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

June Izquierdo,[a] Noémie Demurget,[a] Aitor Landa,[a] Tore Brinck,[b] Jose M. Mercero,[c] Peter Dinér,*[b] Mikel Oiarbide,*[a] Claudio Palomo*[a]

Abstract: Bifunctional amine/squaramide catalyst promoted direct aldol addition of an hydantoin surrogate to pyridine 2-carbaldehyde *N*-oxides to afford aldol adducts bearing two vicinal tertiary/quaternary carbons in high diastereo- and enantioselectivity (*dr* up to >20:1; *ee* up to 98%) is reported. Acid hydrolysis of adducts followed by reduction of the *N*-oxide group yields enantiopure carbinol-tethered quaternary hydantoin-azaarene conjugates with densely functionalized skeletons. DFT studies of the potential energy surface (B3LYP/6-31+G(d) + CPCM (dichloromethane)) of the reaction correlate the activity of different catalysts and support an intramolecular H-bond-assisted activation of the squaramide moiety in the transition state of the catalytic reaction.

Introduction

Molecular complexity, in terms of carbon backbone intricacy and/or functional group and stereochemical crowding, is inherent to many natural products and biologically active substances.[1] Consequently, the development of direct, catalytic C–C bond-forming reactions leading to densely functionalized, stereochemically rich motifs enantio- and diastereoselectively is of significant interest. At the same time, such reactions pose a number of difficulties, among them (i) the attenuated reactivity of sterically congested nucleophilic and/or electrophilic reaction partners, (ii) the propensity of these C–C bond-forming reactions to be reversible, and (iii) the need of stringent control of the facial selectivity on trisubstituted prostereogenic reactive centers.[2] Not surprisingly, enantio- and diastereoselective 1,2-addition reactions involving differently disubstituted enolate or equivalent intermediates are uncommon.[3] In particular, to the best of our

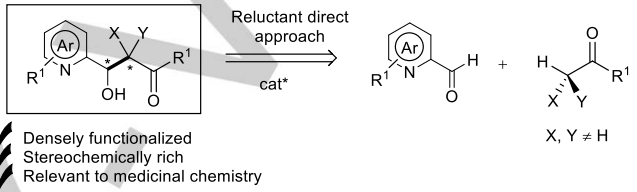
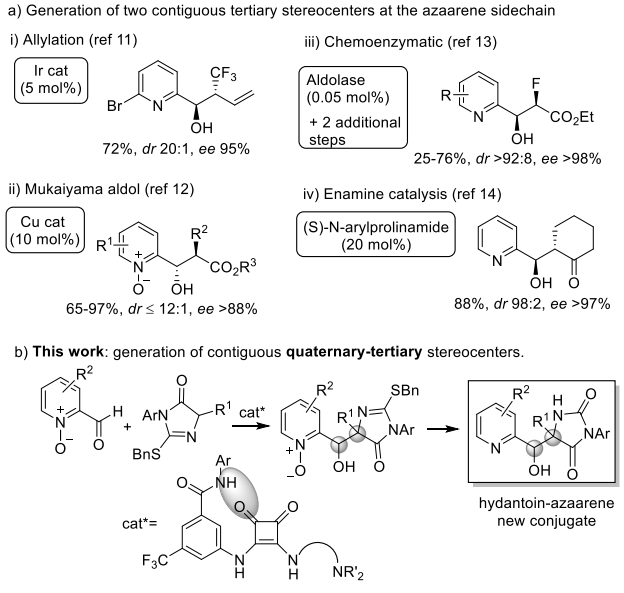


Figure 1. A conceivable direct approach to *ortho*-substituted chiral azaarene compounds featuring a tertiary/quaternary carbon pattern.

knowledge, direct convergent and enantioselective routes that satisfy the bond-disconnection of Figure 1 remain reluctant, despite the resulting *ortho*-substituted azaarene products would be interesting from a medicinal chemistry point of view.[4,5] In this context, asymmetric and non-asymmetric modifications at the *ortho* position of the azaarene ring were investigated intensively in the last years.[6] Among the *ortho*-substituted azaarenes, the chiral 2-(oxymethyl)azaarene skeleton is a frequent structural



Scheme 1. State of the art of aldol and related addition reactions to azaarene-2-carbaldehydes and our proposal.

