Asymmetric Synthesis of Adjacent Tri- and Tetrasubstituted Carbon Stereocenters: Organocatalytic Aldol Reaction of an Hydantoin Surrogate with Azaarene 2-Carbaldehydes.

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Abstract: The first organocatalytic diastereo- and enantioselective addition of N^3-Aryl 2-benzylthio-3,5-dihydroimidazol-4-ones, generated from racemic amino acid derivatives, to C-2 substituted azaarene N-oxide aldehydes has been developed. The reaction affords a series of valuable *syn*-aldol adducts with heteroatom-functionalized contiguous quaternary-tertiary stereocenters in an excellent stereoselective manner. A highly reactive and selective squaramide–tertiary amine catalyst taking advantage of an intramolecular-assisted activation of the squaramide by an additional free NH amide functionality promotes the reaction. Theoretical DFT (B3LYP/6-31+G(d) + CPCM (dichloromethane)) study support the mechanistic activation. Further acidic hydrolysis of the O-benzoyl protected aldol adducts yielded the corresponding optically active 2-(1-hydroxyalkyl) azaarene-functionalized quaternary hydantoins with excellent yields and without the loss of enantiopurity.

Chiral structural skeletons with tetrasubstituted stereogenic centers attached at the α *C*(sp3) position of a carbonyl moiety are prevalent in natural products or bioactive substances[i] and not unexpectedly, the type and extend of activity of these chiral compounds depend, among other factors, on the configuration of this stereocenter.[ii] For this reason, in recent years, much effort has been devoted to the search of new active methylenes with a defined structure that can be easily deprotonated and be used in the synthesis of these targets in a stereochemically-controlled manner. For instance, one of the strategies to obtain these goals is the use of α-enolizable lactam or (thio)lactone based heterocycles as pronucleophiles that under appropriate opening conditions afford α-amino acid, α-hydroxy and α-mercapto derivatives with a tetrasubstituted stereocenter (Figure 1).[iii]

Although the addition of these heterocyclic nucleophiles has been carried out satisfactorily under soft enolization conditions to different electrophiles (essentially to Michael acceptors), only two examples of asymmetric addition to aldehydes exists in the literature,[iv] in spite of that this transformation allow the formation of optically active β-hydroxy carbonyl building blocks with congested neighboring heteroatom-functionalized quaternary-tertiary stereocenters. The use of these substrates in aldol reactions is relatively limited due to the possibility of the retro-aldol reaction occurring under proton transfer conditions, especially with aromatic aldehydes that generate the aldol products more sensitive to the reverse reaction.[v]

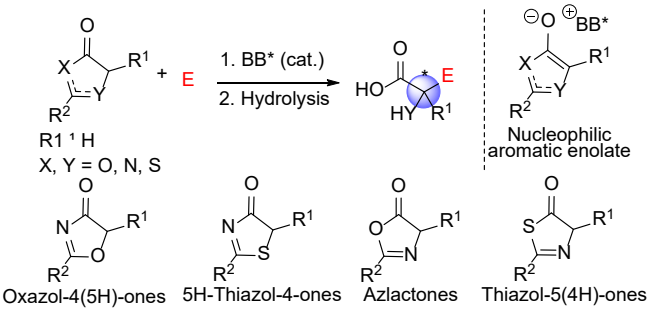


Figure 1. α-enolizable lactam or (thio)lactone-based heterocycles as pronucleophiles.

Nitrogen containing heterocycles are among the most significant structural components of pharmaceutical and agricultural chemicals.[vi] From all *N*-heterocycles approved by U.S. FDA until 2013, azaarenes containing aromatic structure core was the second most commonly used, being the C2 position the preferred one for substitution with a frequency of two-thirds.[vii] For this reason, asymmetric and non-asymmetric modifications in position 2 of the azaarene ring are being studied intensively in the last years and especially in the two last.[viii] Among all these 2-substituted azaarenes chiral 2-(oxymethyl)azaarene skeleton is frequent structural motif in optically active compounds, as agrochemicals,[ix] in biologically active compounds,[x] or, due to their stability and excellent coordinating ability with a wide range of metal ions, as chiral ligands.[xi] Some of the most powerful methods for obtaining 2-(oxymethyl)azaarenes with adjacent tertiary-tertiary stereocenters are by addition of carbon nucleophiles to azaarene-2-carbaldehydes and to a lesser extent by asymmetric transfer hydrogenation of 2-acylazaarenes.[xii] The C-C bond formation approach it has been better developed and the most efficient results have been achieved through the addition of allyl-transition metals complexes (Figure 2a),[xiii] silyl enol ethers (Figure 2b),[xiv] catalytically formed enamines (Figure 2c)[xv] and by chemoenzymatic addition of activate methylene (Figure 2d)[xvi] to azaarene-2-carbaldehydes. As far as we know, no methods that employ the addition of nucleophiles to azaarene-2-carbaldehydes that can generated effectively vicinal tertiary-quaternary stereocenters in a single reaction step has been described so far.[xvii] We envisioned that the synthesis of these targets might be achieved by an aldol reaction between heterocyclic nucleophiles and pyridine-2-carbaldehydes under soft enolization conditions.

