting the Chemoselectivity (Iminium vs Dienamine) of the 1,3-DC of Dipole 1a (or 1a′) with 2k



The experimental results indicated that the reaction of the dipole **1a** with the aldehyde **2k**, catalyzed by **3A**, afforded a 74:26 mixture of **6k** and **5k**. This ratio was completely inverted to 29:71, when **3B** was used as the catalyst. The use of the hemiaminal **1a**′ (instead of dipole **1a**) produced an increase of the proportion of **6k** that was completely chemoselective in the presence of **3A** (left, Scheme 6). Finally, when reactions were

Scheme 5. Chemical Transformations on the Cycloadducts



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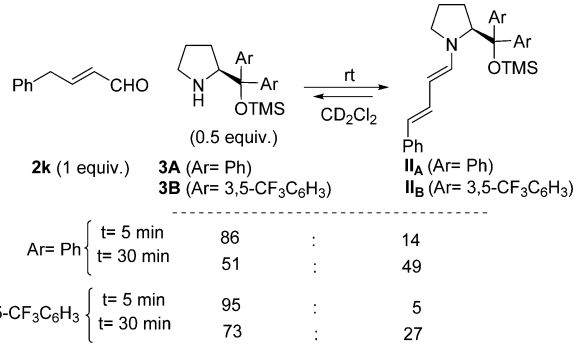
conducted in the presence of tetrabutylammonium bromide (TBAB) a significant increase in the proportion of **5k** was observed with both catalysts (the influence of other additives was much lower). Thus, the reaction catalyzed by **3B** became completely chemoselective, yielding iminium product **5k** (Scheme 6, right). We will try to understand the role of the three factors (catalyst, nature of the dipole, and presence of TBAB) on the chemoselectivity control.

a. Influence of the Catalyst. The strong dependence of the ratio of cycloadducts **5** (generated via iminium ion) and **6** (generated via dienamine) with the nature of the catalyst used (Scheme 6, middle) must be explained by taking into account both the concentration of the intermediates **I** and **II** formed from each catalyst (K in Scheme 2) and, mainly, their relative reactivity with the dipole (K_3 and K_4 in Scheme 2). The relative concentration of dienamine **II** was studied by ^{1}H NMR, by mixing **2k** (1 equiv) with the catalysts **3A** or **3B** (0.5 equiv). According to our results (Scheme 7), the formation of **IIA** was

Scheme 7. ^{1}H NMR Detection of the Dienamines IIA and IIB



faster and its proportion higher than those of **IIB**.[22] As the formation of dienamines involved deprotonation of the iminium species, the lower basicity of **3B**, bearing aromatic rings with stronger −I effects, could explain the slower formation of **IIB**. On the other hand, the higher stability of the dienamines **IIA** had been estimated by theoretical calculations (see Supporting Information).

As expected, the signals corresponding to the unstable iminium species **I** were not visible in the ^{1}H NMR spectra, indicating they exist in a very low concentration (much lower than that of the dienamines **II**). Despite this, significant amounts of compounds **5** are formed in these reactions, thus suggesting a higher reactivity of the iminium species.

Concerning the influence of the catalysts on the reactivity of the different species (**I** and **II**) involved in our reaction, we analyzed, by DFT calculations, the energetic content of the frontier molecular orbitals for dipole **1a**, iminium ions (**IA** and **IB**), and dienamines (**IIA** and **IIB**) (see Figure 2). We took into account the corrections of the solvents used in the reactions (CH_2Cl_2 for reactions of the dienamines and toluene for those of the iminium species). According to a Sustmann−Huisgen type analysis, the reactions of dipole **1** with the dienamines **II** should be mainly governed by the interaction $HOMO_{dienamine}$−$LUMO_{dipole}$ (ΔE value of the $HOMO_{dipole}$−$LUMO_{dienamine}$ interaction is too large for taking it into consideration), which agrees with the IED character expected for the 1,3-dipolar cycloaddition of dienamines. By contrast, the interactions $HOMO_{dipole}$−$LUMO_{iminium}$ should be the most

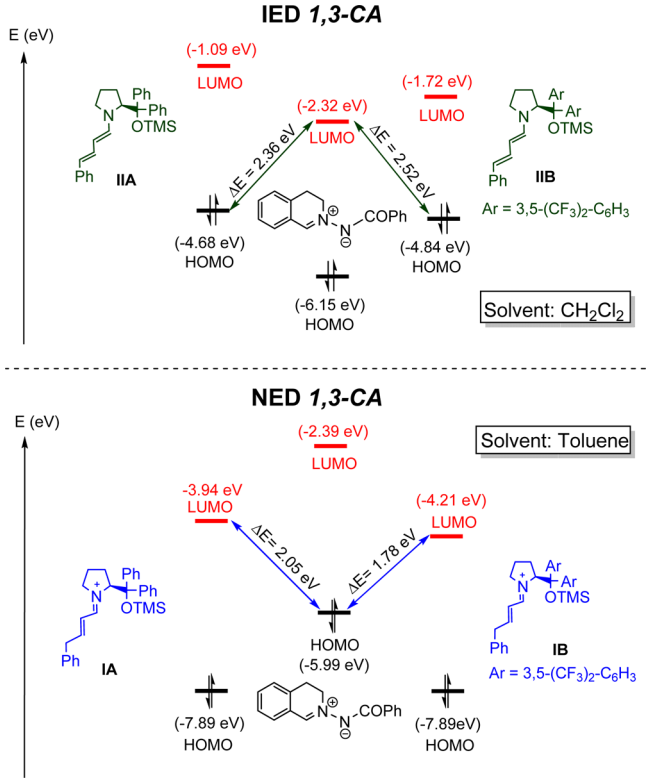


Figure 2. Energies of the FMO calculated for dipole **1a**, and the dienamines (**IIA** and **IIB**) and iminium ions (**IA** and **IB**) formed by **2k** with the catalysts **3A** and **3B**, taking into account the correction of the solvents indicated in each case. DFT calculations were carried out at B3LYP/6-311+g(d,p) level of theory.

important in the reactions of the dipole with the iminium ions, thus confirming their NED character.

Differences in energy induced by the catalysts in the HOMO orbital of the dienamines (top, Figure 2), determined in CH_2Cl_2 (ΔE_{IIB} (2.52) − ΔE_{IIA} (2.36) = ∼0.16 eV, ∼3.7 kcal/mol), allow us to predict that **IIA** should react with **1a** more easily than **IIB**. Thus, taking into account that reactivity and concentration (see above) of **IIA** were both higher than those of **IIB**, the experimentally observed higher amount of compounds **6** obtained in reactions catalyzed by **3A** is completely justified. From the energetic content of the frontier molecular orbitals for dipole **1a** and the iminium ions **IA** and **IB** (bottom, Figure 2), calculated in toluene, we can conclude the higher reactivity of the latter ones (ΔE_{IA} (2.05) − ΔE_{IB} (1.78) = 0.27 eV, ∼6.2 kcal/mol), thus explaining the higher efficiency of the catalyst **3B** observed in reactions at Table 1.

On the other hand, on the basis of this analysis, iminium ions seem to be more reactive than the dienamines with both catalysts, but this tendency is more marked in reactions catalyzed by **3B**, where the energetic difference of the interacting orbitals for each species is larger (ΔE_{IIB} (2.52) − ΔE_{IB} (1.78) = 0.74 eV, ∼17.1 kcal/mol).[23]

The fact that reactions via dienamine, observed in the case of **1a**, have not been detected in organocatalytic reactions of azomethine ylides with β-alkyl α,β-unsaturated aldehydes[9] is intriguing. In order to obtain some explanation, we calculated the energy associated with the frontier orbitals of these dipoles (E_{HOMO} = −5.0 eV, E_{LUMO} = −1.88 eV, see Supporting Information), and found they are substantially higher than those obtained for the *N*-benzoyl *C,N*-cyclic azomethine imines

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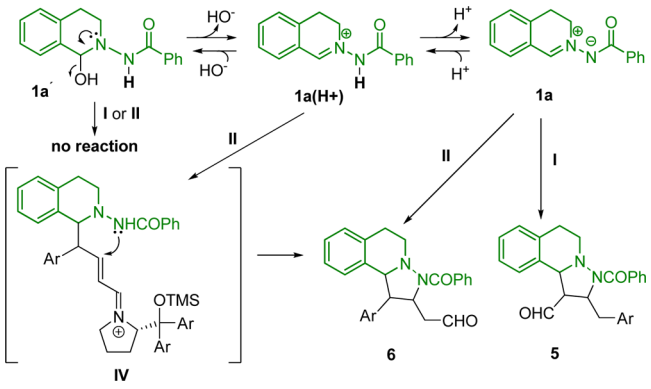
shown in Figure 2. From these values, it can be deduced that reactions of azomethine ylides with the iminium species (**IA** or **IB**) should be substantially easier, and those with the enamines (**IIA** and **IIB**) more difficult, than those observed with our *N*-benzoyl *C*,*N*-cyclic azomethine imines, which could satisfactorily explain (see Figure S1 in Supporting Information) the observed differences in the behavior of both dipoles.[24]

b. Influence of the Dipole Structure. As we have previously indicated, the way to prepare the dipole had important consequences in the chemoselectivity. As the iminium and dienamine species were not able to react directly with the hemiaminal **1a**′, this should be considered as the precursor of the real reactive species. In order to explain the experimental results, we propose that the conversion of **1a**′ into dipole **1a** takes place in two steps, with formation of the protonated species **1a**(**H**$^+$) as intermediate. This species could only react as electrophile with the dienamine species **II**, resulting in the formation of compounds **6**, according to a nonconcerted two-step process involving the formation of intermediates **IV** (Scheme 8). By contrast, dipole **1a** could react with both

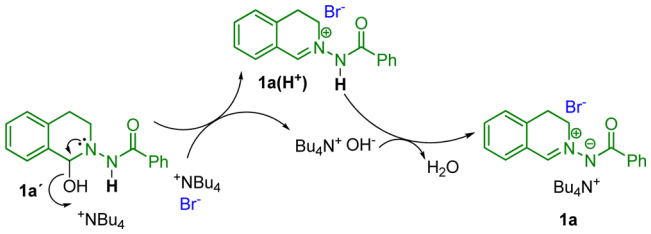
Scheme 8. Influence of the Dipole Source on the Chemoselectivity



iminium ion (**I**) and dienamine (**II**) species, respectively, affording the isomers **5** and **6** according to concerted or two-step processes. From Scheme 8 it can be deduced that the hydration of **1a** into **1a**′ would take also place in two steps (protonation to form **1a**(**H**$^+$) and subsequent attack of the OH$^-$). It would explain the erratic results obtained in different experiences performed when dipole was not freshly prepared, because it would contain a variable amount of **1a**′.[25]

c. Influence of the Additives. The positive influence of the quaternary ammonium salts as efficient cocatalysts on organocatalytic Michael additions to α,β-unsaturated aldehydes catalyzed by **3** had been previously described.[26] Moreover, in our reactions, a double role of TBAB can be postulated. The first one consists of the dehydration of the hemiaminal **1a**′ by assisting the elimination of the OH$^-$ in the first step, and the deprotonation in the second one (Scheme 9). It would allow the quicker transformation of **1a**′ into dipole **1a**, thus minimizing the presence of the species **1a**(**H**$^+$) and therefore reducing the amount of compounds **6** formed. On the other hand, we have investigated by ^{1}H NMR the influence of the TBAB on the concentration of the dienamine **II** generated by mixing compound **2k** with the catalysts **3A** and **3B**.[27] In both cases we observed a substantial decrease in the proportion of dienamine **II**, which becomes undetectable in the presence of **3B** (see Supporting Information). It could be partially