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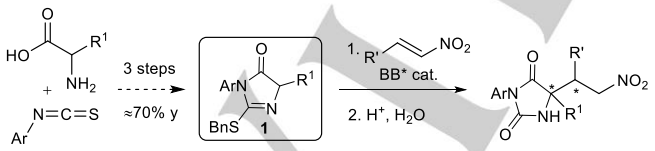
motif in agrochemicals,[7] in biologically active compounds,[8] and as chiral ligand.[9] Some asymmetric catalytic aldol and related addition reactions leading to 2-(oxymethyl)azaarenes with adjacent tertiary-tertiary stereocenters have been developed,[10] but there is virtually not precedent dealing with the construction of such structures bearing two vicinal tri- and tetrasubstituted carbon stereocenters enantioselectively (Scheme 1a, entries i-iv). Krische has reported[11] the Ir-catalyzed addition of allyl-transition metal complexes to pyridyl 2-carbaldehyde (i). Jørgensen developed[12] a Cu-catalyzed Mukaiyama-type addition of silyl enol ethers to various pyridine carbaldehyde *N*-oxides (ii). Chemoenzymatic aldol additions of sodium fluoroacetate to pyridyl-2-carbaldehyde have been documented to proceed with variable yields of isolated ethyl ester (iii).[13] Finally, Nelson reported[14] the only organocatalytic approach consisting of the enamine mediated addition of the symmetric cyclohexanone to pyridyl-2-carbaldehydes (iv). Intrigued by the lack of direct and asymmetric approaches to 2-(oxymethyl)azaarene skeletons with adjacent tri- and tetrasubstituted carbon stereocenters, we envisioned that direct coupling between azaarene-2-carbaldehydes and α-substituted lactam systems that are prone to Brønsted base-promoted enolization might be conceivable.[15] Here, we present initial difficulties during the realization of such an idea, and how the use of azaarene *N*-oxides as transiently activated substrates, in combination with bifunctional catalysts bearing an additional H-bond donor amide group, allowed to overcome them.

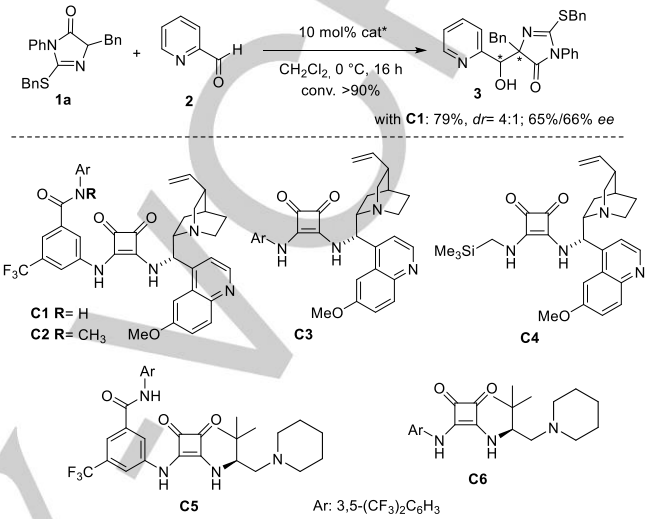
Results and Discussion

Background and working plan. We selected 1*H*-imidazol-5(4*H*)-ones **1**, a type of lactam heterocycle easily prepared from racemic α-amino acids and simple aryl isothiocyanates in three-steps, which has previously been used as an excellent hydantoin surrogate in Brønsted base-catalyzed conjugate additions to nitroolefins (Scheme 2).[16] Hydantoins can be considered masked forms of α-amino acids, and therefore, serving as precursors of non-natural amino acids,[17] and have in addition revealed some unique pharmacological uses,[18] making them of considerable practical importance.



Scheme 2. Imidazolinone **1** as hydantoin surrogate in Brønsted base catalysed conjugate addition reaction.

For initial exploration, the aldol reaction[19] between N^3-phenyl 2-benzylthio-3,5-dihydroimidazol-4-one **1a**, prepared from *DL*-phenylalanine and phenylisothiocyanate,[20] and commercially available pyridine-2-carbaldehyde **2** was evaluated. By using a range of chiral bifunctional catalysts aldol **3** was efficiently produced (almost full conversion at 0 ºC overnight), but with generally low selectivity (Scheme 3). For instance, in the presence of catalyst **C1**, a cinchona alkaloid-derived bifunctional squaramide catalyst previously developed in our laboratory,[21] **3** was obtained in 79% isolated yield, 4:1 diastereomeric ratio and enantioselectivities of 65% and 66% *ee* for each isomer.



Scheme 3. Reaction between **1a** and pyridine-2-carbaldehyde **2** and the set of bifunctional Brønsted base catalysts employed within this work.

