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FULL PAPER

Enantioselective Synthesis of 5,5-Disubstituted Hydantoins via Brønsted Base/H-Bond Catalysts Assisted Michael Reactions of a Design Template.

Joseba Izquierdo, Julen Etxabe, Eider Duñabeitia, Aitor Landa, Mikel Oiarbide,* Claudio Palomo*[a]

Abstract: A new method for the enantioselective synthesis of 5,5-disubstituted (quaternary) hydantoins has been developed based on an organocatalytic Michael reaction approach using 2-benzylthio-3,5-dihydroimidazol-4-ones as key hydantoin surrogates. The method is general with respect to the substitution pattern at the hydantoin N^1 (alkyl, aryl, acyl), N^3 (aryl) and C^5 (linear/branched alkyl, aryl) positions and affords essentially single diastereomeric products with enantioselectivities higher than 95% *ee* in most cases. Among the bifunctional Brønsted base/H-bond catalysts examined, the squaramide-tertiary amine catalyst **C2** and the newly prepared **C3** provided the highest selectivity so far with either nitroolefins or vinyl ketones as the acceptor components. Kinetic measurements support a first order rate dependence on both reaction partners, the donor template and the Michael acceptor, while competitive ^{1}H NMR experiments reveal a high ability of the template for catalyst binding.

Introduction

Hydantoins (2,4-imidazolidinediones) constitute a family of nitrogen heterocycles that are present in natural products[1] and comprise a variety of pharmaceutical uses.[2] In particular, 5-substituted and 5,5-disubstituted hydantoins are important medicinal compounds.[3] Examples include the anticonvulsant phenytoin, used for the treatment of epilepsy and cardiac arrhythmia,[4] and compounds with activity as antidepressant,[5] antiviral,[6] inhibitors of platelet aggregation,[7] of human aldose reductase,[8] and of human leukocyte elastase,[9] or antagonist for use in Hedgehog pathway-dependent malignancies.[10] On the other hand, hydantoins are also interesting from a purely chemical point of view.[11] 5-Substituted hydantoins have been employed in the context of molecular recognition,[12] chiral auxiliaries in organic synthesis,[13] or constituents of optically active polymers[14] and metal complexes.[15] Structurally, they can be viewed as masked α-amino acids and, as such, 5-substituted hydantoins also serve as precursors to unnatural α-amino acid derivatives.[16]

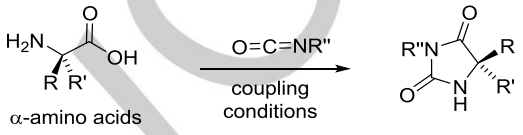
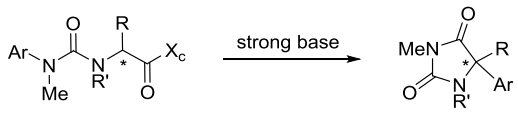


Figure 1. Conventional synthesis of optically active 5,5-disubstituted hydantoins from the *chiral pool.*

Although alternative routes from ketones or α-dicarbonyl compounds exist,[11] the main synthetic route to 5-substituted hydantoins starts from the corresponding α-amino acid derivatives,[17] which is condensed with an isocyanate or equivalent with the assistance of some highly reactive coupling reagent (Figure 1).[18] While this route is in principle simple and straightforward, its realization depends on the availability of the corresponding α-amino acid precursor in enantiomerically pure form. This is a serious problem, especially when 5,5-disubstituted (quaternary) hydantoins are targeted.[19]

a) **Clayden** (ref 20): Substrate-controlled anionic aryl group N→*C* rearrangement on chiral ureas



b) **Terada** (ref 21): Chiral Brønsted acid-catalyzed Friedel-Crafts reaction of in situ-generated ketimines

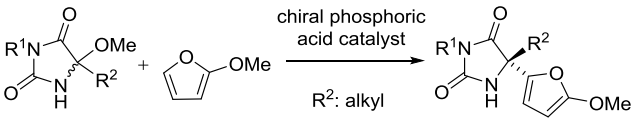


Figure 2. Advances in the asymmetric synthesis of 5,5-disubstituted hydantoins involving *C-C* bond construction.

Only very recently have practical syntheses of enantiomerically enriched quaternary hydantoins involving new carbon-carbon bond forming reactions been reported. Clayden has developed an elegant protocol to access quaternary hydantoins and compounds derived thereof in good diastereoselectivity based on a substrate-controlled anionic aryl group *N→C* rearrangement on lithiated ureas[20] (Figure 2a). On the other hand, Terada has recently reported a chiral phosphoric acid-catalyzed Friedel-

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Crafts-type addition of 2-methoxyfuran to in situ generated ketimines (Figure 2b).[21] Despite these significant advances, the scope of available optically active quaternary hydantoins continues to be rather narrow, essentially restricted to some particular 5-aryl substituted subfamilies.