Scheme 9. Possible Role of TBAB in Reactions of 1a with 2



responsible for the total absence of compounds **6** working under the conditions of Table 4. The influence of TBAB on the proportion iminium ion **I**:dienamine **II** at the equilibrium shown at Scheme 2 could be a consequence of the stabilization of **I** provided by the bromide ion.[28]

d. exo-Selectivity and Enantioselectivity. The complete control of the diastereoselectivity (only *exo*-adducts were obtained) in reactions of cyclic azomethine imines with the iminium species derived from enals **2** had been reported by Maruoka.[13a] Similarly, the very high enantioselectivity of many reactions of nucleophiles and dipoles with these enals catalyzed by prolinol organocatalysts like **3A** and **3B** has been associated with the steric hindrance exerted by the group CAr$_2$OTMS at the iminium species intermediate.[29] If we assume that reactions of species **II** with dipole **1** were concerted processes, both enantioselectivity and *exo*-selectivity can be explained as indicated in Scheme 10. The first one would be consistent with the steric hindrance produced by the CAr$_2$OTMS group on the face it occupies in the presumably most stable conformation (based on theoretical calculations, see Supporting Information) of the dienamine species **II**, shown in Scheme 10, top. The higher ee obtained in Table 4 with respect to those at Table 3 could be a consequence of the longer distance existing between the CAr$_2$OTMS group and the reactive double bond in the dienamines. On the other hand, the *exo*-selectivity could be explained by the strong steric interactions of the aryl ring at **II** with the proton H^3 at dipole **1a**, by assuming it adopts the conformation indicated in Scheme 10, which is the most stable one according to theoretical calculations (see Supporting Information).

Addendum. This section has been added to the manuscript after the publication by Du and Wang et al.[15] concerning the synthesis of alcohols **7** by the *in situ* reduction of the aldehydes resulting in the organocatalytic reaction of the dipole **1** with enals **2** in the presence of different acids as the additives. Under the optimal conditions [catalyst **3B** (20 mol %), 2,4-DNBA (20 mol %), CH_2Cl_2, T = −20 °C], they described the exclusive formation of compounds **7** in very good yields (87% for **7k**) after 12 h. We were surprised with these results because during our optimization process we had checked the influence of the different benzoic acids as additives (see above and Supporting Information), but we were not able to get the complete control of the chemoselectivity in any case. The best **6k**:**5k** ratio we had obtained after 24 h was 77:23 under catalysis of **3A** and *o*-fluorobenzoic acid as additive (20 mol %) in CH_2Cl_2 at rt (entry 10, Table 2). Worse chemoselectivity was obtained with **3B**, which afforded almost equimolecular mixtures of both compounds in the presence of benzoic acid (entry 4, Table 2) and other acidic additives (see Supporting Information). Obviously, the results reported in ref 15 were very different from those presented in this paper, and therefore, they were reinvestigated. In this sense, we reproduced twice the reactions

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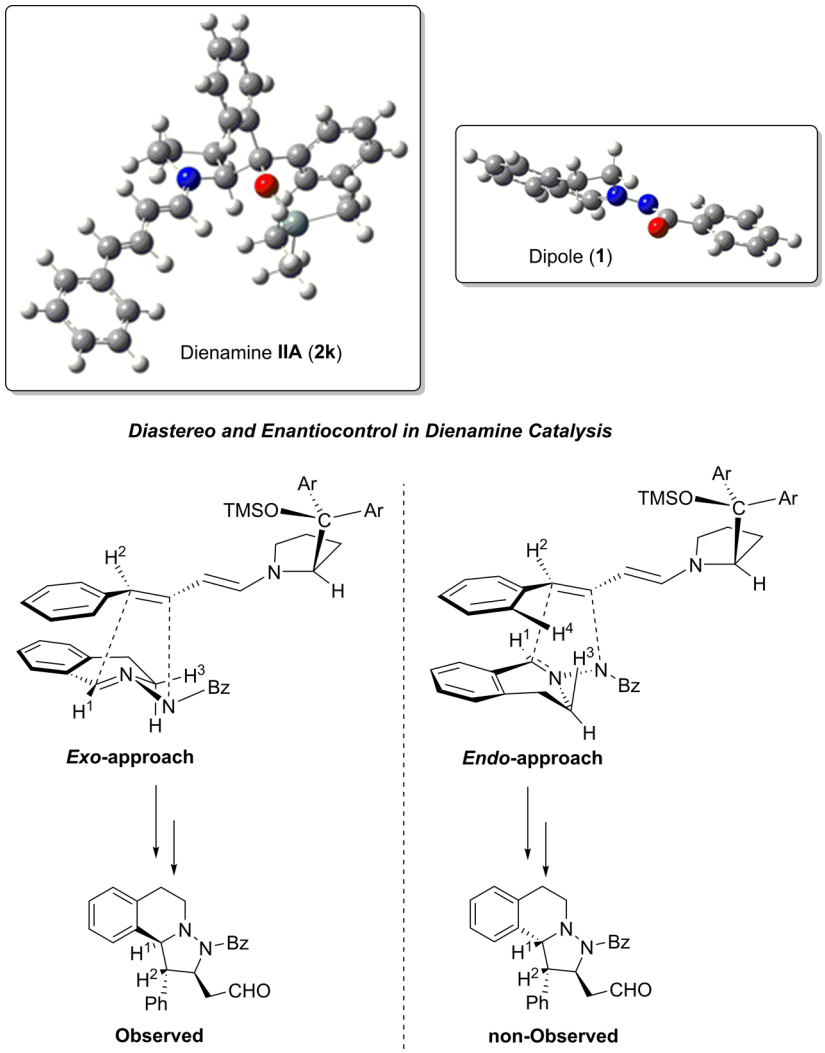
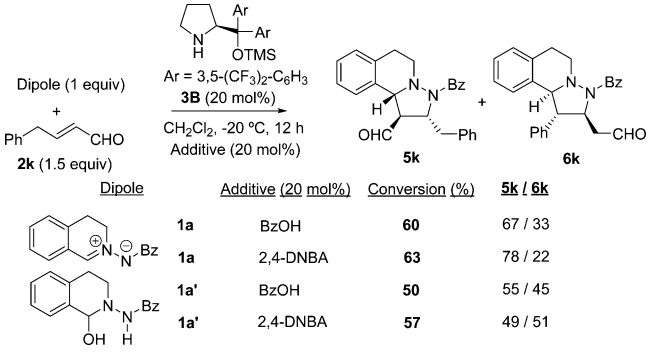
Scheme 10. ***exo*-Selectivity and Enantioselectivity**



of **2k** (1.5 equiv) with dipoles **1a** and **1a′** under the conditions indicated in entries 14 and 15 of Table 1 in ref 15. Results we obtained are shown in Scheme 11 and detailed in Supporting Information. After 12 h, the conversions we observed ranged between 50% and 63% (at this time the aldehyde **2k** had completely disappeared[30]) which is not compatible with the high yields reported in ref 15. Moreover, in all the cases we obtained mixtures of compounds **5k** and **6k**, where the latter one (derived from the dienamine) was never the major component in these reactions catalyzed by **3B**. Even starting from dipole **1a′**, which was more prone to the evolution via dienamine,[31] and using the most acidic additive (2,4-dinitrobenzoic acid), the reaction mixture only contains 51% of **6k**. Some other significant differences concern the specific rotation of compounds **7k**, **7l**, **7m**, **7p**, and **7s** measured under similar conditions,[32] and the configuration assigned to compounds **4i** and **4j**.[33] As the results reported in ref 15 were not reproducible in our hands, we proposed the use of the dipole **1a′** and the catalyst **3A** to get the complete control of the stereoselectivity for exclusively obtaining adducts resulting in the evolution of the dienamine species.

Scheme 11. Wang's Reaction Conditions Applied by Us



Dipole	Additive (20 mol%)	Conversion (%)	5k / 6k
1a	BzOH	**60**	67 / 33
1a	2,4-DNBA	**63**	78 / 22
1a'	BzOH	**50**	55 / 45
1a'	2,4-DNBA	**57**	49 / 51

■ CONCLUSIONS

Reactions of *C,N*-cyclic azomethine imines with *α,β*-unsaturated aldehydes, catalyzed by **3A** and **3B**, evolve with high yields and a complete control of the stereoselectivity. For *β*-arylmethyl enals, mixtures of isomers resulting in the evolution via dienamine and iminium ion are observed, which allow us for the first time to study the chemoselectivity dienamine-iminium control. After finding the proper conditions for getting complete selectivity in both senses, the role of the main factors controlling it has been rationalized by chemical procedures and theoretical calculations. Through these processes, highly

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functionalized optically active tetrahydroisoquinoline derivatives can be obtained from readily available starting materials.

EXPERIMENTAL SECTION

General Methods and Materials. NMR spectra were acquired on a 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. High temperature NMR spectra were acquired on a 500 spectrometer, running at 500 and 126 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR, or $C_2D_2Cl_4$, 5.91 ppm for ^{1}H NMR and 74.2 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broadband decoupled mode. Analytical thin layer chromatography (TLC) was performed using precoated aluminum-backed plates and visualized by ultraviolet irradiation or by phosphomolybdic acid or potassium permanganate stain. Purification of reaction products was carried out by flash chromatography (FC) using silica gel. Optical rotations were measured at room temperature, and $[\alpha]^{20}_D$ values are given in deg cm^3 g^{-1} dm^{-1}; concentration c is listed in g (100 mL)$^{-1}$. The enantiomeric excess (ee) of the products was determined by supercritical fluid chromatography (SFC) using mixtures of supercritical CO_2 and methanol and Chiralpack IA, IB, or ID columns as chiral stationary phases. High resolution mass spectra (HRMS) were recorded using electron impact (E.I.) at 70 eV (TOF analyzer), fast atom bombardment (FAB+) (Magnetic Sector Analyzer), or electrospray (ESI+) (Q-TOF analyzer) techniques. The IR spectra frequencies are given in cm^{-1}. Catalysts and solvents are commercially available and were used without previous purification. Starting enals,[34] dipoles **1a**–**c**,[13a] and the 0.1 M solution of SmI_2[35] were obtained following the standard procedure described in the literature.