At this point we turned our attention to pyridine 2-carbaldehyde *N*-oxides (**4A**) with the expectation that the easy to install[20] and remove *N*-oxide group would impart higher reactivity[22] while providing a potentially coordinating site for catalyst binding.[23] Superior reactivity and stereoselectivity of azaarene *N*-oxides as compared to parent azaarenes have been previously observed by us and others in the realm of metal catalysis[24] and organocatalysis.[25] Gratifyingly, (Table 1, entry 1), reaction of **1a** with **4A** in CH_2Cl_2 at 0 ºC in the presence of catalyst **C1** proceeded to completion within less than 16 h, and most significantly, producing aldol **6Aa** in a high (>10:1) diastereomeric ratio and excellent enantioselectivity (94% *ee*). None of the other catalysts tested, including benchmark catalyst **C3**[26] (1.7:1 *dr*, 30% *ee*, entry 4), the parent cyclohexyldiamine derivatives **C5**[16b] and **C6**[27] (entries 6, 7) and the trimethylsilyl derivative **C4**, which had been previously designed by us for the nucleophilic additions of 2-(cyanomethyl)azaarene *N*-oxides,[26a] (entry 5), showed comparable reactivity. Importantly, by decreasing the reaction temperature to −10 °C the conversion was still complete upon 16 h and the level of *dr* was further increased to a remarkable >20:1 (entry 2). Control experiment (entry 3) showed that the *N*-methylated catalyst **C2** was less stereoselective and did not reach full conversion, demonstrating the crucial role played by the amide NH group to impart good stereocontrol and reactivity. It is worth noting that no retroaldol reaction was observed during isolation and purification of the product through silica gel, and the *syn*-aldol product[28] could be obtained in high purity as a crystalline solid.

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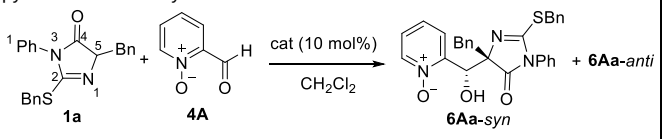
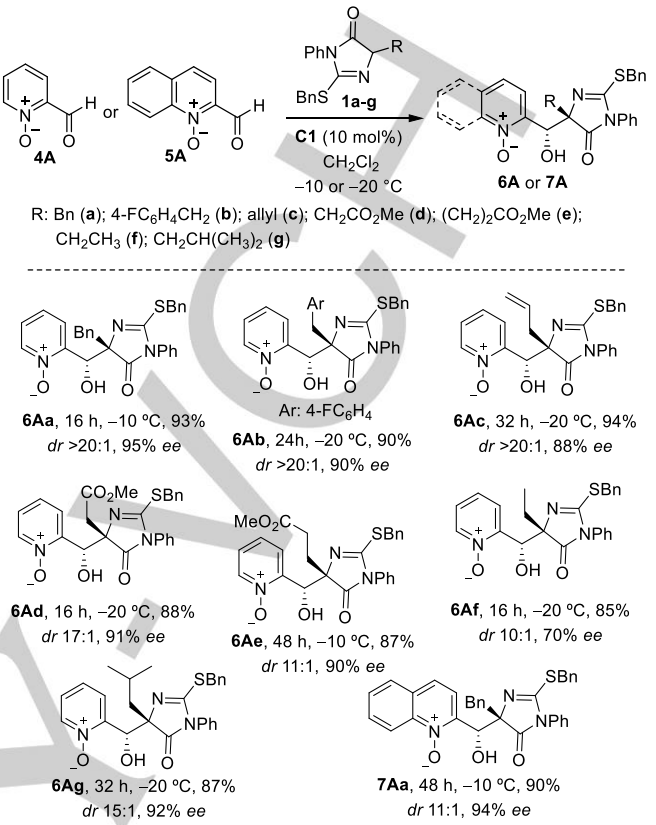
Table 1. Catalyst screening for the reaction of hydantoin surrogate **1a** with pyridine 2-carbaldehyde *N*-oxide **4A**.[a]



Entry	Cat	T [ºC]	t [h]	Conv [%][b]	*dr*[c]	*ee* [%][d]
1	**C1**	0	16	100	>10:1	94
2[e]	**C1**	–10	16	100 (93)	>20:1	95
3	**C2**	0	48	60	2.5:1	45
4	**C3**	0	16	88	1.7:1	30
5	**C4**	0	16	100	1.8:1	ND
6	**C5**	0	16	82	1.5:1	ND
7	**C6**	0	16	100	2:1	ND

[a] The reactions were performed using **4A** (0.11 mmol), **1a** (0.121 mmol) and catalyst (10 mol%) in CH_2Cl_2 (0.6 mL). [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**.