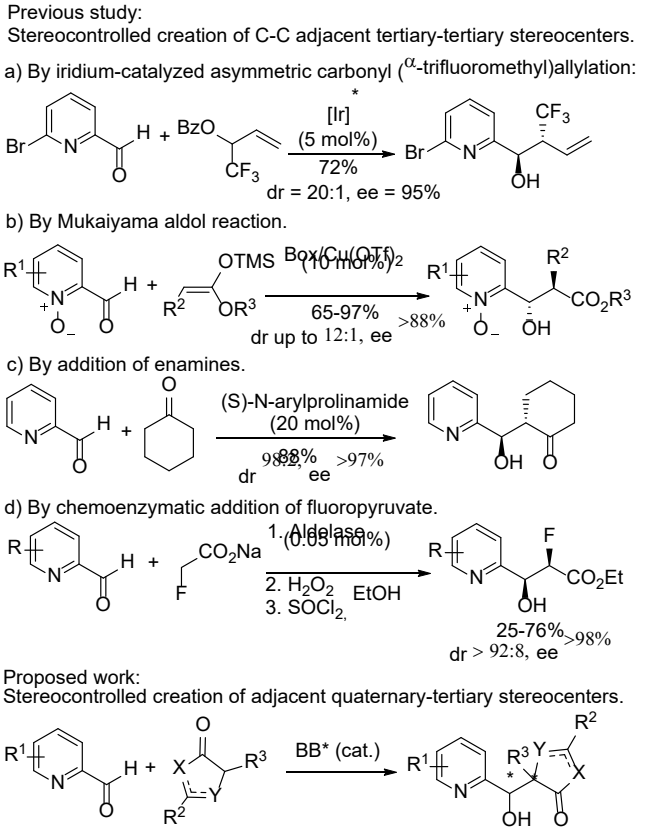


Figure 2. Previous works and our proposal for the formation of optically active quaternary-tertiary chiral 2-(oxymethyl)azaarene derivatives.

Results and Discussion

Background and working plan. Hydantoins are a privileged class of heterocyclic scaffold that are encountered as core structural elements in natural products and pharmaceuticals.[xviii] Recently, we found that heterocycles of type **I**, **II** and **III** reacts selectively with some Michael acceptors (e.g., nitroolefins and acrylate equivalents), using active squaramide-tertiary amine bifunctional catalysts, yielding 5,5-disubstituted hydantoins with a variety of substitution patterns at N_1, N_3 and C_5 positions after an acid or basic hydrolysis (Figure 3).[xix]

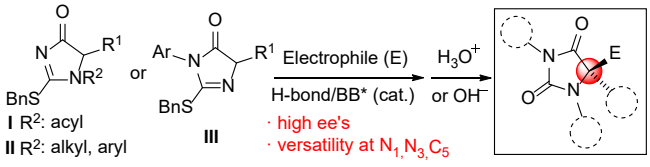
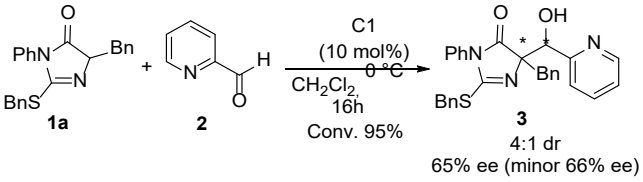


Figure 3. Advances in the asymmetric synthesis of 5,5-disubstituted hydantoins.

We thought that the development of a new and effective method that can generate optically active 5,5-disubstituted hydantoins with a vicinal tertiary (pyridin-2-yl)methan-1-ol group would be important, since it could give access to compounds with high potential medicinal value. Among all classes of hydantoins, N^3-arylated ones are of particular interest since this substitution pattern is often found in valuable pharmaceuticals that are currently being explored by many groups.[xx] For this purpose, we envisioned that the N^3-aryl 2-benzylthio-3,5-dihydroimidazol-4-ones **III** in combination with azaarenes-2-carbaldehydes could be perfect substrates to be used as pro-chiral starting materials for synthesizing optically active 2-(1-hydroxyalkyl) azaarene units having a N^3-aryl 5,5-disubstituted hydantoin functionality group in the adjacent position.

To achieve this goal, the aldol reaction between the N^3-phenyl 2-benzylthio-3,5-dihydroimidazol-4-one **1a**, prepared from DL-phenylalanine and phenylisothiocyanate, and the commercially available pyridine-2-carbaldehyde **2a** in the presence of our recently developed bifunctional catalyst **C1** was evaluated.[xxi] The reaction gave almost full conversion at 0 ºC, but the aldol product **3** was obtained with poor diastereo- and enantioselectivity.



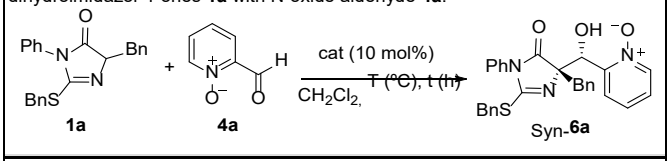
Scheme 1.