Computational Methods. All DFT calculations were run using GAUSSIAN09.[36] Geometries were optimized without symmetry constraints at the B3LYP[37]/6-311+g(d,p) level of theory. All structures were characterized by frequency analysis, and in all cases, imaginaries frequencies were not found. Structural images were created using GAUSSVIEW program. Solvation energy corrections were also calculated by B3LYP/6-311+g(d,p) with Truhlar and co-workers' SMD solvation model.[38]

***N*-(1-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamides (1a–c′).** Starting hydroxyisoquinolines **1a**–**c**′ were obtained following the standard procedure described in the literature for the synthesis of dipoles **1a**–**c** without carrying out the final drying (last step, see Supporting Information for ref 13a).

General Procedure A for the Synthesis of Alcohols (4a–h). A solution of aldehyde **2** (0.2 mmol) and catalyst **3A** (0.01 mmol) in toluene (0.4 mL) was prepared in a screw vial at rt. Then, dipole **1a** (0.3 mmol) was added, and the reaction mixture was stirred at rt until consumption of the aldehyde (monitored by ^{1}H NMR). Once complete conversion was obtained, ethanol (0.4 mL) and $NaBH_4$ (0.4 mmol) were added successively at 0 °C. The reaction mixture was stirred at rt until complete conversion was obtained (followed by thin layer chromatography). The reaction was treated with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuum. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

*(1S,2S,10bR)-1-(Hydroxymethyl)-2-phenyl-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4a**).* The product was obtained following the general procedure A, after 24 h, as a white amorphous solid (65 mg, 84%) after purification by column chromatography (gradient CH_2Cl_2/Et_2O from 9:1 to 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 8.13 min, τ_{minor} = 13.58 min, ee = 98%. $[\alpha]^{20}_D$ = +62.0 (c 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.3 Hz, 2H), 7.47–7.05 (m, 12H), 5.65 (d, J = 8.8 Hz, 1H), 4.49 (d, J = 10.6 Hz, 1H), 4.24–4.10 (m, 1H), 4.01 (dd, J = 11.8, 4.1 Hz, 1H), 3.37–3.13 (m, 2H), 3.12–2.95 (m, 1H), 2.83–2.57 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 142.0, 135.4, 134.1, 133.0, 130.2, 128.5, 128.4, 127.6, 127.4, 127.0, 126.9, 126.1, 126.0, 64.6, 62.2, 58.8, 55.8, 49.9, 29.5 (one peak overlaps). HRMS (FAB+) m/z: calcd for $C_{25}H_{25}N_2O_2$ 385.1916 [M + H$^+$]; found 385.1920 [M + H$^+$].

*((1S,2S,10bR)-1-(Hydroxymethyl)-2-(4-methoxyphenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)-methanone (**4b**).* The product was obtained following the general procedure A, after 24 h, as a white amorphous solid (71 mg, 85%) after purification by column chromatography (CH_2Cl_2/Et_2O 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (70:30), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 6.38 min, τ_{minor} = 10.18 min, ee = 96%. $[\alpha]^{20}_D$ = +65.9 (c 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 2H), 7.43–7.30 (m, 5H), 7.25–7.12 (m, 3H), 7.12–7.05 (m, 1H), 6.80 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 8.8 Hz, 1H), 4.48 (d, J = 10.7 Hz, 1H), 4.19–4.07 (m, 1H), 4.02–3.90 (m, 1H), 3.78 (s, 3H), 3.36–3.13 (m, 3H), 3.03 (ddd, J = 17.2, 11.3, 6.0 Hz, 1H), 2.71 (dt, J = 16.3, 2.7 Hz, 1H), 2.66–2.55 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.7, 158.5, 135.4, 134.2, 134.1, 133.0, 130.1, 128.5, 128.4, 127.6, 127.39, 127.36, 126.9, 126.1, 113.9, 64.2, 62.2, 58.7, 56.0, 55.2, 49.9, 29.5. HRMS (FAB+) m/z: calcd for $C_{26}H_{27}N_2O_3$ 415.2022 [M + H$^+$]; found 415.2029 [M + H$^+$].

*((1S,2S,10bR)-1-(Hydroxymethyl)-2-(2-methoxyphenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)-methanone (**4c**).* The product was obtained following the general procedure A, after 48 h, as a white amorphous solid (73 mg, 88%) after purification by column chromatography (CH_2Cl_2/Et_2O 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 8.79 min, τ_{minor} = 12.73 min, ee = 98%. $[\alpha]^{20}_D$ = +25.3 (c 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92–7.78 (m, 2H), 7.46–7.29 (m, 4H), 7.28–7.08 (m, 5H), 6.99 (td, J = 7.5, 1.1 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 5.84 (d, J = 9.7 Hz, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.15 (brd, J = 12.7 Hz, 1H), 4.04–3.84 (m, 1H), 3.90 (s, 3H), 3.48–3.30 (m, 2H), 3.18–3.00 (m, 1H), 2.79 (dt, J = 16.3, 2.8 Hz, 1H), 2.59–2.42 (m, 2H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 169.74, 156.16, 135.67, 133.76, 133.26, 130.13, 129.92, 128.44, 128.37, 128.16, 127.63, 127.52, 127.02, 126.23, 126.02, 121.45, 111.24, 62.48, 59.78, 58.81, 55.91, 49.91, 29.55 (one peak overlaps). HRMS (FAB+) m/z: calcd for $C_{26}H_{27}N_2O_3$ 415.2022 [M + H$^+$]; found 415.2009 [M + H$^+$].

*((1S,2S,10bR)-2-(4-Chlorophenyl)-1-(hydroxymethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4d**).* The product was obtained following the general procedure A, after 36 h, as a white amorphous solid (65 mg, 78%) after purification by column chromatography (CH_2Cl_2/Et_2O 9:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 7.99 min, τ_{minor} = 10.65 min, ee > 99%. $[\alpha]^{20}_D$ = +74.0 (c 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 6.9 Hz, 2H), 7.47–7.28 (m, 5H), 7.24–7.13 (m, 5H), 7.12–7.05 (m, 1H), 5.68 (d, J = 8.7 Hz, 1H), 4.48 (d, J = 10.5 Hz, 1H), 4.20–4.08 (m, 1H), 4.03–3.90 (m, 1H), 3.55 (brs, 1H), 3.31–3.20 (m, 1H), 3.19–2.95 (m, 2H), 2.78–2.66 (m, 1H), 2.62–2.49 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.7, 140.7, 134.9, 133.9, 132.9, 132.7, 130.5, 128.6, 128.5, 128.4, 127.7, 127.35, 127.3, 127.1, 126.2, 64.0, 62.2, 58.6, 56.0, 49.9, 29.5. HRMS (FAB+) m/z: calcd for $C_{25}H_{24}ClN_2O_2$ 419.1536 [M + H$^+$]; found 419.1526 [M + H$^+$].

*Methyl 4-((1S,2S,10bR)-3-benzoyl-1-(hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-2-yl)benzoate (**4e**).* The product was obtained following the general procedure A, after 36 h, as a white amorphous solid (81 mg, 91%) after purification by column chromatography (CH_2Cl_2/Et_2O 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 16.12 min, τ_{minor} = 22.83 min, ee = 98%. $[\alpha]^{20}_D$ = +92.9 (c 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (app d, J = 6.8 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.49–7.34 (m, 5H), 7.25–7.12 (m, 3H), 7.12–7.04 (m, 1H), 5.80 (d, J = 8.6 Hz, 1H), 4.51 (d, J = 10.6 Hz, 1H), 4.17 (brd, J = 11.1 Hz, 1H), 4.03–3.86 (m, 2H), 3.91 (s, 3H), 3.35–3.23 (m, 1H), 3.19–2.95 (m, 2H), 2.71 (app d, J = 13.2 Hz, 1H), 2.54 (app t, J = 9.7 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.7, 166.8, 147.4, 134.8, 133.9, 132.8, 130.5, 129.7, 128.7, 128.6, 128.4, 127.7, 127.4, 127.0, 126.1, 125.7,

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64.1, 62.2, 58.3, 56.0, 52.0, 49.9, 29.4. HRMS (FAB+) m/z: calcd for $C_{27}H_{27}N_2O_4$ 443.1971 [M + H$^+$]; found 443.1964 [M + H$^+$].

*((1S,2S,10bR)-1-(Hydroxymethyl)-2-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)-methanone (**4f**).* The product was obtained following the general procedure A, after 30 h, as a white amorphous solid (71 mg, 78%) after purification by column chromatography (CH_2Cl_2/Et_2O 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 3.38 min, τ_{minor} = 4.32 min, ee = 94%. $[\alpha]^{20}_D$ = +46.5 (c 0.43, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.89 (m, 2H), 7.56−7.34 (m, 7H), 7.23−7.13 (m, 3H), 7.12−7.05 (m, 1H), 5.78 (d, J = 8.7 Hz, 1H), 4.53 (d, J = 10.6 Hz, 1H), 4.16 (brd, J = 12.2 Hz, 1H), 4.03−3.91 (m, 1H), 3.81 (brs, 1H), 3.33−3.20 (m, 1H), 3.17−2.97 (m, 2H), 2.79−2.65 (m, 1H), 2.61−2.49 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.6, 146.3 (q, J_{C-F} = 1.6 Hz), 134.7, 133.8, 132.8, 130.6, 129.2 (q, J_{C-F} = 32.4 Hz), 128.7, 128.5, 127.8, 127.3, 127.1, 126.2, 126.1, 125.4 (q, J_{C-F} = 3.7 Hz), 124.10 (q, J_{C-F} = 271.9 Hz), 64.2, 62.2, 58.4, 56.0, 50.0, 29.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.5 (s). HRMS (FAB+) m/z: calcd for $C_{26}H_{24}N_2O_2F_3$ 453.1790 [M + H$^+$]; found 453.1791 [M + H$^+$].

*((1S,2S,10bR)-2-(Furan-2-yl)-1-(hydroxymethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4g**).* The product was obtained following the general procedure A, after 24 h, as a white amorphous solid (68 mg, 91%) after purification by column chromatography (CH_2Cl_2/Et_2O 7:1). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 6.21 min, τ_{minor} = 9.34 min, ee = 98%. $[\alpha]^{20}_D$ = +10.7 (c 0.41, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.79 (m, 2H), 7.44−7.29 (m, 4H), 7.24−7.08 (m, 4H), 6.38 (brs, 1H), 6.33 (dd, J = 3.2, 1.9 Hz, 1H), 5.76 (d, J = 8.7 Hz, 1H), 4.46 (d, J = 10.8 Hz, 1H), 4.11 (brd, J = 11.8 Hz, 1H), 4.04−3.92 (m, 1H), 3.54−3.40 (m, 1H), 3.28−3.11 (m, 2H), 3.11−2.89 (m, 2H), 2.76 (dt, J = 16.1, 2.9 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.1, 153.3, 141.8, 135.1, 134.1, 133.0, 130.2, 128.52, 128.48, 127.5, 127.3, 127.0, 126.1, 110.6, 108.0, 61.8, 58.5, 58.4, 52.8, 49.0, 29.4. HRMS (FAB+) m/z: calcd for $C_{23}H_{23}N_2O_3$ 375.1709 [M + H$^+$]; found 375.1705 [M + H$^+$].

