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Investigation of Squaramide Catalysts in the Aldol Reaction En Route to Funapide

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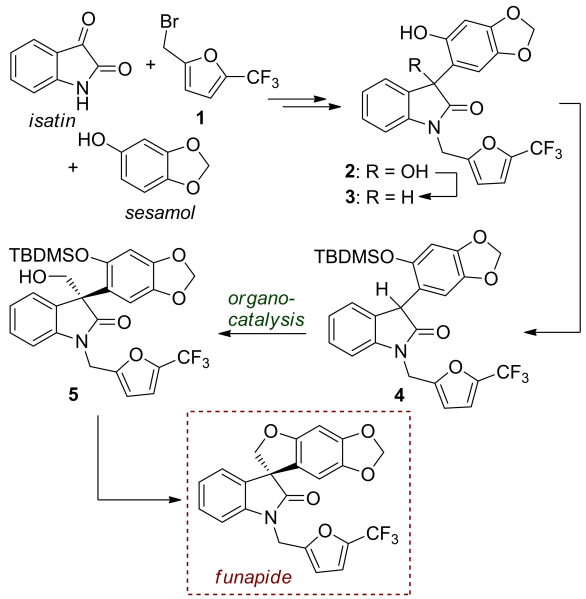
Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday

Funapide is a 3,3'-spirocyclic oxindole with promising analgesic activity. A reported pilot-plant scale synthesis of this chiral compound involves an asymmetric aldol reaction, catalyzed by a common bifunctional thiourea structure. In this work, we show that the swapping of the thiourea unit of the catalyst for a tailored squaramide group provides an equally active, but rewardingly more selective, catalyst for this aldol reaction (from 70.5 to 85% *ee*). The reaction was studied first on a model oxindole compound. Then, the set of optimal conditions was applied to the target funapide intermediate. The applicability of these conditions seems limited to oxindoles bearing the 3-substituent of funapide. Exemplifying the characteristics of target-focused methodological development, this study highlights how a wide-range screening of catalysts and reaction conditions can provide non-negligible improvements in an industrially viable asymmetric transformation.

Introduction

The activity of funapide (Scheme 1) as antagonist of the $Na_V1.7$ sodium channel protein makes this compound a promising analgesic.[1] Disclosed by Xenon Pharmaceuticals under development names XEN-402 and XPF-002, it advanced to phase II clinical trials, wherein topical application reduced pain in patients suffering from primary erythromelalgia, and in patients suffering from postherpetic neuralgia.[2] It received orphan drug status by FDA for the treatment of erythromelalgia. In 2012, the compound was in-licensed to Teva, turning its identification to TV-45070. After discontinuation by Teva in 2017,[3] another company (Flexion Therapeutics) acquired from Xenon the global rights to its development and commercialization. In a new proprietary hydrogel formulation (FX-301), funapide has recently entered a phase I clinical trial for the treatment of post-operatory pain.[4]



Scheme 1. Funapide: reported plant scale synthesis based on an organocatalytic aldol reaction.

Structurally speaking, funapide is a 3,3'-spirocyclic oxindole bearing a (5-(trifluoromethyl)furan-2-yl)methyl appendage at nitrogen, and a sesamol-derived subunit. It presents (*S*)-absolute configuration at the spirocyclic carbon. Progressing from a first racemic synthesis, which mandated a late stage resolution of the enantiomers of funapide by chiral SMB chromatography,[5] Xenon developed a first generation enantioselective approach, built around an asymmetric phase-transfer catalyzed alkylation step.[6] Some shortcomings of this synthesis - length, extensive use of protecting groups, introduction of the