At this point, we decided to change the substrate, pyridine-2-carbaldehyde **2a**, in order to get more rigid transition state with the catalyst and be able to increase the stereoselectivity. The oxidation of **2a** to its corresponding *N*-oxide (**4a**) was successfully carried out in the Cu(II)/Box-catalyzed Mukaiyama aldol and *oxo*-hetero-Diels-Alder reactions.[xxii] It is believe that, the stronger six membered chelated structure of the reacting *N*-oxide intermediate, may induce a different reactivity and selectivity compared with the non-oxidized pyridine. Previously, these substrates have not been used in organocatalytic reactions and could potentially be ideal substrates to perform the aldol reaction with **1a** with high stereoselectivity.

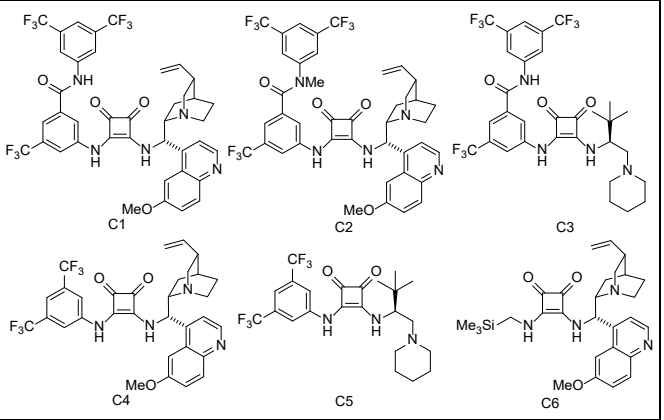
Initially, the reaction of N^3-Phenyl 2-benzylthio-3,5-dihydroimidazol-4-one **1a** with **4a** in CH_2Cl_2 at 0 ºC in the presence of 10 mol% of bifunctional catalyst **C1** (10 mol %) was examined (Table 1). Under these conditions, the reaction gave full conversion, and interestingly the reaction favored the formation of the *syn*-aldol with excellent diastereo- and excellent enantiomeric excess[xxiii] and no retro-aldol reaction was observed even after column chromatographic purification (entry 1). The *N*-methylated catalyst **C2** was less stereoselective and did do not reach full conversion (for a more detailed explanation see below), demonstrating the need of an additional free NH amide group to give good stereocontrol and reactivity (entry 3). However, the conversion and diastereoselectivity dropped significantly after replacing the aminoquinine group in **C1** with the (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine scaffold (**C3**, 82% conv., 1.5:1 dr, entry 4). Similarly, for bifunctional catalysts **C4** and **C5**, widely used in additions involving polar reactivity, the aldol reaction also

proceeded with low selectivity (entries 5 and 6). The **C6** catalyst, which previously was used by our group in the addition of 2-(cyanomethyl) azaarene N-oxides to α'-hydroxy enones, failed to give high stereocontrol. (entry 7).[xxiv] At this point, it was clear that the best reaction conditions were achieved with the catalyst **C1**. In order to achieve better stereocontrol, the reaction was run at lower reaction temperature (-10 °C) which led to a significant enhancement in the diastereoselectitity (entry 2).

Table 1. Catalyst screening for the reaction of N^3-Phenyl 2-benzylthio-3,5-dihydroimidazol-4-ones **1a** with N-oxide aldehyde **4a**.[a]



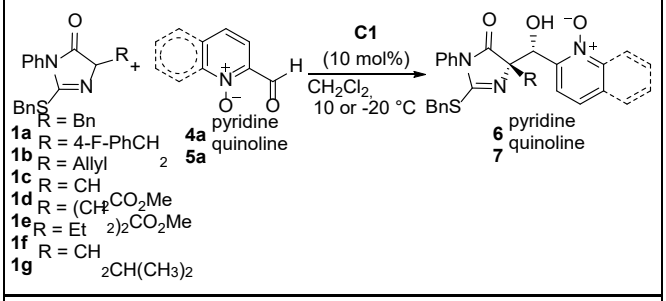
Entry	Catal.	T [ºC]	t [h]	Conv [%][b]	*dr*[c]	*ee* [%][d]
1	**C1**	0	16	100 (93)	>10:1	94
2[e]	**C1**	–10	16	100	>30:1	95
3	**C2**	0	48	60	2.5:1	45
4	**C3**	0	16	82	1.5:1	ND
5	**C4**	0	16	88	1.7:1	30(10)
6	**C5**	0	16	100	2:1	ND
7	**C6**	0	16	100	1.8:1	ND