*((1S,2S,10bR)-1-(Hydroxymethyl)-2-(pyridin-2-yl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4h**).* The product was obtained following the general procedure C, after 5 days, as a white amorphous solid (48 mg, 62%) after purification by column chromatography (gradient CH_2Cl_2/Et_2O from 7:1 to 7:3) (conversion 80%). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 25.35 min, τ_{minor} = 28.68 min, ee = 96%. $[\alpha]^{20}_D$ = +5.5 (c 0.4, $CHCl_3$). The product was also obtained following the general procedure C, after 16 h and using **3B** as catalyst, with a yield of 77%. ee = >99%. $[\alpha]^{20}_D$ = +5.7 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.99−7.88 (m, 2H), 7.74 (td, J = 7.7, 1.8 Hz, 1H), 7.53−7.36 (m, 4H), 7.24−7.13 (m, 3H), 7.12−7.01 (m, 2H), 6.38 (brs, 1H), 5.76 (d, J = 7.7 Hz, 1H), 4.32 (dd, J = 10.0, 3.7 Hz, 1H), 4.07 (d, J = 10.7 Hz, 1H), 4.01 (t, J = 10.0 Hz, 1H), 3.32−3.23 (m, 1H), 3.15−2.93 (m, 3H), 2.77−2.66 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.6, 160.1, 148.1, 137.5, 134.7, 133.6, 132.5, 130.7, 128.7, 128.5, 127.7, 127.3, 126.2, 122.1, 120.3, 68.2, 64.9, 63.3, 54.4, 49.6, 29.3 (one peak overlaps). HRMS (ESI+) m/z: calcd for $C_{24}H_{24}N_3O_2$ 386.1863 [M + H$^+$]; found 386.1872 [M + H$^+$].

General Procedure B for the Synthesis of Alcohols (4i−j). A solution of aldehyde **2** (0.4 mmol) and catalyst **3B** (0.01 mmol) in dichloromethane (0.4 mL) was prepared in a screw vial at rt. Then, dipole **1a** (0.2 mmol) was added, and the reaction mixture was stirred at rt for 3 days. Then, ethanol (0.4 mL) and $NaBH_4$ (0.4 mmol) were added successively at 0 °C. The reaction mixture was stirred at rt until complete conversion was obtained (followed by thin layer chromatography). The reaction was treated with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuum. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

*((1R,2R,10bR)-1-(Hydroxymethyl)-2-methyl-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4i**).* The product was obtained following the general procedure B as a white amorphous solid (49 mg, 76%) after purification by column chromatography (hexane/AcOEt 1:1). The ee was determined by SFC using a Chiralpak ID column [CO_2/MeOH (85:15), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 5.72 min, τ_{minor} = 7.72 min, ee = 85%. $[\alpha]^{20}_D$ = +3.29 (c 0.79, $CHCl_3$). The product was also obtained in 61% yield and >99% ee using 20 mol % of **3B** after 17 h at 0 °C. $[\alpha]^{20}_D$ = +9.0 (c 1.43, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.79 (m, 2H), 7.43−7.29 (m, 3H), 7.23−7.15 (m, 3H), 7.15−7.06 (m, 1H), 4.54 (dq, J = 8.5, 6.3 Hz, 1H), 4.30 (d, J = 10.8 Hz, 1H), 4.12 (app d, J = 11.5 Hz, 1H), 4.05−3.91 (m, 1H), 3.30−3.07 (m, 2H), 2.95 (ddd, J = 17.4, 12.4, 5.2 Hz, 1H), 2.80−2.63 (m, 2H), 2.41 (dtd, J = 10.7, 5.1, 2.4 Hz, 1H), 1.64 (d, J = 6.4 Hz, 3H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 169.1, 135.4, 134.6, 132.9, 130.0, 128.5, 128.4, 127.5, 127.4, 126.9, 126.1, 61.8, 59.2, 58.1, 55.0, 49.8, 29.5, 22.3. HRMS (FAB+) m/z: calcd for $C_{20}H_{23}N_2O_2$ 323.1760 [M + H$^+$]; found 323.1757 [M + H$^+$].

*((1R,2R,10bR)-2-Ethyl-1-(hydroxymethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**4j**).* The product was obtained following the general procedure B as a white amorphous solid (53 mg, 78%) after purification by column chromatography (hexane/AcOEt 3:2). The ee was determined by SFC using a Chiralpak ID column [CO_2/MeOH (85:15), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 6.69 min, τ_{minor} = 9.36 min, ee = 98%. $[\alpha]^{20}_D$ = −12.0 (c 0.86, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.73 (m, 2H), 7.42−7.29 (m, 3H), 7.21−7.14 (m, 3H), 7.14−7.07 (m, 1H), 4.48 (td, J = 7.9, 5.7 Hz, 1H), 4.28 (d, J = 10.4 Hz, 1H), 4.15−3.96 (m, 2H), 3.30−3.12 (m, 2H), 2.95 (ddd, J = 17.1, 11.9, 5.3 Hz, 1H), 2.71 (dt, J = 16.2, 2.6 Hz, 1H), 2.53−2.41 (m, 1H), 2.20−2.03 (m, 2H), 1.88 (dq, J = 14.2, 7.4 Hz, 1H), 1.08 (t, J = 7.5 Hz, 3H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.6, 135.8, 134.8, 133.0, 129.9, 128.4, 128.2, 127.5, 127.3, 126.8, 126.1, 62.5, 62.0, 60.2, 53.2, 49.5, 29.7, 29.6, 11.0. HRMS (FAB+) m/z: calcd for $C_{21}H_{25}N_2O_2$ 337.1916 [M + H$^+$]; found 337.1909 [M + H$^+$].

General Procedure C for the Synthesis of Alcohols 7k−s and Aldehyde 6q. A solution of aldehyde **2** (0.2 mmol) and catalyst **3A** (0.02 mmol) in dichloromethane (0.2 mL) was prepared in a screw vial. The solution was cooled at 0 °C, and dipole **1** (0.1 mmol) was added. The reaction was stirred at 0 °C for 24 h. Then, ethanol (0.2 mL) and $NaBH_4$ (0.4 mmol) were added successively at 0 °C. The evolution of the reaction was followed by thin layer chromatography (TLC). When the reaction was complete, the mixture was treated with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuum. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

*((1S,2S,10bS)-2-(2-Hydroxyethyl)-1-phenyl-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7k**).* The product was obtained following the general procedure C as a white foam (27 mg, 68%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 11.87 min, τ_{minor} = 14.00 min, ee = 94%. $[\alpha]^{20}_D$ = −66.1 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.80 (m, 2H), 7.50−7.33 (m, 6H), 7.32−7.24 (m, 2H), 7.15−7.06 (m, 2H), 6.93−6.83 (m, 1H), 6.17 (d, J = 7.8 Hz, 1H), 4.81 (ddd, J = 11.3, 8.1, 3.6 Hz, 1H), 4.38 (d, J = 10.6 Hz, 1H), 4.34−4.23 (m, 1H), 3.84−3.63 (m, 2H), 3.48 (dd, J = 10.7, 8.1 Hz, 1H), 3.43−3.28 (m, 2H), 3.04 (ddd, J = 17.2, 12.0, 5.4 Hz, 1H), 2.78 (dt, J = 16.2, 2.7 Hz, 1H), 2.35−2.20 (m, 1H), 1.91−1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.7, 135.1, 133.8, 132.6, 130.4, 129.1, 128.6, 128.3, 128.3, 127.7, 127.6, 127.1, 126.7, 125.8, 69.8, 66.0, 60.2, 59.5, 49.5, 40.8, 29.7. HRMS (FAB+) m/z: calcd for $C_{26}H_{27}N_2O_2$ 399.2073 [M + H$^+$]; found 399.2076 [M + H$^+$].

*((1S,2R,10bS)-2-(2-Hydroxyethyl)-1-(p-tolyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7l**).* The product was obtained following the general procedure C as a white foam (31 mg, 75%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a

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Chiralpak IA column [CO_2/MeOH (90:10), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 11.53 min, τ_{minor} = 13.47 min, ee = 90%. $[\alpha]^{20}_D$ = −88.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.78 (m, 2H), 7.48−7.34 (m, 3H), 7.24−7.06 (m, 6H), 6.93−6.84 (m, 1H), 6.21 (d, *J* = 7.7 Hz, 1H), 4.76 (ddd, *J* = 11.3, 7.9, 3.5 Hz, 1H), 4.35 (d, *J* = 10.6 Hz, 1H), 4.32−4.19 (m, 1H), 3.83−3.63 (m, 2H), 3.50−3.27 (m, 3H), 3.03 (ddd, *J* = 17.1, 12.0, 5.3 Hz, 1H), 2.76 (app d, *J* = 16.5 Hz, 1H), 2.40 (s, 3H), 2.36−2.15 (m, 1H), 1.89−1.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 137.3, 135.5, 135.2, 133.9, 132.6, 130.4, 129.8, 128.5, 128.3, 127.6, 127.0, 126.7, 125.7, 69.6, 66.0, 59.8, 59.5, 49.5, 40.8, 29.7, 21.1. HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{29}N_2O_2$ 413.2229 [M + H$^+$]; found 413.2225 [M + H$^+$].

*((1S,2S,10bS)-2-(2-Hydroxyethyl)-1-(o-tolyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7m**).* The product was obtained following the general procedure C as a white foam (17 mg, 40%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 9.04 min, τ_{minor} = 10.82 min, ee = 87%. $[\alpha]^{20}_D$ = +34.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 363 K) δ 7.82−7.77 (m, 2H), 7.43−7.32 (m, 4H), 7.29 (td, *J* = 7.5, 1.6 Hz, 1H), 7.18 (td, *J* = 7.4, 1.4 Hz, 1H), 7.14 (dd, J = 7.8, 1.5 Hz, 1H), 7.09−7.02 (m, 2H), 6.83 (td, *J* = 6.9, 1.7 Hz, 1H), 6.12 (d, *J* = 7.7 Hz, 1H), 4.75 (ddd, *J* = 9.9, 8.0, 4.1 Hz, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 3.85 (dd, *J* = 10.5, 8.1 Hz, 1H), 3.73−3.52 (m, 3H), 3.37 (ddd, *J* = 12.2, 10.5, 3.3 Hz, 1H), 3.28 (ddd, *J* = 10.4, 5.3, 2.2 Hz, 1H), 2.95 (ddd, *J* = 17.1, 12.3, 5.3 Hz, 1H), 2.72 (dt, *J* = 16.1, 2.8 Hz, 1H), 2.15 (ddt, *J* = 14.0, 9.3, 4.5 Hz, 1H), 1.98 (s, 3H), 1.89 (ddt, *J* = 13.9, 9.9, 3.7 Hz, 1H). ^{13}C NMR (126 MHz, $C_2D_2Cl_4$, 393 K) δ 172.4, 137.4, 137.3, 136.0, 134.2, 132.8, 131.1, 130.3, 128.5, 128.4, 127.8, 127.4, 127.3, 126.3, 126.1, 70.5, 66.4, 60.1, 55.4, 50.0, 41.6, 30.0, 19.8 (two peaks overlaps). HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{29}N_2O_2$ 413.2229 [M + H$^+$]; found 413.2232 [M + H$^+$].