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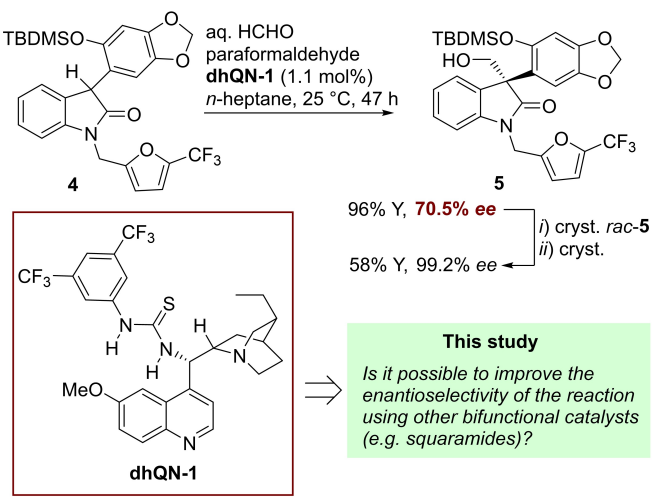
furyl side chain with a genotoxic alkylating agent at a late stage - prompted Teva to attempt an alternative enantioselective process. These efforts led up to the sequence briefly sketched in Scheme 1,[7] which, bypassing some of the above-mentioned issues, was amenable to the preparation of funapide on a plant scale.

In short, alkylation of isatin with **1**, followed by addition of sesamol, affords the 3-hydroxy oxindole **2**. Reductive dehydroxylation giving **3**, and protection of the phenolic oxygen, delivers the substrate **4** for the enantioselective step of the synthesis, an asymmetric aldol reaction with formaldehyde catalyzed by a dihydroquinine (dhQN)-derived bifunctional organocatalyst.[8] The aldol adduct **5** is then converted to funapide in two steps (deprotection and cyclization through activation of the primary alcohol).

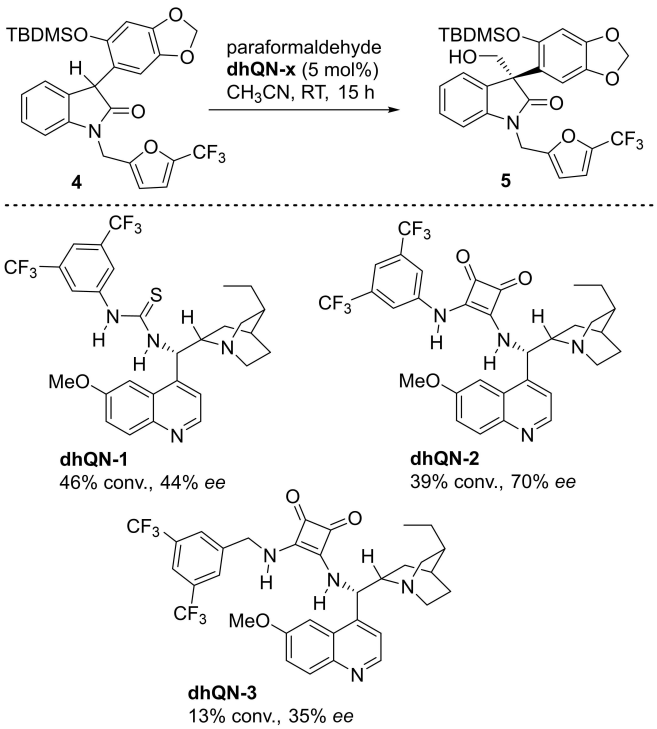
The enantioselective aldol step (Scheme 2) of the sequence involves the reaction of TBDMS protected substrate **4** with an aqueous formaldehyde/paraformaldehyde mixture, promoted by the common dihydroquinine derived thiourea catalyst **dhQN-1**[9,10] at a relatively low loading (1.1 mol%). The reaction is performed at 25 °C as a slurry in *n*-heptane, allowing the recovery of **5** in 96% crude yield and 70.5% ee by filtration. Removal of racemic-**5** by crystallization from MeOH/AcOH, followed by crystallization, induced by addition of water to the mother liquors, results in the obtainment of pure **5** in 58% yield, with an upgraded 99% *ee*. Despite its overall effectiveness, which makes it a remarkable example of application of asymmetric organocatalysis on scale,[11] this aldol reaction is characterized by a relatively poor enantioselectivity (70.5% *ee*). In connection with our interest on the use of bifunctional catalysts like **dhQN-1** to effect catalytic asymmetric reactions,[12] we wondered if variations in the catalyst structure, perhaps combined with tailored conditions, could provide an improvement in the enantiomeric excess obtained in this synthetic step. In this paper, we show that common squaramide catalysts, related to thiourea **dhQN-1** but omitted from the reported catalysts screening,[7] can indeed offer rewardingly higher enantioselectivities in this reaction. It is worth stressing that organocatalytic enantioselective reactions of 3-substitued oxindoles with formaldehyde reported in the literature[13] typically leverage an electron withdrawing carbamoyl group (*e.g.* Boc) at the oxindole nitrogen. These reported procedures are thus not readily adaptable to substrate **4**.