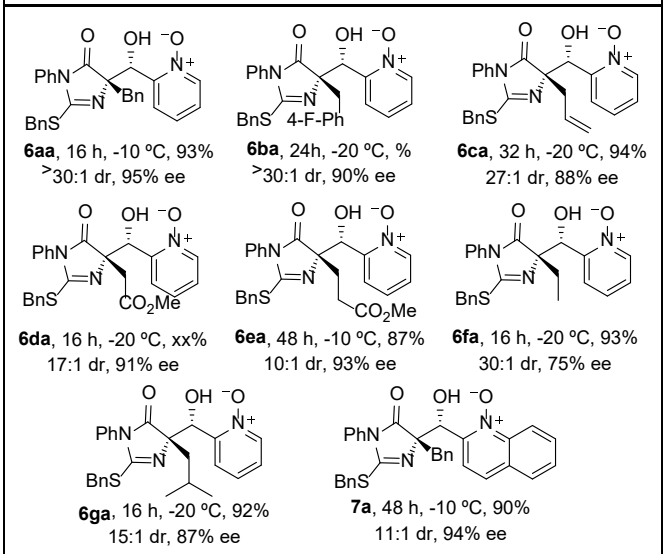


[a] The reactions were performed using 0.11 mmol of **4a**, 0.121 mmol of **1a** and 10 mol% catalyst in 0.6 mL CH_2Cl_2. [b] Data in parentheses refer to the yield after chromatography. [c] dr estimated by ^{1}H NMR spectroscopy and by HPLC. [d] *Ee* of major diastereomer as determined by HPLC. [e] Reaction conducted using 2 equivalents of **1a** (0.22 mmol).

With the established optimal reaction conditions, we then examined the scope of the aldol addition reaction of structurally diverse 2-benzylthiodihydroimidazolones (**1a**-**g**), with different substituents at the amino acid site location, in the reaction with a series of naked azaarene-carbaldehyde N-oxides **4a** and **5a**. As shown in Table 2, different substitution patterns can efficiently engage at the C5 position of the heterocycle. In general, the aldol reaction proceeds smoothly in a highly stereoselective manner and with excellent yields (>87%, isolated as a mixture of diastereomers). Imidazolones from phenylalanine and other α-amino acid derived imidazolones with different functional groups (allyl and alkylesters) are employable as nucleophilic reacting partners (adducts **6c**, **6d** and **6e**). The weakest acidity of adducts provided with simple alkyl groups (R = Et, *i*-Bu) did not make difficult to form the reactive carbanion at –20 ºC, however, a marked variation of selectivity was observed between these substituents based probably on the steric differences (adduct **6f** *vs* **6g**). Fortunately, the process was not limited to pyridine-2-carbaldehyde N-oxide. For instance, quinoline-2-carbaldehyde **5a** afforded the desired aldol product **7a** in 90% yield and a high stereoeselectivity (94% ee and 11:1 d.r.).

Table 2. Catalytic and asymmetric Aldol reaction between **1b**-**g** and azaarene-2-carbaldehyde N-oxides **4a** and **5a**.[a]





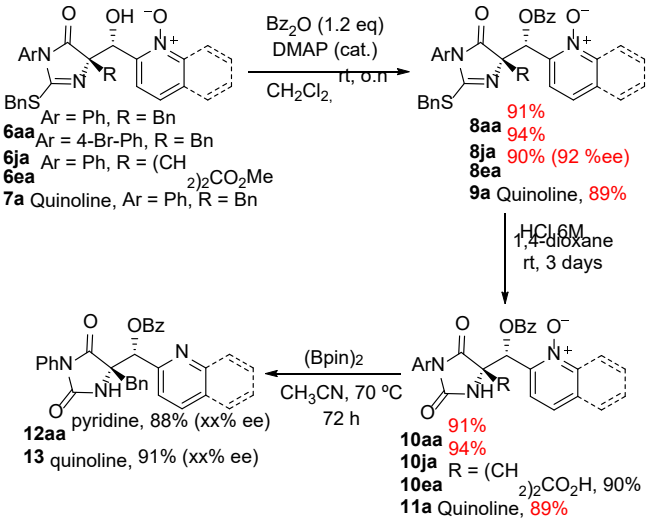
[a] The reactions were performed using 0.11 mmol of **4a-5a**, 0.22 mmol of **1a-g** and 10 mol% catalyst **C1** in 0.6 mL CH_2Cl_2. [b] dr estimated by ^{1}H NMR spectroscopy and by HPLC. [c] *Ee* of major diastereomer as determined by HPLC.

The scope of substituted N^3-aryl 2-benzylthio-3,5-dihydroimidazol-4-ones and azaarene *N*-oxide aldehydes was also evaluated (Table 3). N^3-aryl Imidazolones bearing either para-substituted electron-donating groups or electron-withdrawing groups on the N^3-aromatic ring were well tolerated in the reaction with **2a** and provided the aldol adducts **7h**, **7i**, and **7j** in excellent yield (>90%) and with high stereoselectivity (>19:1; >90% ee). Interestingly, this reaction also occurred efficiently with substituent at the *meta*- and *ortho*-position position relative to the aniline group of the imidazolone (**7k** and **7l**). Under these conditions, the reaction tolerated both electron-donating and -withdrawing groups attached at different positions of the pyridine ring regardless of the substituent on the prochiral center of the

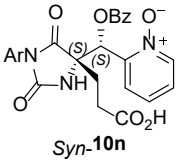
imidazolone ring (**7m**, **7n**, **7o**, and **7p**). ***Size 7q*** Similarly, substrates bearing both electron-rich and electron-poor aryl substituents were equally effective in providing the corresponding addition adduct **7r** in high yield and excellent stereoselectivity. Finally, other alkylazaarenes were also used successfully in the aldol reaction and the substituent on the N^3-Aryl imidazolones could be varied with a range of electron-donating and withdrawing functionalities without major impact on the yield and stereoselectivity (**8b**, **8c**, **8d**, and **9xxx**).