*(1S,2S,10bS)-2-(2-Hydroxyethyl)-1-(4-methoxyphenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7n**).* The product was obtained following the general procedure C as a white foam (31 mg, 73%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IC column [CO_2/MeOH (75:25), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 10.59 min, τ_{minor} = 13.86 min, ee = 87%. $[\alpha]^{20}_D$ = −106.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.78 (m, 2H), 7.50−7.32 (m, 3H), 7.19 (app d, *J* = 8.7 Hz, 2H), 7.13−7.05 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.92−6.84 (m, 1H), 6.21 (d, *J* = 7.7 Hz, 1H), 4.73 (ddd, *J* = 11.2, 8.1, 3.5 Hz, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 4.31−4.20 (m, 1H), 3.85 (s, 3H), 3.82−3.63 (m, 2H), 3.48−3.26 (m, 3H), 3.02 (ddd, *J* = 17.2, 11.9, 5.4 Hz, 1H), 2.76 (app d, *J* = 16.2 Hz, 1H), 2.32−2.18 (m, 1H), 1.88−1.73 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 173.0, 159.1, 135.2, 133.8, 132.6, 130.5, 130.4, 129.6, 128.3, 127.6, 127.0, 126.7, 125.7, 114.5, 69.6, 65.9, 59.5, 59.3, 55.3, 49.5, 40.7, 29.7 (one peak overlaps). HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{29}N_2O_3$ 429.2178 [M + H$^+$]; found 429.2167 [M + H$^+$].

*((1S,2R,10bS)-1-(Benzo[d][1,3]dioxol-5-yl)-2-(2-hydroxyethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)-methanone (**7o**).* The product was obtained following the general procedure C as a white foam (34 mg, 76%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (80:20), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 5.94 min, τ_{minor} = 7.82 min, ee = 89%. $[\alpha]^{20}_D$ =+133.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.75 (m, 2H), 7.48−7.32 (m, 3H), 7.17−7.03 (m, 2H), 6.97−6.87 (m, 1H), 6.84−6.76 (m, 2H), 6.68 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.30 (d, *J* = 7.7 Hz, 1H), 6.01 (s, 2H), 4.70 (ddd, *J* = 11.2, 8.0, 3.5 Hz, 1H), 4.33−4.21 (m, 2H), 3.83−3.63 (m, 2H), 3.44−3.26 (m, 3H), 3.02 (ddd, *J* = 17.1, 11.6, 5.7 Hz, 1H), 2.75 (dt, *J* = 16.3, 2.8 Hz, 1H), 2.32−2.17 (m, 1H), 1.86−1.72 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 173.1, 148.4, 147.1, 135.1, 133.7, 132.6, 132.4, 130.4, 128.32, 128.27, 127.6, 127.1, 126.7, 125.8, 122.3, 108.6, 108.1, 101.2, 69.5, 65.8, 59.9, 59.43, 49.5, 40.7, 29.7. HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{27}N_2O_4$ 443.1971 [M + H$^+$]; found 443.1975 [M + H$^+$].

*((1S,2S,10bS)-1-(4-Fluorophenyl)-2-(2-hydroxyethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7p**).* The product was obtained, following the general procedure C, as a white foam (26 mg, 63%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IB column [CO_2/MeOH (95:5), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 15.49 min, τ_{minor} = 17.14 min, ee = 92%. $[\alpha]^{20}_D$ = +87.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.79 (m, 2H), 7.53−7.33 (m, 3H), 7.30−7.20 (m, 3H), 7.19−7.05 (m, 3H), 6.94−6.85 (m, 1H), 6.15 (d, *J* = 7.8 Hz, 1H), 4.82−4.69 (m, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 4.27−4.16 (m, 1H), 3.83−3.63 (m, 2H), 3.47 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.43−3.30 (m, 2H), 3.03 (ddd, *J* = 17.1, 11.6, 5.6 Hz, 1H), 2.77 (app d, *J* = 16.1 Hz, 1H), 2.33−2.17 (m, 1H), 1.88−1.73 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 173.1, 162.3 (d, J_{C-F} = 246.5 Hz), 135.0, 134.4 (d, J_{C-F} = 3.2 Hz), 133.5, 132.6, 130.5, 130.1 (d, J_{C-F} = 8.0 Hz), 128.4, 128.3, 127.7, 127.2, 126.6, 125.8, 116.1 (d, J_{C-F} = 21.4 Hz), 69.9, 65.9, 59.41, 59.37, 49.5, 40.7, 29.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.6 (s). HRMS (FAB +) *m*/*z*: calcd for $C_{26}H_{26}FN_2O_2$ 417.1978 [M + H$^+$]; found 417.1968 [M + H$^+$].

*((1S,2S,10bS)-2-(2-Hydroxyethyl)-1-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)-methanone (**7q**).* The product was obtained, following the general procedure C, as a white foam (28 mg, 61%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IB column [CO_2/MeOH (95:5)], 3.0 mL/min. τ_{mayor} = 11.50 min, τ_{minor} = 14.76 min, ee = 92%. $[\alpha]^{20}_D$ = −43.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.79 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.52−7.34 (m, 5H), 7.18−7.07 (m, 2H), 6.96−6.85 (m, 1H), 6.11 (d, *J* = 7.8 Hz, 1H), 4.82 (ddd, *J* = 11.3, 8.0, 3.6 Hz, 1H), 4.37 (d, *J* = 10.5 Hz, 1H), 4.16 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.83−3.63 (m, 2H), 3.57 (dd, *J* = 10.6, 8.1 Hz, 1H), 3.47−3.31 (m, 2H), 3.05 (ddd, *J* = 17.2, 11.6, 6.0 Hz, 1H), 2.79 (app d, *J* = 16.4 Hz, 1H), 2.30−2.15 (m, 1H), 1.90−1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 143.1 (q, J_{C-F} = 1.2 Hz), 134.9, 133.3, 132.6, 130.7, 130.1 (q, J_{C-F} = 32.6 Hz), 129.0, 128.5, 128.4, 127.7, 127.4, 126.4, 126.1 (q, J_{C-F} = 3.8 Hz), 126.0, 124.0 (q, J_{C-F} = 272.1 Hz), 69.9, 66.0, 60.0, 59.3, 49.6, 40.8, 29.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.5 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{26}F_3N_2O_2$ 467.1946 [M + H$^+$]; found 467.1948 [M + H$^+$].

*((1S,2S,10bS)-8-Fluoro-2-(2-hydroxyethyl)-1-phenyl-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7r**).* The product was obtained, following the general procedure C, as a white foam (29 mg, 69%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IB column [CO_2/MeOH (95:5)], 3.0 mL/min. τ_{mayor} = 17.64 min, τ_{minor} = 18.75 min, ee = 86%. $[\alpha]^{20}_D$ = −71.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.77 (m, 2H), 7.50−7.30 (m, 6H), 7.30−7.21 (m, 2H), 6.79 (dd, *J* = 9.3, 2.7 Hz, 1H), 6.58 (td, *J* = 8.6, 2.7 Hz, 1H), 6.10 (dd, *J* = 8.7, 5.6 Hz, 1H), 4.80 (ddd, *J* = 11.3, 8.1, 3.6 Hz, 1H), 4.31 (d, *J* = 10.6 Hz, 1H), 4.23 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.83−3.63 (m, 2H), 3.47−3.29 (m, 3H), 3.01 (ddd, *J* = 17.2, 11.6, 5.9 Hz, 1H), 2.75 (dt, *J* = 16.4, 2.7 Hz, 1H), 2.34−2.18 (m, 1H), 1.81 (ddt, *J* = 14.1, 10.9, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 161.6 (d, J_{C-F} = 246.1 Hz), 138.3, 135.1, 134.9 (d, J_{C-F} = 7.6 Hz), 130.5, 129.4 (d, J_{C-F} = 3.0 Hz), 129.2, 128.6, 128.22, 128.20 (d, J_{C-F} = 8.1 Hz), 127.8, 127.7, 114.7 (d, J_{C-F} = 21.1 Hz), 113.1 (d, J_{C-F} = 21.5 Hz), 69.4, 65.9, 60.1, 59.4, 49.0, 40.7, 29.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.2 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{26}H_{26}FN_2O_2$ 417.1978 [M + H$^+$]; found 417.1977 [M + H$^+$].

*((1S,2S,10bS)-2-(2-Hydroxyethyl)-8-methoxy-1-phenyl-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl)(phenyl)methanone (**7s**).* The product was obtained, following the general procedure C, as a white foam (22 mg, 51%) after purification by column chromatography (CH_2Cl_2/AcOEt 95:5). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (85:15)], 3.0 mL/min. τ_{mayor} = 7.80 min, τ_{minor} = 9.20 min, ee = 90%. $[\alpha]^{20}_D$ = −76.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.78 (m, 2H), 7.49−7.30 (m, 6H), 7.30−7.22 (m, 2H), 6.61 (brs, 1H), 6.45 (brd, *J* = 8.6 Hz, 1H), 6.08 (d, *J* = 8.6 Hz, 1H), 4.83−4.72 (m, 1H), 4.34−4.18 (brs, 1H), 4.31 (d, *J* = 10.5 Hz, 1H), 3.82−3.62 (m, 2H), 3.71 (s, 3H),

3.49−3.24 (m, 3H), 3.08−2.91 (m, 1H), 2.72 (d, J = 16.4 Hz, 1H), 2.35−2.15 (m, 1H), 1.89−1.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 158.5, 138.7, 135.2, 134.0, 130.4, 129.1, 128.6, 128.3, 127.7, 127.6, 126.0, 113.0, 112.1, 69.5, 66.0, 60.4, 59.5, 55.2, 49.4, 40.8, 30.0 (one peak overlaps). HRMS (FAB+) m/z: calcd for $C_{27}H_{29}N_2O_3$ 429.2178 [M + H$^+$]; found 429.2168 [M + H$^+$].

*2-((1S,2S,10bS)-3-Benzoyl-1-(4-(trifluoromethyl)phenyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-2-yl)-acetaldehyde (**6q**).* Following the general procedure C, after complete consumption of aldehyde **2**, the reaction mixture was directly subject to silica gel flash chromatography (hexane/AcOEt 7:3) affording **6q** as an orange foam (40 mg, 85%). $[\alpha]^{20}_D$ = +32.5 (c 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, J = 2.6 Hz, 1H), 7.97−7.89 (m, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.50−7.31 (m, 5H), 7.19−7.06 (m, 2H), 6.95−6.84 (m, 1H), 6.08 (d, J = 7.8 Hz, 1H), 5.06 (dt, J = 8.7, 6.6 Hz, 1H), 4.49 (d, J = 10.6 Hz, 1H), 3.56 (dd, J = 10.6, 8.7 Hz, 1H), 3.37−3.19 (m, 2H), 3.18−2.95 (m, 2H), 2.87 (ddd, J = 15.2, 6.2, 2.2 Hz, 1H), 2.76 (dt, J = 16.3, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 169.4, 141.9 (q, J_{C-F} = 1.5 Hz), 134.5, 132.7, 130.7, 130.3 (q, J_{C-F} = 32.7 Hz), 129.2, 128.7, 128.6, 127.7, 127.5, 126.5, 126.2 (q, J_{C-F} = 3.8 Hz), 125.9, 124.0 (q, J_{C-F} = 272.3 Hz), 69.5, 63.3, 58.6, 50.5, 49.8, 29.6 (one peak overlaps). ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.5 (s). HRMS (FAB+) m/z calcd for $C_{27}H_{24}F_3N_2O_2$ 465.1790 [M + H$^+$]; found 465.1780 [M + H$^+$].