Results and Discussion

At the beginning of this study, since hydrogen-bonding interactions between the catalyst and the substrates play a key role in the enantioinduction, we envisioned the use of catalysts carrying double H-bond donors different from a thiourea. Our choice fell on squaramides.[14,15] The geometric and electronic properties of the H-bond network offered by these units differ slightly from their thiourea counterparts. More importantly, bifunctional squaramides are well known for their modular and relatively easy preparation,[16] and proficiency in a variety of asymmetric transformations. However, we were concerned about the poor solubility in *n*-heptane of many of the catalysts we planned to test. Thus, we decided to perform a preliminary screening of catalysts using acetonitrile as solvent, wherein the reaction catalyzed by **dhQN-1** affords product **5** with approximately 45–50% *ee*. Paraformaldehyde was used as the only aldehyde source in these reported experiments.[7] After successfully reproducing these results (Scheme 3), we were delighted to observe a remarkable improvement, in terms of enantiomeric excess, using the corresponding *N*-aryl squaramide **dhQN-2**[17] as catalyst. Conversely, catalyst **dhQN-3**, carrying the equally



Scheme 2. Catalytic asymmetric aldol reaction used in the synthesis of funapide.



Scheme 3. Preliminary screening of catalysts.

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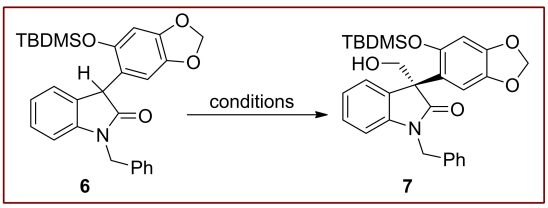
common 3,5-bis(trifluoromethyl) benzyl structural motif,[18] gave worse results.

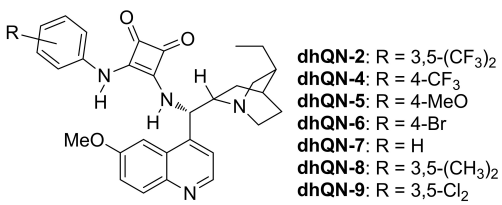
With these promising results in hand, we switched to using the *N*-benzyl oxindole derivative **6** as a model compound for a thorough screening of catalysts and reaction conditions (Table 1). This compound can be prepared (see Supporting Information, section 5.4) using cheap benzyl bromide as alkylating agent, instead of the relatively expensive furanylmethyl bromide **1** required for funapide precursor **4**. In order to confirm that catalytic studies carried out using the model compound **6** can be extended to the synthetic intermediate **4**, we firstly verified that **4** and **6** present similar reaction profiles. A comparison of the first three entries of Table 1 with the results displayed in Scheme 3 shows that this is indeed the case, since similar trends in terms of enantioselectivity were observed for the two substrates. After a wider-range screening of quinine-derived catalysts, the *N*-aryl squaramide derivative **dhQN-2** was confirmed as the lead catalyst (see Supporting Information, section 1). Subsequently, we tested the related *para*-trifluoromethylphenyl derivative **dhQN-4**, which seemed to give a small improvement in terms of enantiomeric excess (entry 4). Thus, we tried two additional *para*-substituted *N*-aryl squaramides (**dhQN-5,6**) and the aniline derived **dhQN-7** in the reaction (entries 5–7). However, these experiments did not provide any clear improvement. In parallel, a solvent screening performed with the parent catalyst **dhQN-2** suggested toluene as a promising medium to optimize the enantioinduction offered by this and related catalysts, although the reaction was sluggish.