With the established optimal reaction conditions, the scope of the catalytic aldol reaction with respect to the 2-benzylthioimidazolinone reagent **1** was investigated using as azaarene carbaldehyde *N*-oxides both the pyridine derivative **4A** and the quinoline derivative **5A**. As data in Scheme 4 show, various substitution patterns at the Cα(sp^3) position of the heterocycle are tolerated well. Thus, the aldol reaction proceeded smoothly even at –20 ºC with benzyl, *p*-fluorobenzyl or allyl substituted 2-benzylthioimidazolinones **1a**–**c** affording the *syn* aldol product in isolated yields above 93%, diastereomeric ratios higher than 20:1 and *ee*'s of 93%, 90% and 94%, respectively (adducts **6Aa**–**6Ac**). The reaction also tolerated ester groups at the side chain (products **6Ad**, **6Ae**) without loss of enantioselectivity and still high diastereoselectivity (*dr* >10:1 in both cases). The enantioselectivity eroded a little bit with substrates **1f** and **1g** bearing simple ethyl and isopropyl substituents (**6Af**, **6Ag**), but both yield and *dr* remained high. Finally, the process was not limited to pyridine derivative **4A**, and quinoline-2-carbaldehyde *N*-oxide **5A** also afforded the desired aldol product **7Aa** in 90% isolated yield and a high selectivity (*dr* 11:1, 94% *ee*). Although the diastereoselectivity was very high in most cases, even for the less favourable substrates essentially single diastereomer was isolated in >80% yield after simple crushing with Et_2O.[20]



Scheme 4. Scope of the catalytic aldol reaction of azaarene-2-carbaldehyde *N*-oxides **4A**/**5a** with hydantoin surrogates **1**. (Conditions of entry 2, Table 1.)

The scope of substituted N^3-aryl 2-benzylthio-3,5-dihydroimidazol-4-ones with a range of azaarene *N*-oxide aldehydes was also evaluated (Scheme 5). Various N^3-aryl imidazolinone systems bearing electron-donating (4-Me, 4-MeO) or electron-withdrawing (4-Br) groups on the N^3-aromatic ring were well tolerated in the reaction with **4A**, leading to aldols **6Ah**, **6Ai**, **6Aj** in excellent yields (>90%) and high stereoselectivity (*dr* >20:1, >90% *ee*). Interestingly, the *para*-, *meta*- or *ortho* position of the substituent does not affect the reaction chemical and sterechemical efficiency (compare reactions leading to adducts **6Aj**, **6Ak** and **6Al**).

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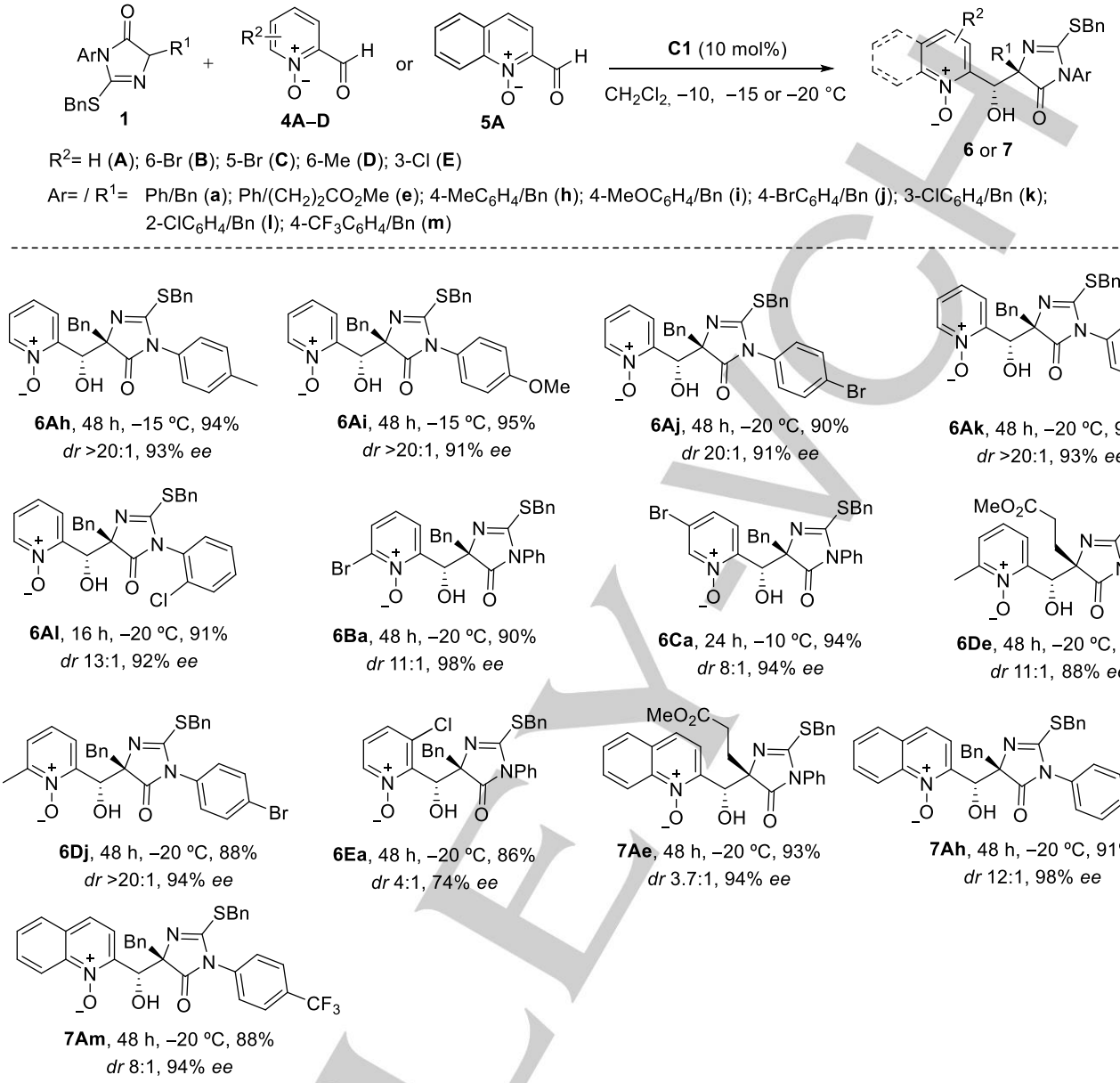