General Procedure D for the Synthesis of Products 8k−s and Aldehyde 5k. A solution of aldehyde **2** (0.2 mmol), tetrabutylammonium bromide (2 equiv), and catalyst **3B** (0.01 mmol) in toluene (0.2 mL) was prepared in a screw vial. The mixture was cooled to 0 °C, and dipole **1** (0.1 mmol) was added. The reaction mixture was stirred at 0 °C for 24 h. Then, dichloromethane (0.8 mL) and ethyl (triphenylphosphoranylidene)acetate (0.24 mmol) were added at room temperature. The mixture was stirred at room temperature for 24 h. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-benzyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8k**).* The product was obtained, following the general procedure D, as a white foam (33 mg, 70%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 9.33 min, τ_{minor} = 11.16 min, ee = 98%. $[\alpha]^{20}_D$ = −29.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93−7.84 (m, 2H), 7.52−7.36 (m, 3H), 7.37−7.05 (m, 8H), 7.02−6.91 (m, 2H), 5.61 (d, J = 15.5 Hz, 1H), 4.75−4.64 (m, 1H), 4.32−4.21 (m, 2H), 4.18 (d, J = 9.9 Hz, 1H), 3.41−3.27 (m, 2H), 3.18 (q, J = 9.7 Hz, 1H), 2.95−2.72 (m, 2H), 2.61−2.47 (m, 1H), 2.42−2.27 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.6, 144.7, 136.8, 135.5, 133.2, 132.9, 130.2, 130.1, 128.4, 128.3, 128.2, 127.6, 127.3, 127.1, 126.8, 125.8, 124.9, 66.6, 65.7, 60.4, 53.6, 48.9, 38.6, 29.3, 14.2. HRMS (FAB+) m/z: calcd for $C_{30}H_{31}N_2O_3$ 467.2335 [M + H$^+$]; found 467.2328 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-(4-methylbenzyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8l**).* The product was obtained, following the general procedure D, as a white foam (35 mg, 73%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 9.95 min, τ_{minor} = 12.36 min, ee = 94%. $[\alpha]^{20}_D$ = −29.7 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.78 (m, 2H), 7.46−7.31 (m, 3H), 7.20−7.01 (m, 7H), 6.96−6.84 (m, 2H), 5.50 (d, J = 15.5 Hz, 1H), 4.62 (td, J = 8.2, 3.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.13 (d, J = 10.2 Hz, 1H), 3.31 (dd, J = 13.4, 3.7 Hz, 1H), 3.25−3.04 (m, 2H), 2.92−2.74 (m, 2H), 2.58−2.32 (m, 2H), 2.29 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.6, 144.8, 136.3, 135.6, 133.7, 133.2, 133.0, 130.1, 129.0, 128.4, 128.2, 127.6, 127.3, 127.1, 125.9, 124.7, 66.7, 65.8, 60.4, 53.7, 49.0, 38.4, 29.4, 20.9, 14.2 (one peak overlaps). HRMS (FAB+) m/z: calcd for $C_{31}H_{33}N_2O_3$ 481.2491 [M + H$^+$]; found 481.2486 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-(2-methylbenzyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8m**).* The product was obtained, following the general procedure D, as a white (34 mg, 71%) foam after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 8.98 min, τ_{minor} = 10.48 min, ee > 99%. $[\alpha]^{20}_D$ = −51.8 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.78 (m, 2H), 7.47−7.32 (m, 3H), 7.21−7.02 (m, 7H), 6.90−6.85 (m, 1H), 6.81 (dd, J = 15.5, 9.7 Hz, 1H), 5.32 (d, J = 15.5 Hz, 1H), 4.73 (td, J = 8.7, 4.4 Hz, 1H), 4.17 (qd, J = 7.1, 2.5 Hz, 2H), 4.09 (d, J = 10.1 Hz, 1H), 3.63 (dd, J = 13.5, 4.4 Hz, 1H), 3.20 (app q, J = 9.8 Hz, 1H), 3.14−2.98 (m, 2H), 2.98−2.80 (m, 2H), 2.71−2.60 (m, 1H), 2.44 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.6, 144.8, 137.0, 135.4, 135.3, 133.1, 133.0, 131.0, 130.4, 130.2, 128.5, 128.2, 127.6, 127.3, 127.2, 127.0, 125.9, 125.6, 124.4, 67.2, 64.5, 60.3, 54.2, 49.3, 38.4, 29.5, 19.6, 14.2. HRMS (FAB+) m/z: calcd for $C_{31}H_{33}N_2O_3$ 481.2491 [M + H$^+$]; found 481.2497 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-(4-methoxybenzyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8n**).* The product was obtained, following the general procedure D, as a white foam (42 mg, 85%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 11.48 min, τ_{minor} = 14.30 min, ee = 98%. $[\alpha]^{20}_D$ = −26.7 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.78 (m, 2H), 7.46−7.31 (m, 3H), 7.20−6.99 (m, 5H), 6.98−6.85 (m, 2H), 6.79 (app d, J = 8.5 Hz, 2H), 5.56 (d, J = 15.5 Hz, 1H), 4.59 (dt, J = 8.9, 5.5 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.13 (app d, J = 10.0 Hz, 1H), 3.76 (s, 3H), 3.22 (d, J = 5.5 Hz, 2H), 3.10 (q, J = 9.7 Hz, 1H), 2.94−2.69 (m, 2H), 2.57−2.44 (m, 1H), 2.39−2.24 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 165.6, 158.6, 144.8, 135.6, 133.2, 133.0, 131.2, 130.1, 129.0, 128.4, 128.2, 127.6, 127.3, 127.1, 125.9, 124.8, 113.8, 66.6, 66.0, 60.5, 55.2, 53.6, 49.0, 37.7, 29.4, 14.2. HRMS (FAB+) m/z: calcd for $C_{31}H_{33}N_2O_4$ 497.2440 [M + H$^+$]; found 497.2432 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-benzoyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)-acrylate (**8o**).* The product was obtained, following the general procedure D, as a white foam (40 mg, 78%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (93:7), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 19.20 min, τ_{minor} = 21.19 min, ee = 98%. $[\alpha]^{20}_D$ = −34.8 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.79 (m, 2H), 7.46−7.31 (m, 3H), 7.20−7.02 (m, 3H), 6.97−6.84 (m, 2H), 6.74−6.60 (m, 3H), 5.89 (app d, J = 4.1 Hz, 2H), 5.56 (d, J = 15.5 Hz, 1H), 4.57 (td, J = 8.2, 3.7 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.13 (d, J = 10.2 Hz, 1H), 3.26 (dd, J = 13.5, 3.7 Hz, 1H), 3.19−3.05 (m, 2H), 2.94−2.78 (m, 2H), 2.61−2.40 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.6, 147.6, 146.4, 144.7, 135.5, 133.2, 133.0, 130.6, 130.2, 128.5, 128.2, 127.6, 127.3, 127.2, 125.9, 124.8, 123.2, 110.5, 108.1, 100.8, 66.6, 65.9, 60.5, 53.7, 49.1, 38.6, 29.4, 14.2. HRMS (FAB+) m/z: calcd for $C_{31}H_{31}N_2O_5$ 511.2233 [M + H$^+$]; found 511.2227 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-(4-fluorobenzyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8p**).* The product was obtained following the general procedure D as a white (35 mg, 72%) foam after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 120 bar, 40 °C], 3.0 mL/min. τ_{mayor} = 6.95 min, τ_{minor} = 9.01 min, ee = 99%. $[\alpha]^{20}_D$ = −17.1 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.79 (m, 2H), 7.47−7.32 (m, 3H), 7.21−7.02 (m, 5H), 7.00−6.85 (m, 4H), 5.55 (d, J = 15.5 Hz, 1H), 4.61 (td, J = 7.8, 3.8 Hz, 1H), 4.30−4.13 (m, 2H), 4.13 (d, J = 10.3 Hz, 1H), 3.30 (dd, J = 13.5, 3.8 Hz, 1H), 3.22 (dd, J = 13.5, 7.6 Hz, 1H), 3.08 (q, J = 9.8 Hz, 1H), 2.93−2.75 (m, 2H), 2.61−2.47 (m, 1H), 2.45−2.30 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 165.5, 161.9 (d, J_{C-F} = 245.4 Hz), 144.6, 135.4, 133.1, 132.8, 132.7 (d, J_{C-F} = 3.3 Hz), 131.6 (d, J_{C-F} = 7.9 Hz), 130.2, 128.5, 128.2, 127.6, 127.3, 127.2, 125.9, 125.0, 115.2 (d, J_{C-F} = 21.2 Hz), 66.6, 65.7 (d, J_{C-F} = 1.1 Hz), 60.5, 53.8, 49.1, 38.1, 29.3, 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.9 (s). HRMS (FAB+) $m/$

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z: calcd for $C_{30}H_{30}FN_2O_3$ 485.2240 [M + H$^+$]; found 485.2231 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-(4-(trifluoromethyl)-benzyl)-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)-acrylate (**8q**).* The product was obtained, following the general procedure D, as a white foam (40 mg, 75%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IA column [CO_2/MeOH (90:10), 100 bar, 60 °C], 3.0 mL/min. τ_{mayor} = 5.99 min, τ_{minor} = 8.23 min, ee = 96%. $[\alpha]^{20}_D$ = −11.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.81 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.48−7.29 (m, 5H), 7.21−7.03 (m, 3H), 6.92−6.80 (m, 2H), 5.45 (d, *J* = 15.5 Hz, 1H), 4.65 (td, *J* = 8.5, 3.7 Hz, 1H), 4.24−4.06 (m, 3H), 3.51 (dd, *J* = 13.2, 3.5 Hz, 1H), 3.22 (dd, *J* = 13.2, 8.4 Hz, 1H), 3.09 (q, *J* = 9.8 Hz, 1H), 2.97−2.79 (m, 2H), 2.64−2.41 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 165.4, 144.4, 141.1 (q, J_{C-F} = 1.2 Hz), 135.2, 133.0, 132.7, 130.4, 129.2 (q, J_{C-F} = 32.4 Hz), 128.5, 128.3, 127.7, 127.29, 127.28, 126.0, 125.3 (q, J_{C-F} = 3.7 Hz), 125.0, 124.09 (q, J_{C-F} = 272.0 Hz), 66.7, 65.4, 60.5, 54.2, 49.2, 39.5, 29.4, 14.0 (one peak overlaps). ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.5 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{31}H_{30}F_3N_2O_3$ 535.2209 [M + H$^+$]; found 535.2202 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-benzyl-8-fluoro-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8r**).* The product was obtained, following the general procedure D, as a white foam (38 mg, 78%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak IB column [CO_2/MeOH (95:5)], 3.0 mL/min. τ_{mayor} = 10.39 min, τ_{minor} = 11.28 min, ee > 99%. $[\alpha]^{20}_D$ = −22.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.75 (m, 2H), 7.47−7.32 (m, 3H), 7.31−7.13 (m, 5H), 6.94−6.68 (m, 4H), 5.56 (d, *J* = 15.5 Hz, 1H), 4.68−4.58 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.07 (d, *J* = 10.2 Hz, 1H), 3.27 (brd, *J* = 5.8 Hz, 2H), 3.06 (q, *J* = 9.6 Hz, 1H), 2.87−2.67 (m, 2H), 2.51−2.39 (m, 1H), 2.30−2.15 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 165.5, 161.65 (d, J_{C-F} = 246.6 Hz), 144.5, 136.8, 135.54, 135.53 (d, J_{C-F} = 7.5 Hz), 130.3, 130.2, 128.8 (d, J_{C-F} = 8.3 Hz), 128.64 (d, J_{C-F} = 3.1 Hz), 128.4, 128.1, 127.7, 126.9, 125.2, 114.9 (d, J_{C-F} = 21.1 Hz), 113.2 (d, J_{C-F} = 21.7 Hz), 66.2, 65.7, 60.5, 53.7, 48.5, 38.6, 29.5, 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.0 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{30}H_{30}FN_2O_3$ 485.2240 [M + H$^+$]; found 485.2234 [M + H$^+$].