Fortunately, resorting to the strategy used for funapide, that is, applying a mixture of paraformaldehyde and aqueous formaldehyde as the aldehyde source, restored sufficient

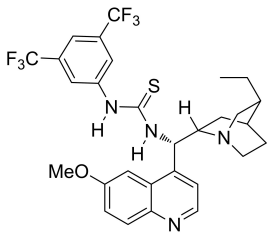
Table 1. Screening of catalysts and reaction conditions in the aldol reaction of model substrate **6** with formaldehyde. Representative results.



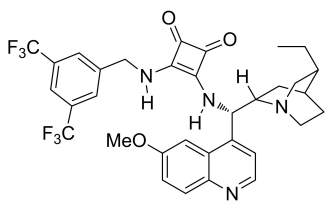
6 **7**



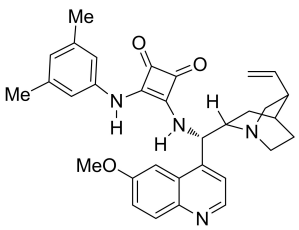
dhQN-2: R = 3,5-$(CF_3)_2$
dhQN-4: R = 4-CF_3
dhQN-5: R = 4-MeO
dhQN-6: R = 4-Br
dhQN-7: R = H
dhQN-8: R = 3,5-$(CH_3)_2$
dhQN-9: R = 3,5-Cl_2



dhQN-1



dhQN-3



QN-8

Entry[a]	Catalyst (mol%)	Formaldehyde source[b]	Solvent (M)	t [h]	Conv. [%][c]	ee [%][d]
1	**dhQN-1** (10)	A	CH_3CN (0.1)	15	59	45
2	**dhQN-2** (10)	A	CH_3CN (0.1)	15	67	66
3	**dhQN-3** (10)	A	CH_3CN (0.1)	15	n.d.	23
4	**dhQN-4** (10)	A	CH_3CN (0.1)	15	65	76
5	**dhQN-5** (10)	A	CH_3CN (0.1)	15	28	75
6	**dhQN-6** (10)	A	CH_3CN (0.1)	15	29	78
7	**dhQN-7** (10)	A	CH_3CN (0.1)	15	43	76
8	**dhQN-1** (10)	B	toluene (0.1)	15	71	48
9	**dhQN-2** (10)	B	toluene (0.1)	15	54	67
10	**dhQN-4** (10)	B	toluene (0.1)	15	44	76
11	**dhQN-5** (10)	B	toluene (0.1)	15	44	75
12	**dhQN-6** (10)	B	toluene (0.1)	15	24	81
13	**dhQN-7** (10)	B	toluene (0.1)	15	16	91
14	**dhQN-8** (10)	B	toluene (0.1)	15	52	93
15	**dhQN-9** (10)	B	toluene (0.1)	15	24	85
16	**dhQN-8** (10)	B	toluene (0.2)	15	60	86
17	**dhQN-8** (10)	B	toluene (0.2)	39	73	85
18	**dhQN-8** (10)	C	toluene (0.2)	39	79	90
19[e]	**dhQN-8** (1)	C	toluene (0.5)	42	83[f]	89
20[e]	**dhQN-8** (1)	B	n-heptane (0.17)	60	<10	–
21[e]	**QN-8** (1)	C	toluene (0.5)	144	70	90

[a] Conditions: oxindole **6** (0.05 mmol), catalyst (x mol%), solvent, formaldehyde (0.1 mmol, 2 equiv.), RT. After the corresponding time, the reaction mixture is filtered on silica and evaporated. [b] A: paraformaldehyde (0.1 mmol, 2 equiv.). B: paraformaldehyde + aq. formaldehyde 37% w/w (0.05 + 0.05 mmol, overall 2 equiv.). C: aq. formaldehyde 37% w/w (0.1 mmol, 2 equiv.). [c] Determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by CSP HPLC. [e] 0.2 mmol scale reaction. [f] Isolated yield after purification by column chromatography on silica gel.