Recently we found[22a] that heterocycles **I** can react smoothly with some Michael acceptors (i.e., nitroolefins and an acrylate equivalent) triggered by bifunctional Brønsted base/H-bond catalysts, thus serving, via the intermediate hydantoin, as *N*-substituted α-amino acids surrogates. Here we present a full study on the ability not only of **I**, but also of the related heterocycles **II** and **III**, to engage in bifunctional Brønsted base/H-bond catalysed highly enantioselective Michael reactions with some selected acceptors, including simple vinyl ketones. This work, which discloses a newly prepared and active squaramide-tertiary amine catalyst **C3**, represents the first catalyst-controlled, enantioselective and broad-scope method for the synthesis of 5,5-disubstituted (quaternary) hydantoins with a variety of substitution patterns at N^1, N^3 and C^5. (Figure 3).

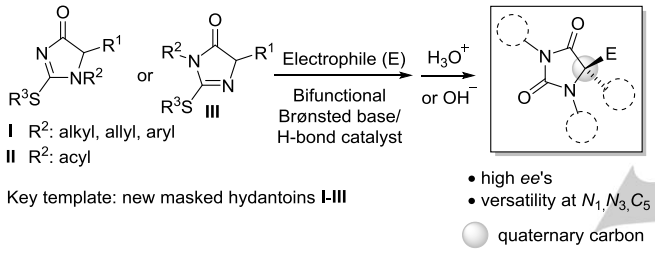
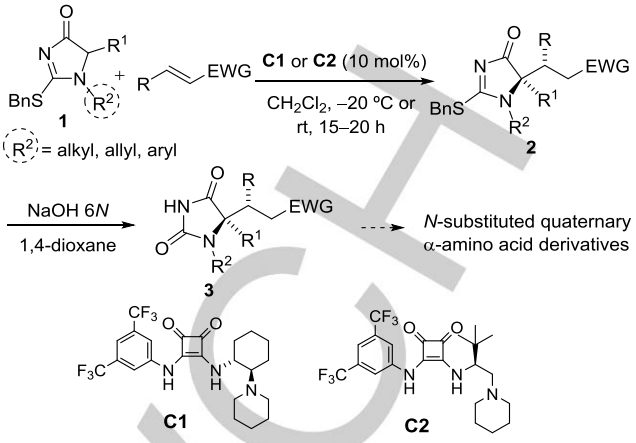


Figure 3. Template-based catalytic enantioselective synthesis of diversely substituted quaternary hydantoins.

Results and Discussion

Background and working plan. We have recently communicated a novel, highly enantioselective approach for the synthesis of *N*-substituted α-amino acid derivatives via the corresponding enantioenriched 1,5,5-trisubstituted hydantoins **3** (Scheme 1).[22] A distinguishing feature of this sequence is that the synthesis of hydantoins **3** no longer relies on the availability of the precursor α-amino acid in enantiopure form; instead, **3** is prepared through a Brønsted base catalyzed conjugate addition[23, 24] of racemic dihydroimidazolones **1**, followed by basic hydrolysis of the resulting Michael adduct **2**. The **1**→**2** transformation serves to install a second substituent at C^5 of the heterocycle while creating a new tetrasubstituted carbon stereocenter adjacent to a tertiary one with high diastereo- and enantioselectivity. To the best of our knowledge, methods for that goal have not been described yet.[11] During these preliminary studies we found that the squaramide/tertiary amine catalysts pioneered by Rawal,[25] such as **C1**, efficiently promoted the addition reaction of **1** to aromatic nitroolefins under very smooth conditions (CH_2Cl_2 at –20 ºC) affording the corresponding adducts **3** (EWG=NO_2) in diastereomeric ratios typically higher than 9:1 and excellent



Scheme 1. Our preliminary finding (ref 22a).

enantioselectivity. In some instances, particularly with aliphatic nitroolefins (R= alkyl), catalyst **C1** led to modest diastereoselectivities, but using **C2**[26] instead, both the diastereo- and the enantioselectivity were high. Importantly, this system tolerated well a range of dihydroimidazolones **1** with varying substituents at N^1 (R^2: alkyl, allyl, aryl) and C^5 (R^1: linear and branched alkyl groups), including bicyclic dihydroimidazoles (R^1, R^2= $(CH_2)_3$). One of the problems of using template **1**, or in general structures **I** (R^2: alkyl or aryl), is their limited thermal stability as they partially decompose upon storage at room temperature for several hours, or during standard silica gel chromatographic purification, making storage in the freezer at –40 °C necessary.