Scheme 5. Scope of the catalytic aldol reaction of azaarene-2-carbaldehyde *N*-oxides **4/5** with hydantoin surrogates **1**. (Conditions of entry 2, Table 1.)

Most relevant, the reactions involving azaarene systems of electronically different nature did also proceed satisfactorily. For instance, 6-Br and 5-Br pyridine systems (**4B** and **4C**) as well as the 2-Me pyridine system **4D** all behaved well affording adducts **6Ba**, **6Ca**, **6De** and **6Dj** in high yield and excellent stereoselectivity. Substitution on the pyridine ring at the most proximal position (ortho) was also well tolerated, but the reaction stereoselectivity resulted eroded (3-Cl: **4Ea** to give adduct **6Ea**, 4:1 dr, 74% *ee*). Finally, the quinoline-2-carbaldehyde *N*-oxide **5A** reacted with the phenylalanine-derived heterocycles **1h** and **1m** to provide adducts **7Ah** and **7Am** in good yields, good diastereomeric ratios (12:1 and 8:1) and excellent enantioselectivity (98%, 94% *ee*). The reaction between **5A** and **1e**, this latter bearing a methylpropanoate appendage, was an exception leading to **7Ae** in eroded diastereoselectivity.[29]

Elaboration of adducts toward carbinol-tethered new azaarene-hydantoin conjugates. The experimental study was complemented by carrying out the final conversion of the *N*-oxide functionality into the parent azaarene system and the regeneration of the hydantoin heterocycle. To that end, treatment of some aldol adducts **6A** with aqueous HCl was examined first, but unfortunately did not lead to the corresponding hydrolysed hydantoin products. Instead, products from a retro-aldol reaction were detected. Shifting the hydrolytic conditions from acidic to basic (NaOH 6M, 1,4-dioxane, room temperature) did not change

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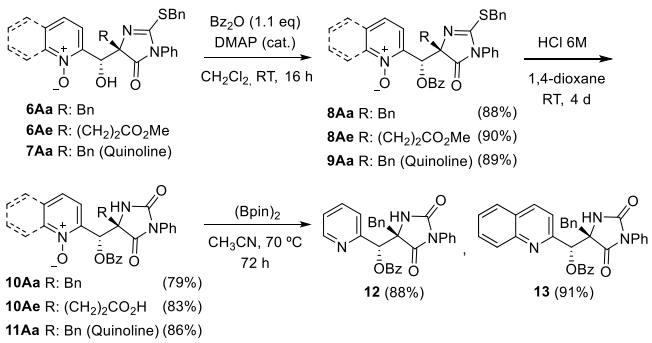
the result and retroaldol products were again observed. We decided to block the hydroxyl group on adducts as a benzoyl ester, which gratifyingly avoided the undesired retro addition.[30] Thus, upon benzoylation of adducts **6Aa** to **8Aa** and subsequent treatment with 6M HCl in dioxane at RT for 4 days gave rise to hydantoin **10Aa** in 83% yield over the two steps (Scheme 6). Similarly, adducts **6Ae** and **7Aa** were converted into hydantoin-azaarene *N*-oxide conjugates **10Ae** and **11Aa** in combined yields of 81% and 79%, respectively. Finally, treatment of adducts **10Aa** and **11Aa** with $(Bpin)_2$[31] afforded the pyridine-hydantoin and quinoline-hydantoin conjugates **12** and **13** in 88% and 91% isolated yields, respectively, and without loss of enantiopurity.