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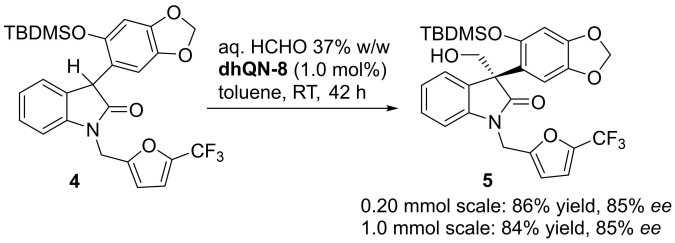
reactivity in toluene, allowing performing a second catalyst screening in this reaction medium (entries 8–15). The general trend of the performances displayed by catalysts **dhQN-1-7** in toluene parallels the results obtained in acetonitrile, in terms of enantioselectivities. In more detail, the *N*-aryl squaramides were confirmed as superior catalysts compared to the thiourea **dhQN-1**, and catalysts **dhQN-5-7** generally gave better results than the 3,5-bis-(trifluoromethyl)phenyl derivative **dhQN-2**. Moreover, we included in this second screening two new 3,5-disubstituted aniline derived structures, **dhQN-8** and **dh-QN-9** (entries 14 and 15). These catalysts, which were tested to confirm the negative influence of 3,5-disubstituted anilines on catalyst performances, gave instead good results. The 3,5-dimethyl aniline **dhQN-8** provided the best enantioselectivity observed so far for product **7** (entry 14, 93% *ee*), accompanied by a moderate conversion. Thus, we started to optimize the remaining reaction parameters in order to increase the conversion of substrate **6** in the reaction. While using a more concentrated reaction mixture and an increased reaction time was not useful (entries 16 and 17), the application of both of these variations in combination with the sole aqueous formaldehyde as aldehyde source turned out to be fruitful (entry 18).[19] Fortunately, lowering of the catalyst loading to the 1 mol% used in funapide synthesis was rather straightforward. Slight increases in reaction concentration and time were sufficient to obtain the aldol adduct **7** in 83% isolated yield and 89% *ee*, even at this rather low loading (entry 19). **dhQN-8** and most other squaramide catalysts are poorly soluble in toluene, as visually observed in the reactions performed at 10 mol% loading. We speculate that only a small portion of these catalysts is available in the homogeneous mixture of the reactions performed at 10 mol% loading, thus justifying the comparable results of reactions performed at very different loadings. Conversely, the lower solubility of **dhQN-8** compared to thiourea **dhQN-1** in nonpolar media made not possible to use *n*-heptane as reaction solvent (entry 20). At last, we tested catalyst **QN-8** derived from quinine (entry 21), instead of dihydroquinine. Teva mentioned that a quinine-derived catalyst related to thiourea **dhQN-1** had similar performances in the aldol reaction used for funapide synthesis, while being noticeably cheaper and more readily available.[10] In our case, **QN-8** performed in fact rather well, delivering the aldol adduct **7** with even slightly higher enantioselectivity than **dhQN-8** (entry 19). However, its activity seems lower (compare entry 19 *vs* 21). It afforded only 70% conversion in product **7** even after prolonged reaction time.

We then tested if the protecting group at the phenolic oxygen is required to achieve good results in this reaction, as its unnecessity would alluringly remove two concession steps from the synthetic sequence (Scheme 1). Unfortunately, none of the representative catalysts tested in the reaction of the unprotected form of **6** with formaldehyde was able to provide promising enantioselectivity. On the other hand, a reaction on a potential funapide precursor unprotected at both nitrogen and phenolic oxygen was reported to give a racemic aldol adduct when catalyzed by **dhQN-1**.[7]



Scheme 4. Optimized conditions in the synthesis of funapide precursor **5**.