Hydrolysis of adducts into 5,5-disubstituted hydantoins. Since both optically active (azaaryl-2-yl)methanol and quaternary hydantoins units are important structures in medicinal compounds, we thought that the combination of these features in the same molecule could provide adducts of high synthetic value. In order to demonstrate the applicability of the present method, a larger scale experiment with the synthesis hydantoin unit and removal of the *N*-oxide moiety were examined (Scheme 2). First, we proposed to access the corresponding hydantoins by directly treating the aldol adducts **6a** under acidic or basic hydrolytic conditions, but unfortunately, we observed that the starting compounds under these conditions decomposed due to the retro-aldol reaction. Therefore, we thought it was necessary to protect the hydroxyl group of the aldol reaction adduct. Fortunately, we were able to establish a high performance protocol in three steps to convert **6a, 6j, 6n** and **7a** into our desired hydantoin goal (Scheme 2). First, treatment of the aldol adducts with 1 equivalent of benzoic anhydride in the presence of catalytic amount of DMAP furnished the corresponding O-protected adducts **8** and **9** as a white solids in 75–93% yields. In the second step, nucleophilic displacement of the benzylthioether group using HCl (6 M) in dioxane at r. t. for 3 days gave rise to the corresponding N-phenyl hydantoins **10** and **11** in good yields yields without the loss of enantiopurity. Finallly, reduction of the amine N-oxide group on adducts **10a** and **11a** by treatment with diboron reagent $(Bpin)_2$ afforded pyridine **12** and quinoline **13** in 88% and 91% isolated yield and unaltered enantioselectivity.[xxv]

The absolute and relative configurations of the new formed stereogenic centers were established, assuming a uniform reaction mechanism, by a single-crystal X-ray crystallographic analysis of the adduct **10n** (Figure N).



Scheme 2. Hydrolysis of cycloadducts to 5,5-disubstituted hydantoins and removal of the *N*-oxide.



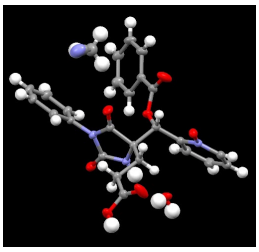


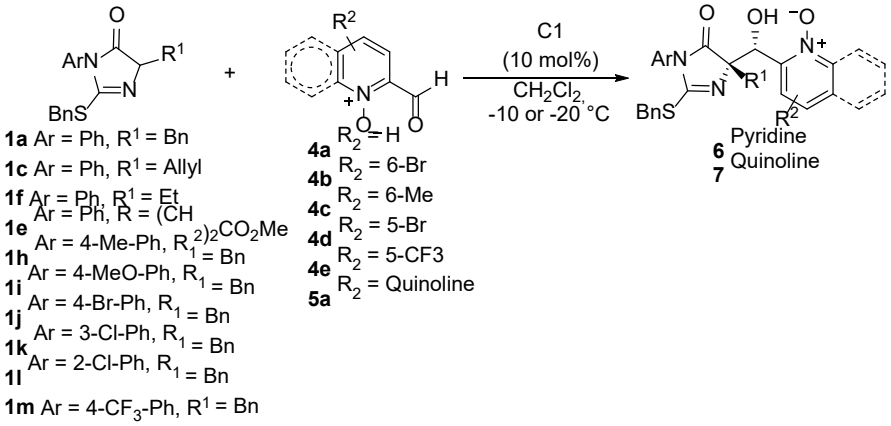
Figure 1. X-ray crystallographic structure of **10n**. Color code: C gray, H white, O red, N blue.

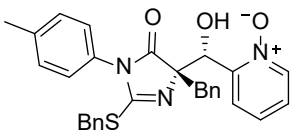
Catalyst design and mechanistic insights. The desire of developing efficient synthetic methods encourage chemists to design novel catalysts with high activity and selectivity. To achieve these objectives, much effort has been done in the search of new multifunctional chiral organocatalysts, i.e. catalysts possessing two, or more, distinct functional groups to activate the substrates in a controlled chiral environment. [xxvi] Among all the multifunctional activation procedures, the organocatalyst assisted activation model is relatively less explored than the other methods, but recently synthetic chemists are gradually recognizing its potential.[xxvii]

Our initial design idea of the new catalyst **C1** was that the additional amide group on the "non-chiral" part of the catalyst (left part of catalyst **C1**, Figure 2) could hydrogen-bond to the carboxyl group of the square amide and thereby influence the electrostatic potential and hydrogen bonding ability of the hydrogens in the square amide. In the methylated catalyst **C2**, the amide in "non-chiral" part of the catalyst is instead pointing away from the carbonyl oxygen and hence no hydrogen bond activation is possible.