Scheme 6. Elaboration of adducts through hydrolysis and reduction to give carbinol-tethered quaternary hydantoin-azaarene conjugates.

The absolute and relative configurations of the *syn* adduct **10Ae** (Figure 2) was determined by a single-crystal X-ray crystallographic analysis[32] and that of the remaining adducts was established assuming a uniform reaction mechanism.[33]

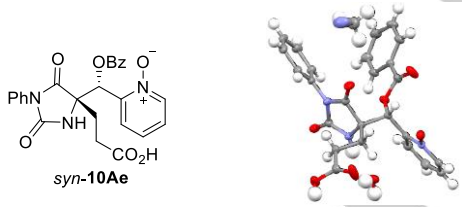


Figure 2. X-ray crystallographic structure of **10Ae**. Color code: C gray, H white, O red, N blue.

Catalyst electronic and conformational features and mechanistic insights. In an attempt to correlate catalyst structure with its chemical reactivity, quantum calculations of the surface electrostatic potential and conformational bias of catalysts **C1** and its *N*-methyl analogue **C2**, due to their presumed H-bonding ability, were performed. We calculated the structures of **C1** and **C2** at the B3LYP(D3)/6-31+G(d) level of theory[34] in aqueous phase (by means of the CPCM[35] using dichloromethane as solvent as implemented in the Gaussian 16 code[36]). The electrostatic surface potential of the two catalysts shows a strongly positive potential around the two hydrogens of the squaramide and the maximum is located in between the two hydrogens as best visualized in the front views represented in Figure 3 (bottom depictions, red region)[37] This charge distribution explains the potential of squaramide group to bind polar groups, such as carbonyl, through H-bonding. Catalyst **C1** has a larger positive potential at the maximum compared to **C2**, but the difference is relatively small (**C1**: $V_{S,max}$= 79.8 kcal/mol; **C2**: $V_{S,max}$= 76.0 kcal/mol). Another consequence of the intramolecular NH…O=C binding[38] in catalyst **C1** is that the two extended π systems at the opposite ends of the molecule are approximately perpendicular one another, leading to a *pseudohelical* structure. By contrast, both extended π systems in **C2** adopt a more flexible, roughly *antiperiplanar* disposition.

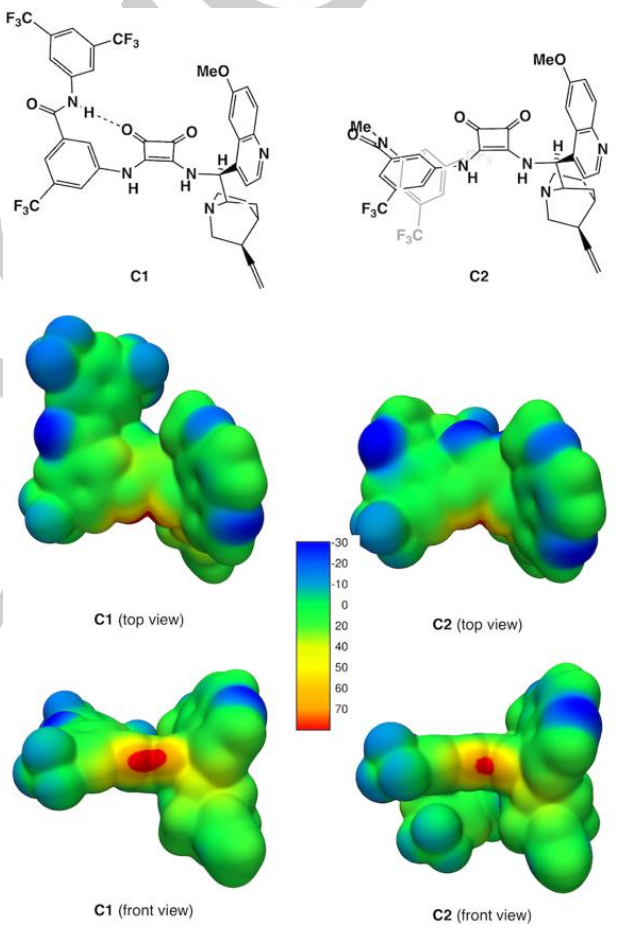


Figure 3. Calculated electrostatic potential on the 0.001 a.u. isodensity surface catalysts **C1** and **C2**. Colour coding in kcal/mol.

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 by optimising all the geometries at the same level of theory described above. All the energies were recalculated at the B3LYP/6-311++G(3df,2p) level of theory. The calculations were

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performed with the *N*-oxide aldehyde **4A** and a simplified 2-methylthio imidazolone **1n**.