We thus moved to test the applicability of the optimal conditions to the protected funapide precursor **4**. Preliminary tests (see Supporting Information, section 3) showed that the enantioselectivity trend offered by a set of representative catalysts matches the trend observed for the model substrate **6**. Thus, **dhQN-8** appears to be the optimal catalyst also in this case, and **dhQN-4** (the *para*-trifluoromethyl derivative) gives higher enantioselectivity than the 3,5-bis(trifluoromethyl)phenyl counterpart **dhQN-2**. The superior performances of squaramides, compared to thiourea **dhQN-1**, already suggested by the experiments reported in Scheme 3, were ultimately confirmed. As additional observations, preliminary tests indicated that this pronucleophile substrate **4** is slightly more reactive than model **6**, and at the same time its product **5** is more prone to racemization than **7**. Equilibration through a retro-aldol reaction was considered the most plausible pathway accounting for the racemization, which was observed only at prolonged reaction times. Nevertheless, the optimal conditions devised for model **6** could be finally directly translated to funapide precursor **4** (Scheme 4). The aldol adduct **5** was obtained in good yield and enantioselectivity, though slightly lower than model **7**. Importantly the reaction gave essentially the same results on a preparative scale, wherein, thanks to the low catalyst loading, 5.20 mg of catalyst **dhQN-8** were sufficient to produce 474 mg of product **5**.

Unfortunately, an attempt to extend this methodology to a simpler oxindole substrate lacking the sesamol unit, that is 1-benzyl-3-phenyl oxindole, was not successful. The enantioselectivity trend provided by a few representative catalysts in this reaction followed the one observed with substrates **4** and **6** (that is, **dhQN-8** > **dhQN-4** > **dhQN-2** ≫ **dhQN-1**). However, the best catalyst (**dhQN-8**) afforded the product with only a modest 56% *ee* (see Supporting Information, section 4).

Conclusion

In summary, we reinvestigated the key aldol step of the asymmetric synthesis of the analgesic funapide, currently performed with a common thiourea catalyst and characterized by a moderate enantioselectivity (70.5% *ee*). Using a model compound, a screening of catalysts identified the squaramide catalyst **dhQN-8** which, at 1 mol% loading, could produce the aldol adduct with enhanced enantiomeric excess (89% *ee*) under modified reaction conditions. These conditions could be

successfully applied to the target funapide substrate. Overall, this study shows how a wide-range screening of catalysts and reaction conditions has the potential to provide non-negligible improvements in an industrially viable asymmetric transformation. On the other hand, the specificity of the oxindole structures rendering good results in the reaction highlights the features of a target-oriented approach to methodological development.

Experimental Section

Optimized procedure for the catalytic enantioselective aldol reactions: To a test tube, equipped with a magnetic stirring bar, were sequentially added the substrate **6** (94.7 mg, 0.20 mmol) or **4** (106.3 mg, 0.20 mmol), catalyst **dhQN-8** (1.00 mg, 0.0020 mmol, 1.0 mol%), toluene (0.40 mL) and aqueous formaldehyde (37% w/w, 30 μL, 0.40 mmol). The resulting mixture was stirred gently for 42 h at RT (ca. 30 °C), then directly purified by chromatography on silica gel, affording compound **7** or **5** as a white solid.

(*S*)-1-Benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one (7): Following the optimized procedure, the title compound was obtained as a white solid in 83% yield (84.2 mg), after column chromatography on silica gel (*n*-hexane/EtOAc 8:2→75:25). The enantiomeric excess of **7** (89% *ee*) was determined by CSP HPLC (Chiralcel OD-H; flow: 0.75 mL/min; n-hexane/i-PrOH 90:10; UV detector: 254 nm): t_{maj} = 18.3 min; t_{min} = 14.4 min. m.p. 157–159 °C; $[\alpha]_D^{25°C} = -92.2$ ($c = 0.35$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 4H), 7.29–7.24 (m, 2H), 7.16–7.11 (m, 1H), 6.95–6.90 (m, 2H), 6.77 (dt, J = 7.8, 0.7 Hz, 1H), 6.39 (s, 1H), 5.95 (d, J = 1.6 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.54 (d, J = 15.3 Hz, 1H), 4.39 (d, J = 15.4 Hz, 1H), 4.27 (dd, J = 11.6, 10.2 Hz, 1H), 3.74 (dd, J = 11.6, 10.2 Hz, 1H), 2.89 (dd, J = 10.1, 2.7 Hz, 1H), 0.72 (s, 9H), 0.06 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (APT, 100 MHz, $CDCl_3$): δ = 178.9, 149.0, 147.1, 142.5, 141.2, 136.0, 131.3, 128.8, 127.9, 127.7, 127.4, 123.1, 122.7, 118.4, 109.5, 109.1, 101.3, 100.3, 66.5, 55.6, 43.9, 26.2, 19.0, −3.5, −3.6; IR (ATR): $\tilde{\nu}$ = 3478 (br w), 3396 (br w), 2957 (w), 2929 (w), 2901 (w), 2857 (w), 1700 (vs), 1610 (m), 1505 (m), 1486 (s), 1465 (s), 1428 (m), 1361 (s), 1247 (s), 1197 (vs), 1169 (s), 1044 (s), 841 (vs), 786 (vs), 735 (vs), 697 (vs) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_5Si + Na^+$: 526.2020 $[M + Na]^+$; found: 526.2020.