*Ethyl-(E)-3-((1R,2R,10bR)-3-benzoyl-2-benzyl-8-methoxy-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-1-yl)acrylate (**8s**).* The product was obtained, following the general procedure D, as a white foam (20 mg, 41%) after purification by column chromatography (hexane/AcOEt 6:1). The ee was determined by SFC using a Chiralpak ID column [CO_2/MeOH (75:25), 100 bar, 60 °C], 3.0 mL/min. τ_{minor} = 8.27 min, τ_{mayor} = 9.58 min, ee = 96%. $[\alpha]^{20}_D$ = −39.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.78 (m, 2H), 7.45−7.31 (m, 3H), 7.30−7.13 (m, 5H), 6.89 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.66 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 5.56 (d, *J* = 15.5 Hz, 1H), 4.62 (dt, *J* = 8.9, 5.6 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.4 Hz, 2H), 4.08 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 3.28 (brd, *J* = 5.6 Hz, 2H), 3.07 (q, *J* = 9.6 Hz, 1H), 2.87−2.64 (m, 2H), 2.50−2.37 (m, 1H), 2.32−2.17 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.6, 158.6, 144.9, 136.9, 135.6, 134.6, 130.3, 130.1, 128.3, 128.2, 127.6, 126.8, 125.1, 124.9, 113.2, 112.1, 66.3, 65.8, 60.4, 55.2, 53.8, 48.8, 38.6, 29.6, 14.2 (one peak overlaps). HRMS (FAB+) *m*/*z*: calcd for $C_{31}H_{33}N_2O_4$ 497.2440 [M + H$^+$]; found 497.2441 [M + H$^+$].

*(1R,2R,10bR)-3-Benzoyl-2-benzyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinoline-1-carbaldehyde (**5k**).* Following the general procedure D, after complete consumption of aldehyde **2**, the reaction mixture was directly subject to silica gel flash chromatography (gradient hexane/AcOEt 7:3 to 7:1) affording **5k** as an orange foam (36 mg, 90%). $[\alpha]^{20}_D$ = −9.3 (*c* 0.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (d, *J* = 2.9 Hz, 1H), 7.94−7.84 (m, 2H), 7.51−7.08 (m, 11H), 6.97−6.91 (m, 1H), 5.00 (td, *J* = 9.2, 3.8 Hz, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 3.71 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.52 (ddd, *J* = 10.2, 8.6, 3.0 Hz, 1H), 3.16−3.06 (m, 1H), 3.06−2.79 (m, 2H), 3.00 (dd, *J* = 13.0, 9.7 Hz, 1H), 2.68 (dt, *J* = 15.6, 2.7 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 198.9, 169.5, 136.8, 135.0, 133.02, 132.98, 130.3, 129.5, 128.8, 128.6, 128.3, 127.6, 127.4, 127.1, 126.9, 126.4, 63.6, 63.4, 63.2, 49.8, 41.5, 29.3. HRMS (FAB+) *m*/*z*: calcd for $C_{26}H_{25}N_2O_2$ 397.1916 [M + H$^+$]; found 397.1914 [M + H$^+$].

Synthesis of ((1*R*,2*R*,10b*R*)-2-Benzyl-1-(((2-bromobenzyl)-amino)methyl)-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]-isoquinolin-3(2*H*)-yl)(phenyl)methanone (9). A solution of aldehyde **5k** (0.126 mmol), (2-bromophenyl)methanamine (0.126 mmol), magnesium sulfate anhydrous (0.252 mmol), and acetic acid (0.176 mmol) in 1,2-dichloroethane (1 mL) was prepared in a screw vial. The mixture was stirred at room temperature for 1 h. Then, sodium triacetoxyborohydride (0.176 mmol) was added, and the mixture was stirred at room temperature for 24 h. Hereafter, saturated solution $NaHCO_3$ and dichloromethane were added to the reaction mixture. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (hexane:AcOEt 4:1) affording **9** as a colorless oil (68 mg, 95%). $[\alpha]^{20}_D$ = −32.3 (*c* 0.84, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.78 (m, 2H), 7.59−7.52 (m, 1H), 7.43−7.30 (m, 3H), 7.29−6.94 (m, 12H), 4.57 (td, *J* = 8.6, 3.5 Hz, 1H), 4.20 (d, *J* = 10.4 Hz, 1H), 3.78 (AB system, *J* = 13.8 Hz, 2H), 3.55−3.44 (m, 1H), 3.20−3.06 (m, 1H), 2.87−2.43 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 138.9, 137.8, 135.8, 134.4, 133.2, 132.8, 130.4, 129.92, 129.88, 128.6, 128.42, 128.36, 128.3, 127.5, 127.34, 127.26, 126.9, 126.6, 125.9, 124.0, 63.7, 63.6, 54.2, 49.9, 49.0, 47.6, 40.7, 29.4. HRMS (FAB+) *m*/*z*: calcd for $C_{33}H_{33}BrN_3O$ 566.1807 [M + H$^+$]; found 566.1805 [M + H$^+$].

The hydrochloride salt **9·HCl** was obtained by addition of hydrogen chloride solution (2.0 M) in diethyl ether to a solution of amine **9** in diethyl ether at 0 °C. The solid was filtered in vacuum, washed with cold diethyl ether, and collected in quantitative yield.

Synthesis of ((1*S*,2*S*,10b*S*)-2-(2-((2-Bromobenzyl)amino)-ethyl)-1-(4-(trifluoromethyl)phenyl)-1,5,6,10*b*-tetrahydro-pyrazolo[5,1-*a*]isoquinolin-3(2*H*)-yl)(phenyl)methanone (10). A solution of aldehyde **6q** (0.1 mmol), (2-bromophenyl)methanamine (0.1 mmol), and magnesium sulfate anhydrous (0.2 mmol) in 1,2-dichloroethane (1 mL) was prepared in a screw vial. The mixture was stirred at room temperature for 1 h. Then, sodium triacetoxyborohydride (1.4 equiv) was added, and the mixture was stirred at room temperature for 18 h. Hereafter, saturated solution $NaHCO_3$ and dichloromethane were added to the reaction mixture. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (hexane:AcOEt 2:1) affording **10** as a yellow oil (22 mg, 35%). $[\alpha]^{20}_D$ = +26.1 (*c* 0.79, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.79 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.52−7.33 (m, 6H), 7.25−7.14 (m, 2H), 7.14−7.02 (m, 3H), 6.92−6.83 (m, 1H), 6.03 (d, *J* = 7.8 Hz, 1H), 4.81 (q, *J* = 7.3 Hz, 1H), 4.29 (d, *J* = 10.4 Hz, 1H), 3.74 (AB system, *J* = 14.4 Hz, 2H), 3.58 (dd, *J* = 10.4, 8.1 Hz, 1H), 3.45−3.26 (m, 2H), 3.09−2.92 (m, 1H), 2.82−2.55 (m, 3H), 2.34 (dq, *J* = 13.9, 6.8 Hz, 1H), 2.04 (dq, *J* = 13.9, 7.2 Hz, 1H), 1.81 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 143.8 (q, J_{C-F} = 0.9 Hz), 139.0, 135.5, 133.4, 132.8, 132.7, 130.3, 130.2, 129.79 (q, J_{C-F} = 32.6 Hz), 129.1, 128.51, 128.48, 128.3, 127.6, 127.34, 127.27, 126.5, 126.0 (q, J_{C-F} = 3.7 Hz), 125.8, 124.9 (q, J_{C-F} = 272.0 Hz), 123.9, 70.5, 66.3, 59.5, 53.5, 49.6, 46.5, 38.2, 29.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.4 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{34}H_{32}BrF_3N_3O$ 634.1681 [M + H$^+$]; found: 634.1684 [M + H$^+$].

The hydrochloride salt **10·HCl** was obtained by addition of hydrogen chloride solution (2.0 M) in diethyl ether to a solution of amine **10** in diethyl ether at 0 °C. The solid was filtered in vacuum, washed with cold diethyl ether, and collected in quantitative yield.

Synthesis of ((1*S*,2*S*,10b*S*)-2-((1,3-Dioxolan-2-yl)methyl)-1-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-3(2*H*)-yl)(phenyl)methanone (11). A solution of aldehyde **2q** (1.218 mmol) and catalyst **3A** (0.122 mmol) in

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dichloromethane (1.22 mL) was prepared in a screw vial. The solution was cooled at 0 °C, and then, dipole **1a′** (0.609 mmol) was added. The reaction was stirred at 0 °C for 24 h. Then, 2-ethyl-2-methyl-1,3-dioxolane (18.27 mmol) and 4-methylbenzenesulfonic acid monohydrate (0.183 mmol) were added successively, and the reaction mixture was stirred at room temperature overnight. The solvent and excess of 2-ethyl-2-methyl-1,3-dioxolane were eliminated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (hexane:AcOEt 7:3) affording the acetal **11** in as an orange foam (235 mg, 76%). $[\alpha]^{20}_{D}$ = +50.7 (*c* 0.33, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.82 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.50−7.32 (m, 5H), 7.18−7.05 (m, 2H), 6.93−6.85 (m, 1H), 6.04 (d, *J* = 7.8 Hz, 1H), 4.94 (td, *J* = 8.2, 5.0 Hz, 1H), 4.89 (t, *J* = 4.3 Hz, 1H), 4.31 (d, *J* = 10.4 Hz, 1H), 3.75 (dd, *J* = 10.6, 8.2 Hz, 1H), 3.71−3.59 (m, 4H), 3.44−3.23 (m, 2H), 3.02 (ddd, *J* = 17.1, 12.1, 5.3 Hz, 1H), 2.76 (dt, *J* = 16.2, 2.8 Hz, 1H), 2.62 (dt, *J* = 14.0, 4.7 Hz, 1H), 2.16 (ddd, *J* = 13.9, 8.3, 4.5 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 169.7, 143.8 (q, J_{C-F} = 1.7 Hz), 135.4, 133.3, 132.7, 130.1, 129.32 (q, J_{C-F} = 32.5 Hz), 129.27, 128.34, 128.30, 127.5, 127.1, 126.5, 125.6, 125.5 (q, J_{C-F} = 3.9 Hz), 124.1 (q, J_{C-F} = 272.0 Hz), 101.8, 70.6, 64.38, 64.35, 64.0, 58.5, 49.4, 40.5, 29.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.2 (s). HRMS (FAB+) *m*/*z*: calcd for $C_{29}H_{28}F_3N_2O_3$ 509.2052 [M + H^+]; found 509.2045 [M + H^+].