As shown in Figures 4 and 5, the encounter between the imidazolone **1n** and the catalyst **C1** or **C2** leads to a pre-assemble TS complex (**C•1n**) that is stabilized compared to the free catalyst and the imidazolone (–3.2 and –5.6 kcal mol^{-1}, respectively). From the pre-assemble complex, the α-CH is deprotonated by the catalyst quinuclidine nitrogen via **TS$_{enolate}$** leading to the enolate. The calculations show that the Gibbs free energy of activation, calculated from the pre-assemble complex, is similar for both catalysts (13.0 and 12.9 kcal mol^{-1}, respectively) and leads to a complex between catalyst and the formed enolate.

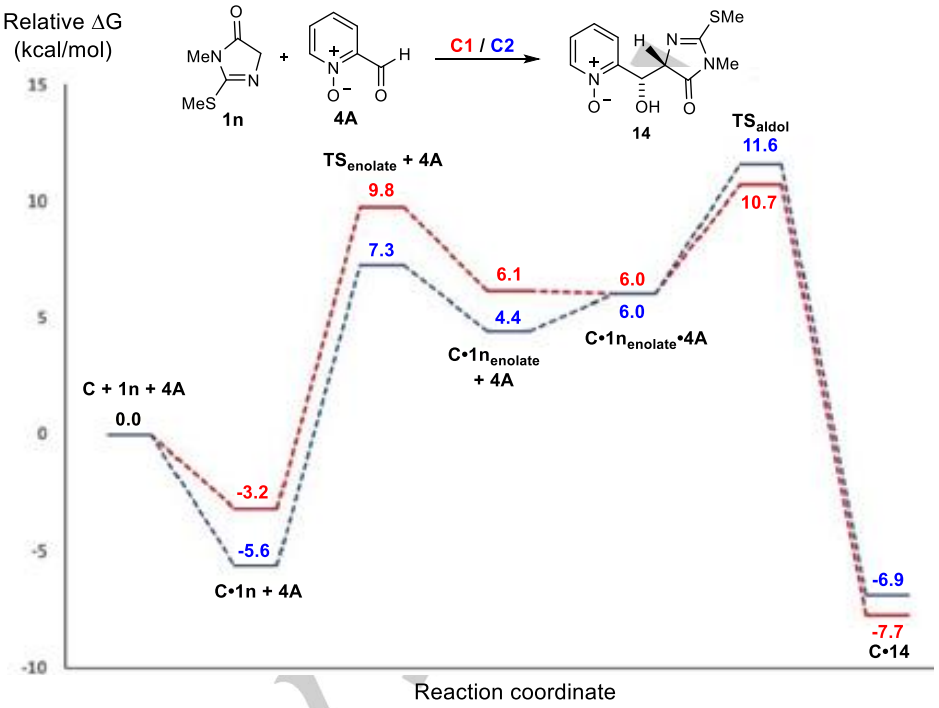

Figure 4. Gibbs free energy diagram of the enolization and the aldol reaction of the model imidazolinone **1n** and *N*-oxide aldehyde **4A** with catalyst **C1** and **C2**.