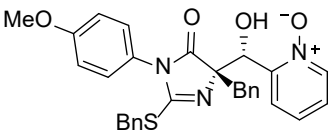
In order to investigate the effect of the hydrogen–bond assisted activation in the different catalysts (**C1** and **C2**), we calculated the structures of the different catalysts at the B3LYP/6-31+G(d) level of theory using both the D3 correction for dispersion and CPCM solvent calculation (DCM) in the optimization (see Figure 5). The surface electrostatic potential of the two catalysts shows a strongly positive potential around the two hydrogens of the square amide and the maximum is located in between the two hydrogen (red region in Figure 5). This explains the square amide catalysts potential to bind to carbonyl compounds. The **C1** catalyst has a larger positive potential at the maximum compared to the **C2** catalyst, but the difference is relatively small (**C1**: $V_{S,max}$ =79.8 kcal/mol; **C2**: $V_{S,max}$ = 76.0 kcal/mol).

Table 3. Scope of the reaction of both substituted N^3-aryl 2-benzylthio-3,5-dihydroimidazol-4-ones **1a-f** and N-oxide azaares **4a-f**.[a]





6ha, 48 h, -15 ºC, 94%
>32:1 dr, 93% ee



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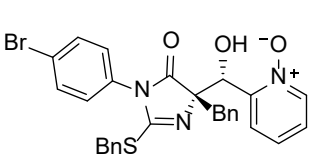
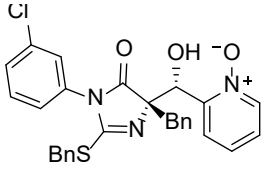
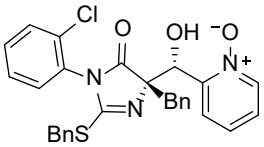
>49:1 dr, 91% ee



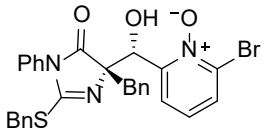
6ja, 48 h, -20 ºC, 94%
>19:1 dr, 90% ee



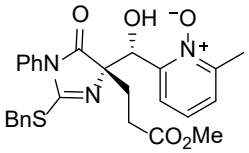
6ka, 48 h, -20 ºC, xx%
>24:1 dr, 93% ee



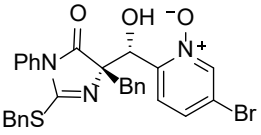
6la, 16 h, -20 ºC, 91%
>13:1 dr, 92% ee



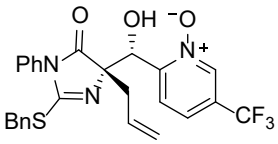
6ab, 48 h, -20 ºC, 90%
11:1 dr, 98% ee



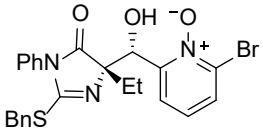
6ec, h, -20 ºC, xx%
>11:1 dr, 88% ee



6ad, 24 h, -10 ºC, 94%
8:1 dr, 88% ee



6ce, h, -20 ºC, xx%
> x:x dr, xx% ee



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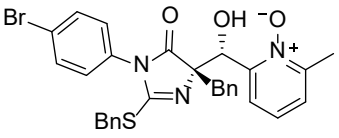
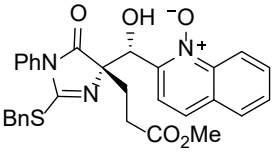
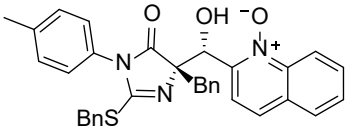
9:1 dr, 61% ee



6jc, 48 h, -20 ºC, 88%
> 20:1 dr, 94% ee



7ea, 48 h, -20 ºC, xx%
3.7:1 dr, 94% ee



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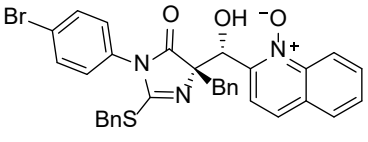

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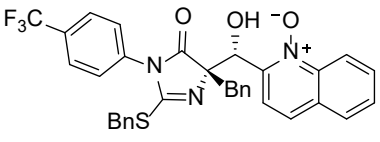
8:1 dr, 88% ee



7ma, 48 h, -20 ºC, xx%
8:1 dr, 94% ee

[a] The reactions were performed using 0.11 mmol of **2a**, 0.165 mmol of **1a** and 10 mol% catalyst in 0.6 mL CH_2Cl_2. [b] dr estimated by ^{1}H NMR spectroscopy and by HPLC. [c] *Ee* of major diastereomer as determined by HPLC.