(*S*)-3-(6-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one (5):[7] Following the optimized procedure, the title compound was obtained as a white foam in 86% yield (97.1 mg), after chromatography on silica gel (*n*-hexane/EtOAc 75:25). The enantiomeric excess of **5** (85% *ee*) was determined by CSP HPLC (Chiralcel OD-H; flow: n-hexane/i-PrOH 90:10; UV detector: 254 nm): t_{maj} = 15.2 min; t_{min} = 10.7 min. Application of the optimized procedure on a 1.00 mmol scale, that is, using 531.6 mg of substrate **4** (1.00 mmol), 5.20 mg of catalyst **dhQN-8** (0.01 mmol, 1 mol%), 1.00 mL of toluene, and 148 μL of aq. formaldehyde (37% w/w, 2.00 mmol), afforded the title compound in 84% yield (474.3 mg) and 85% *ee*. m.p. 139–140 °C; $[\alpha]_D^{25°C} = -41.5$ ($c = 0.38$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (td, J = 7.6, 1.5 Hz, 1H), 7.19 (br s, 1H), 6.98 (td, J = 7.4, 0.9 Hz, 1H), 6.94 (br d, J = 7.4 Hz, 1H), 6.90 (br d, J = 7.8 Hz, 1H), 6.72–6.69 (m, 1H), 6.38 (s, 1H), 6.36 (br d, J = 3.3 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.92 (d, J = 1.4 Hz, 1H), 5.44 (d, J = 16.4 Hz, 1H), 4.54 (d, J = 16.3 Hz, 1H), 4.23 (dd, J = 11.4, 9.8 Hz, 1H), 3.76 (dd, J = 11.4, 3.2 Hz, 1H), 2.61 (dd, J = 9.7, 3.1 Hz, 1H), 0.69 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (APT, 100 MHz, $CDCl_3$): δ = 178.4, 152.3 (q, J = 1.6 Hz), 148.9, 147.2, 141.9. 141.5 (q, J = 42.5 Hz), 141.3, 131.2, 128.1, 123.2, 123.1, 118.8 (q, J = 266.0 Hz), 118.2, 112.6 (q, J = 2.9 Hz), 109.2, 108.8, 108.6, 101.4, 100.3, 66.6, 55.6, 36.9, 26.1, 18.9, −3.6, −3.7; IR (ATR): $\tilde{\nu}$ = 3417 (br w), 2956 (w), 2931 (w), 2901 (w), 2884 (w), 2862 (w), 1702 (vs), 1613 (s), 1490 (vs), 1464 (s), 1426 (m), 1362 (s), 1318 (s), 1194 (vs), 1166 (vs), 1134 (br vs), 1102 (vs), 1036 (vs), 860 (vs), 837 (vs), 821 (vs), 785 (vs), 753 (vs), 741 (vs), 699 (m), 678 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}F_3NO_6Si + Na^+$: 584.1687 $[M + Na]^+$; found: 584.1697.

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Conflict of Interest

The authors declare no conflict of interest.

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