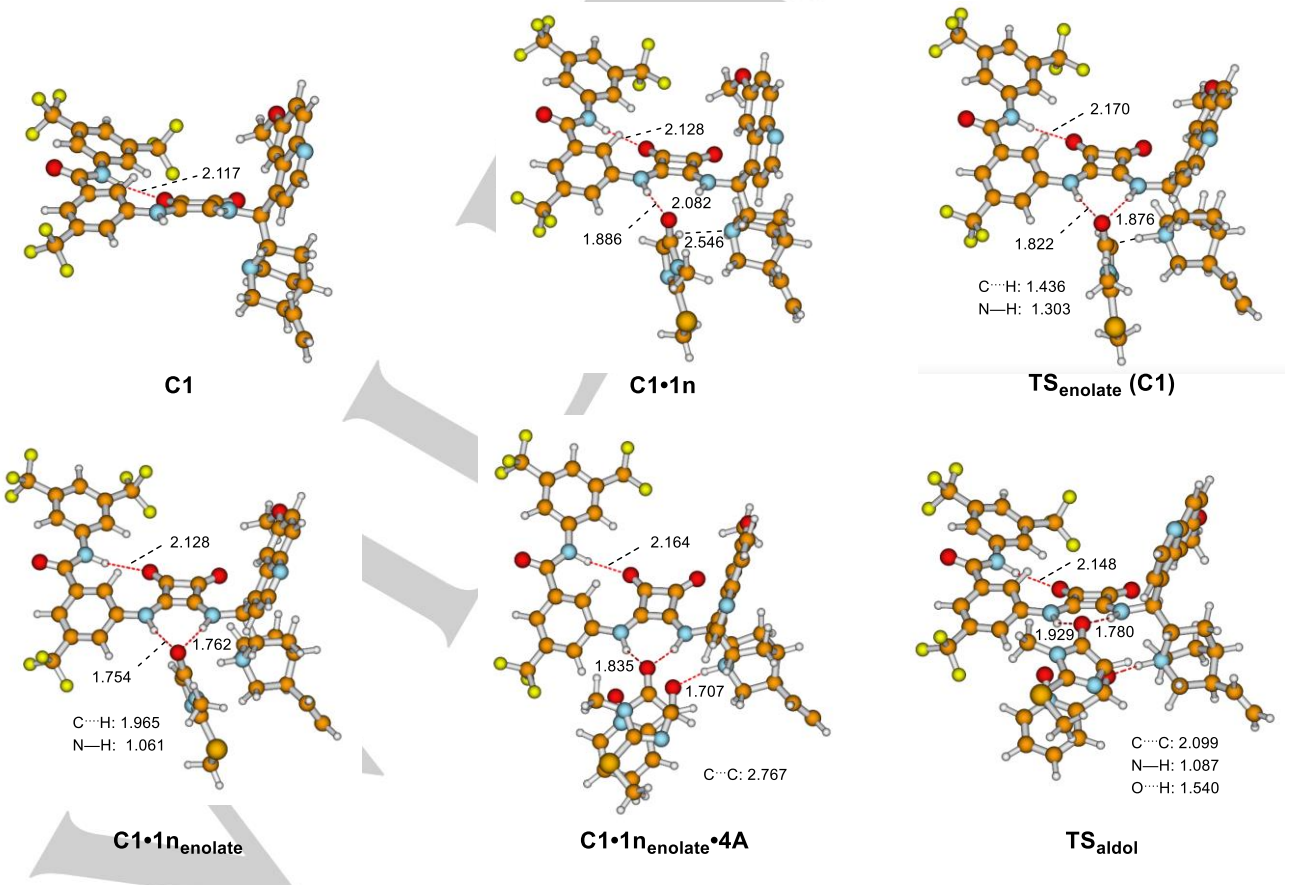

Figure 5. Optimised structures of the catalyst, intermediates and transition states of the aldol reaction with catalyst **C1**.

The encounter between the aldehyde and catalyst complex leads to a new pre-assemble TS complex (**C•1n•4A**) before passing through the transition state ($\mathbf{TS_{aldol}}$) leading the aldol product. In this transition state, the new C–C bond between the enolate and the *N*-oxide aldehyde **4A** is forming while the proton from the ammonium nitrogen is transferred to the oxygen in the aldehyde in a concerted fashion. The calculated Gibbs free energy of activation for the various steps shows that this latter ($\mathbf{TS_{aldol}}$) 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} vs. 11.6 kcal mol^{-1}). This is in agreement with the experimental observation that the aldol reaction in the presence of **C1** proceeds faster than with **C2** (see Table 1).

Conclusions

Aldol addition reactions between azaarene 2-carbaldehyde *N*-oxides and α-substituted hydantoin surrogates are promoted efficiently by a multifunctional Brønsted base/H-bonding chiral catalyst, furnishing vicinal tertiary/quaternary carbon motifs. The use of the *N*-oxide derivatives instead of the parent azaarene carbaldehydes is crucial, as is the design chiral catalyst, for attaining high enantio- and diastereoselectivity. Alcohol protection in adducts followed by acid hydrolysis and diborane reduction of the *N*-oxide group afforded carbinol-tethered new azaarene-hydantoin conjugates as essentially single stereoisomer. DFT calculations provide some insights on how internal H-bonding in the catalyst enhances its activity and induces catalyst preorganization.

Experimental Section

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

Acknowledgements

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Keywords: hydantoins • azaarenes • quaternary stereocenters • asymmetric catalysis • Brønsted bases

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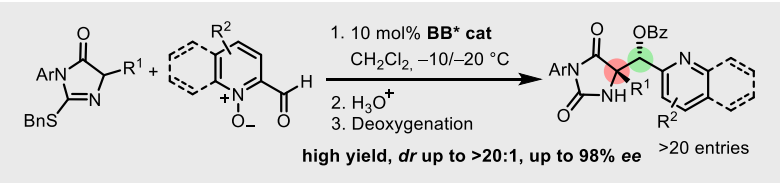

Assembled by aldol: a highly diastereo- and enantioselective direct aldol reaction between an hydantoin surrogate and azaarene 2-carbaldehyde *N*-oxides is enabled by a multifunctional amine-squaramide-amide catalyst. The process serves to assemble carbinol-tethered hydantoin-azaarene conjugates featuring vicinal tertiary/quaternary carbon stereocenters.

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