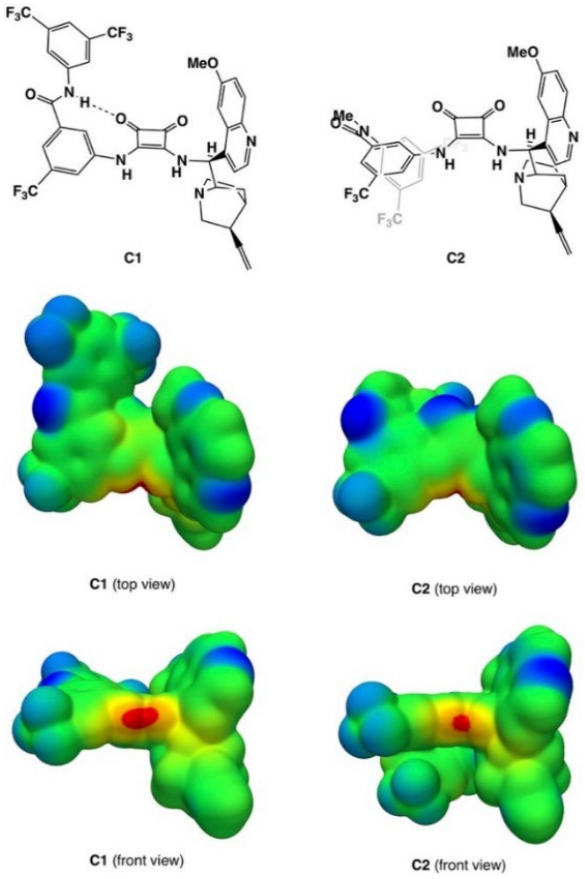


Figure 5. Electrostatic potential of catalysts **C1** and **C2** calculated at the B3LYP/6-31+G(d) level of theory using both the D3 correction for dispersion and CPCM solvent calculation (DCM) in the optimization.

In order to better understand the action of the two catalysts (**C1** and **C2**), the potential energy surface of the reactants, intermediates and transition states of the aldol reaction was investigated at the B3LYP/6-31+G(d)// B3LYP/**6-31+G(d) (Txema)** level of theory using both the D3 correction for dispersion and CPCM solvent calculation (DCM). The calculations were performed with the *N*-oxide aldehyde **4a** and a simplified imidazolones from Table 1 (Ph = Me, Bn = Me, Bn = H). The encounter between the imidazolone **1h** and the catalyst (**C1** and **C2**) lead to a pre-assemble TS complex (**C•1h**) that is stabilized compared to the free catalyst and the imidazolone (Figure 6: –3.2 and -5.6 kcal mol^{-1}, respectively). From the pre-assembly complex, the α-hydrogen is deprotonated by the quinuclidine nitrogen in the bifunctional catalyst (via **TS$_{enolate}$**) leading the enolate. The calculations show that the Gibbs free energy of activation, calculated from the pre-assembly complex, is similar for the both catalyst (13 kcal mol^{-1}) and leads to a complex between catalyst and the formed enolate. The encounter between the aldehyde and catalyst complex leads to a new pre-assemble TS complex (**C•4a•1h**) before passing through the transition state (TS$_{aldol}$) leading the aldol product. In the transition state for the aldol reaction, the nucleophilic enolate is attacking the *N*-oxide aldehyde **4a** while the proton from the ammonium nitrogen is transferred to the oxygen in the aldehyde in a concerted fashion. The Gibbs free energy of activation for shows that the aldol reaction is the rate-limiting step of the reaction and that the barrier is slightly lower for catalyst **C1** compared to catalyst **C2** (10.7 kcal mol^{-1} compared to 11.6 kcal mol^{-1}). This is in agreement with the

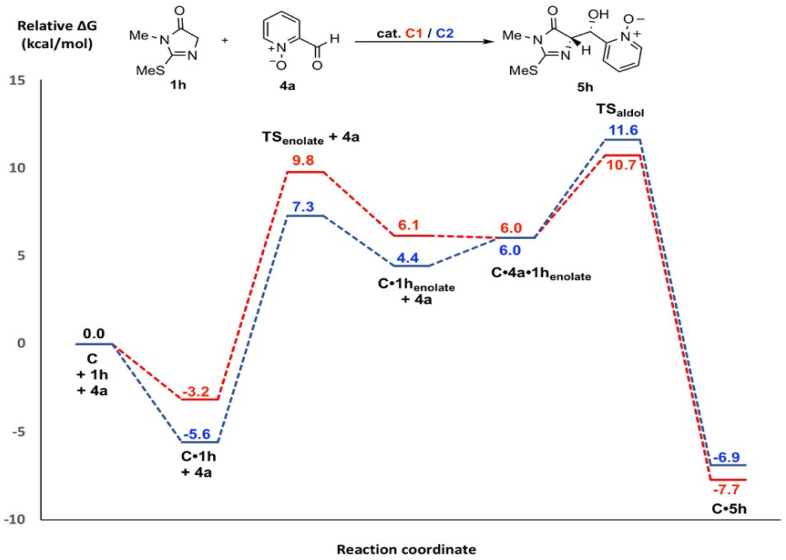


Figure 6. Gibbs free energy diagram of the enolisation and the aldol reaction of the model imidazolinone 1h and *N*-oxide aldehyde **4a** with catalyst **C1** and **C2** at the B3LYP/6-31+G(d)//B3LYP/XXXXXX using the D3 dispersion and CPCM solvation (DCM).

experimental observation that the **C1** catalyst reacts faster than the **C2** catalyst in the aldol reaction (**See Table 1 and SI**).