Synthesis of *N*-((1*S*,2*S*)-3-(1,3-Dioxolan-2-yl)-1-((*S*)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-(trifluoromethyl)phenyl)-propan-2-yl)benzamide (12). To a stirred solution of acetal **11** (135 mg, 0.27 mmol) in MeOH (1.8 mL) under argon atmosphere was added a freshly prepared 0.1 M THF solution of SmI_2 (14.0 mL, 1.40 mmol) dropwise at room temperature. After stirring for 30 min at room temperature, the reaction solution was poured into saturated $NaHCO_3$(aq), and the organic solvents were eliminated under reduced pressure. The residue was extracted with ethyl acetate, and then, the organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuum. The resulting residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH 97:3) affording the amine **12** as a yellow foam (113 mg, 82%). $[\alpha]^{20}_{D}$ = −2.4 (*c* = 0.59, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.48−7.24 (m, 5H), 7.09−6.92 (m, 3H), 6.83 (d, *J* = 6.8 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 5.12 (qd, *J* = 8.6, 3.4 Hz, 1H), 4.94 (t, *J* = 4.7 Hz, 1H), 4.27 (d, *J* = 4.9 Hz, 1H), 3.95−3.72 (m, 5H), 3.43 (dt, *J* = 12.9, 5.2 Hz, 1H), 2.90 (ddd, *J* = 13.1, 8.5, 5.0 Hz, 1H), 2.81−2.67 (m, 1H), 2.56 (dt, *J* = 16.3, 4.9 Hz, 1H), 1.99 (ddd, *J* = 14.4, 5.3, 3.5 Hz, 1H), 1.73 (ddd, *J* = 14.4, 8.5, 4.3 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 166.5, 145.3 (q, *J* = 1.7 Hz), 138.5, 135.8, 134.2, 131.2, 130.0, 129.7, 129.2 (q, *J* = 32.4 Hz), 128.2, 126.6, 125.9, 125.58, 125.55, 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.0 Hz), 102.8, 64.9, 64.6, 59.2, 52.2, 47.3, 41.5, 36.5, 29.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.4 (s). HRMS (ESI+) *m*/*z*: calcd for $C_{29}H_{30}F_3N_2O_3$ 511.2189 [M + H^+]; found 511.2203 [M + H^+].

Synthesis of Methyl-(*E*)-3-((1*R*,2*R*,10b*R*)-3-Benzoyl-2-benzyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinolin-1-yl)-acrylate (13). A solution of aldehyde **5k** (96.4 mg, 0.243 mmol) and methyl (triphenylphosphoranylidene)acetate (97.63 mg, 0.292 mmol) in dichloromethane was stirred at room temperature overnight. The resulting residue was purified by silica gel flash chromatography (cyclohexane/AcOEt 7:3) to afford **13** as a white foam (99 mg, 90%). $[\alpha]^{20}_{D}$ = −32.6 (*c* = 0.31, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.83 (m, 2H), 7.48−7.35 (m, 3H), 7.33−7.04 (m, 8H), 6.96 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.94−6.88 (m, 1H), 5.59 (d, *J* = 15.5 Hz, 1H), 4.67 (ddd, *J* = 8.8, 7.2, 4.1 Hz, 1H), 4.16 (d, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.40−3.23 (m, 2H), 3.16 (q, *J* = 9.7 Hz, 1H), 2.94−2.74 (m, 2H), 2.59−2.46 (m, 1H), 2.42−2.27 (m, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 169.9, 166.0, 145.1, 136.8, 135.5, 133.2, 132.9, 130.2, 130.1, 128.4, 128.3, 128.2, 127.6, 127.3, 127.1, 126.8, 125.9, 124.4, 66.7, 65.7, 53.6, 51.6, 48.9, 38.7, 29.3. HRMS (ESI+) *m*/*z*: calcd for $C_{29}H_{29}N_2O_3$ 453.2159 [M + H^+]; found 453.2172 [M + H^+].

Synthesis of *N*-((*R*)-1-((1*R*,11b*R*)-4-Oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)-2-phenylethyl)-benzamide (14). Step 1 follows: To a solution of alkene **13** (44.2 mg, 0.097 mmol) in methanol (0.42 mL) was added Pd/C (10%) (10.3 mg, 10 mol %). The mixture was stirred under hydrogen pressure (1 atm) at room temperature overnight. The reaction mixture was filtered through a Celite pad and the cake washed with methanol. The filtrate was concentrated at reduced pressure. The obtained aliphatic ester was used in the next step without further purification. Step 2 follows: To a stirred solution of crude aliphatic ester in MeOH (0.50 mL) under argon atmosphere was added a freshly prepared 0.1 M THF solution of SmI_2 (3.9 mL, 0.39 mmol) dropwise at room temperature. After stirring for 1 h at room temperature, the reaction solution was poured into saturated $NaHCO_3$(aq), and the organic solvents were eliminated under reduced pressure. The residue was extracted with ethyl acetate, and then, the organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuum. The resulting residue was purified by silica gel flash chromatography (hexane/AcOEt 1:3) to afford **14** as a yellow oil (21 mg, 52%). $[\alpha]^{20}_{D}$ = +29.5 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.32 (m, 1H), 7.29−7.06 (m, 9H), 7.01−6.88 (m, 3H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.33 (d, *J* = 8.2 Hz, 1H), 5.03−4.95 (m, 1H), 4.87−4.75 (m, 1H), 4.61−4.47 (m, 1H), 3.03−2.50 (m, 7H), 2.30−2.09 (m, 2H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.2, 166.1, 137.3, 135.4, 134.9, 133.9, 131.2, 129.3, 128.4, 128.1, 126.8, 126.6, 126.4, 125.5, 59.3, 49.5, 39.6, 38.6, 37.8, 28.9, 28.7, 23.4 (two peaks overlaps). HRMS (ESI+) *m*/*z*: calcd for $C_{28}H_{29}N_2O_2$ 425.2209 [M + H^+]; found 425.2223 [M + H^+].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete screening tables; IR spectra of **1a** and **1a′**; TGA studies; NMR spectra of all new compounds; SFC chromatograms; X-ray ORTEP and crystallographic data for compounds **1a′**, **9·HCl**, and **10·HCl** (CIF); collections of ^{1}H RMN experiments for dienamine formation and obtained by us using Wang's reaction conditions; comparison between $[\alpha]$ values measured and described in the literature; approach models and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The aldehyde can be isolated and purified following the procedure used by Maruoka's group in ref 13a. However, the evaluation of the enantiomeric excess by SFC of the aldehyde was not possible.

(17) The NMR spectra of the complex mixtures obtained from **2i** and **2j** contain the signals corresponding to compounds **4i** and **4j**.

(18) This comparison revealed that both types of compounds are enantiomers, which is understandable taking into account the (*S*)-configuration of the catalysts **3A** and **3B** used in our experiences (see approach models in Supporting Information).

(19) Initially, the enantioselectivity of these reactions was determined on the alcohols resulting in the $NaBH_4$ reduction of the resulting aldehydes. Once separated by flash chromatography, the yield of the major product could be established. However, as this reduction did not work in the presence of TBAB (required for exclusively obtaining **5k**), we performed the *in situ* transformation of the aldehydes into the a,b-unsaturated esters by reaction with Ph_3PCHCO_2Et. These olefin mixtures could not be separated, and their combined yield after purification is indicated in entries 1−8 in Table 2.

(20) CCDC 1004254 (**1a′**) contains the crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk.

(21) CCDC 1004255 and 1004256 (**10·HCl** and **9·HCl**, respectively) contain the crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk.

(22) On the other hand, the ^1H NMR spectra obtained by mixing the β-alkyl enal **2j** with **3B** did not reveal the formation of any significant amount of its corresponding dienamine **IIB** (see Supporting Information), which could be partially responsible for the absence of **6j** in the reaction conducted under the conditions of entry 12 in Table 1.

(23) Strictly, this comparison should be carried out in the same solvent. However, we have checked that the solvent did not induce significant differences in the case of dienamine **IA** and iminium **IIA** (see Supporting Information).

(24) The presence of the benzoyl group at azomethine imine **1a** seems to be crucial in determining that its relative reactivity with iminium and dienamine species was not too different, thus justifying the observed competition, undetected with other dipoles. In this sense, we have calculated the energy associated to the frontier orbitals of the dipole resulting when the benzoyl group at **1a** is changed by the Ph one (E_{HOMO} = −4.95 eV, E_{LUMO} = −2.09 eV). These values, which are similar to those calculated for azomethine ylides, would also predict a much higher reactivity with the iminium species than with the dienamines. Taking into account that the benzoyl group should reduce the nucleophilicity of the nitrogen at the azomethine imine **1a** (and therefore its facility to react with iminium species), it is not unexpected that its reactivity with dienamines becomes competitive, thus justifying the chemoselectivity control difficulties observed for this dipole.

(25) However, the formation of the hemiacetal **1a′** from **1a** should be very slow because the addition of 1.0 equiv of water to the reaction mixture with the dried dipole **1a** had any influence in the final ratio **5k**:**6k**, which is similar to that of entry 9 at Table 2.

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(27) Similar studies to Scheme 7, performed by adding **3B** to mixtures of **2k** with TBAB, demonstrated that the signals corresponding to the dienamine were not detected after 30 min (see spectrum in Supporting Information).

(28) Theoretical calculations about the stability of the iminium species **I** where the OH^- is acting as the counterion were unsuccessful because the couple of ions always collapse into the hemiaminal structure. By contrast, similar calculations with the Br^- as the counterion can be optimized, which suggest the higher stabilization of the iminium species **I** (see Supporting Information).

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(30) During our optimization we had observed the instability of aldehyde **2k**, which was partially decomposed under the conditions of the experiment, which determined the use of 2.0 equiv of **2k** in our trials.

(31) As this is the predominant structure of dipoles which are not freshly prepared, it was probably used in the experiences of ref 15,

because the authors indicate that the samples of dipoles were provided by Professor Maruoka.
(32) We found [α] values ranging between +35 and +89 in our samples, whereas the values described in ref 15 are close to zero (see Supporting Information).
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