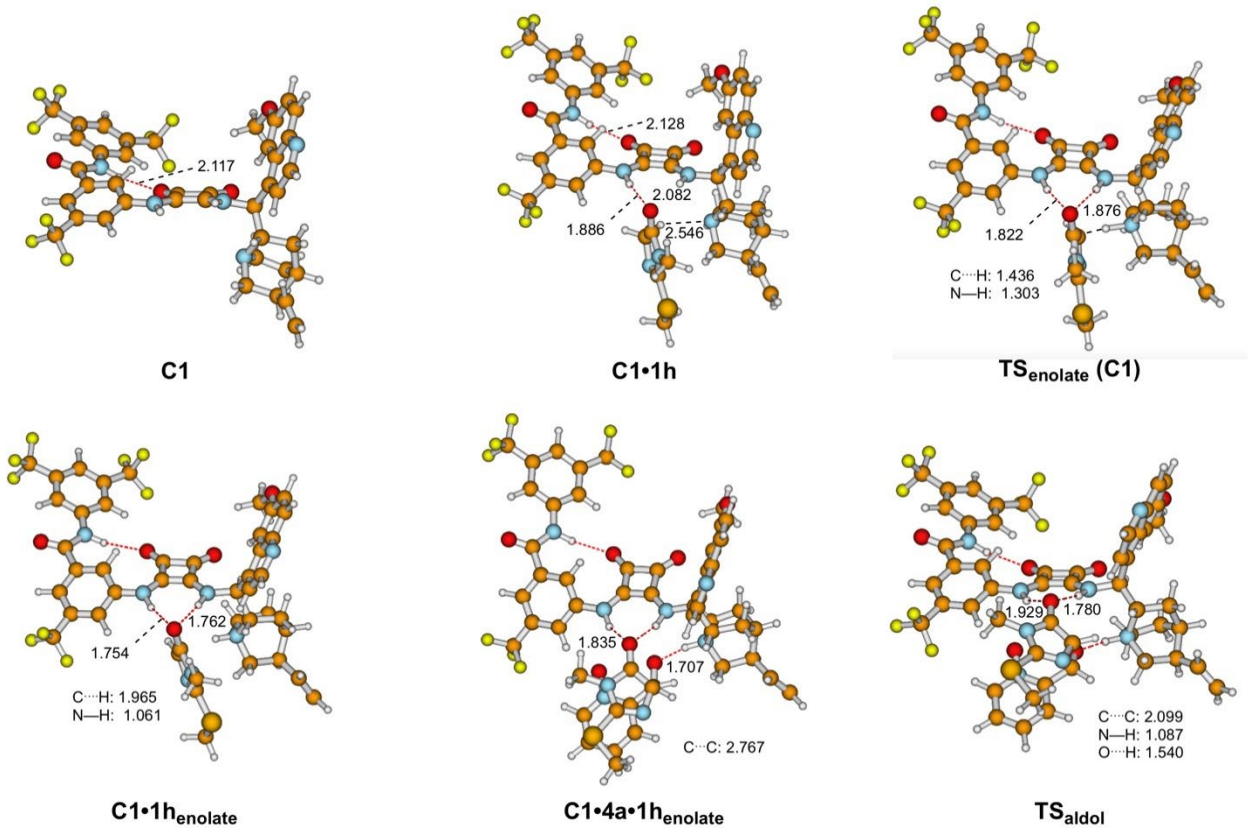


Figure 7. Optimised structures of the catalyst, intermediates and transition states of the aldol reaction with catalyst **C1** at the B3LYP/6-31+G(d) level of theory using the D3 dispersion and CPCM solvation (DCM).

Conclusions

This work represents the first example of an asymmetric C(sp3)-H addition of an organic compound to acyclopropene moiety as well as the first example of an asymmetric C(sp3)-H addition of a pyridine compound to an alkene.

A new, quick entry to the enantioselective synthesis of 5,5-hydantoin surrogates. The method is general with respect to the substitution pattern at the N_1 (alkyl, aryl, acyl), N_3 (aryl) and C_5 (

Experimental Section

For detailed description of the experimental procedures (preparation of templates, catalytic enantioselective reactions, transformations of adducts, kinetic measurements), characterization of compounds, and spectroscopic/chromatographic information, please see the Supporting Information.

CCDC 1581118 and 1581122 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

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Keywords: hydantoins • α-amino acids • quaternary stereocenters • asymmetric catalysis • Brønsted bases

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Entry for the Table of Contents

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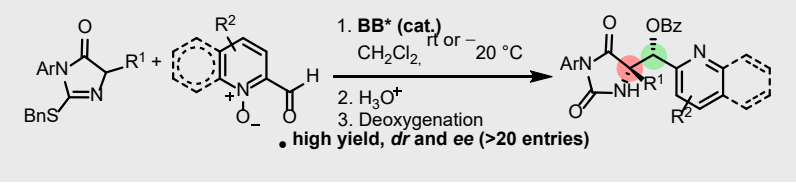

Hydantoins made easy: a general, catalytic and asymmetric procedure to access 5,5-disubstituted (quaternary) hydantoins is developed relying on the Brønsted base catalyzed enantioselective C-functionalization of a design dihydroimidazo.

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Direct Asymmetric Aldol Reaction of N^3-Phenyl 2-benzylthio-3,5-dihydroimidazol-4-ones with Azaarene N-Oxide Aldehydes Catalyzed by Cooperative Assisted Bifunctional Organocatalyst.

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