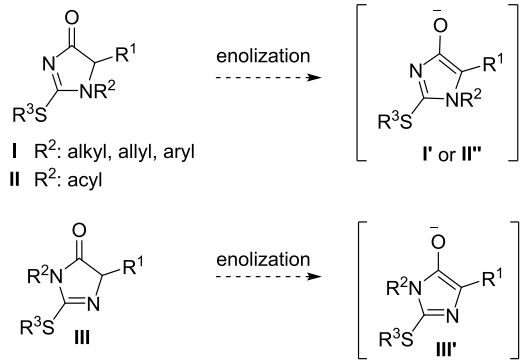


Figure 4. Enolization of templates leading to enolates with aromatic character.

Given the simplicity and the high selectivity of the method, and the mild reaction conditions involved, we sought to investigate the behaviour of the related heterocyclic systems **II** and **III**. If successful, a broad-scope approach for the enantioselective synthesis of diversely 1,3,5-substituted hydantoins would be at hand. The effectiveness of template **I** to react under the above soft enolization conditions may be ascribed to the aromatic character of the transiently formed enolate **I**' (Figure 4). From a

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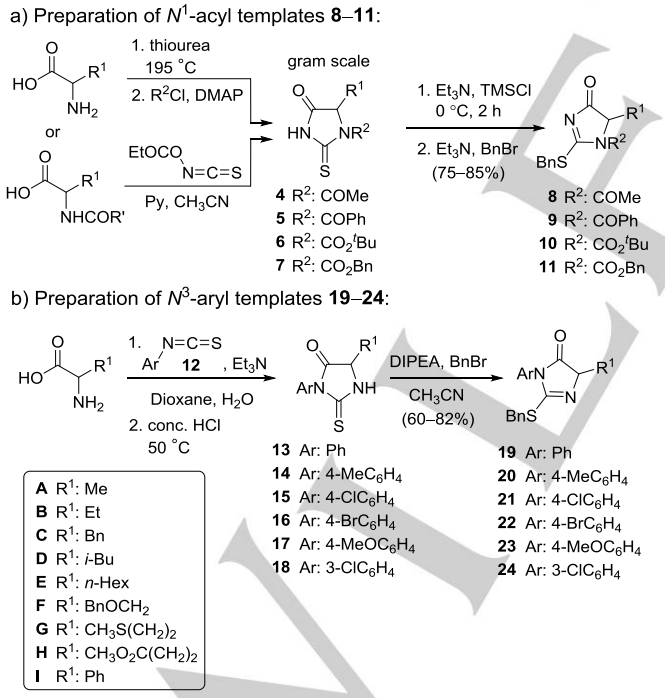
similar reasoning, it was envisaged that the related heterocylic systems **II** (N^1-acyl) and **III**, would lead, in the presence of a base promoter, the corresponding aromatic enolates **II'** and **III'**. Moreover, in view of the structural similarities of the three enolates, their interaction with the protonated amine/squaramide catalyst might be equally productive in affording the Michael addition adducts.

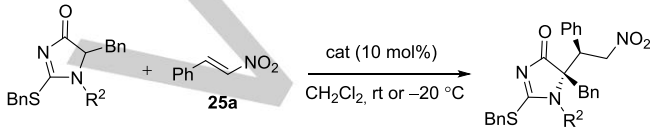
Preparation of substrates. The preparation of *N*-acyl templates **8–11** was carried out by the sequence described in Scheme 2a. Racemic hydantoins **4–7**, prepared in bulk quantities through classic condensation reactions of the corresponding free or *N*–acyl amino acids and suitable reagents,[27, 28, 29] were first silylated with trimethylchlorosilane and triethylamine, and then treated with benzyl bromide, to afford, after aqueous work-up, the desired N^1-acyl 2-benzylthioimidazolone **8–11**. It is important to note at this point that these compounds turned out to be solids and comparatively more stable than the corresponding *N*-alkyl and aryl compounds **I**. For instance, compounds **8–11** showed to be perfectly stable at room temperature for several days. On the other hand, the preparation of the N^3-aryl templates **19–24** (Scheme 2b) started with the condensation of the respective amino acid with phenyl(aryl) isothiocyanate **12** and triethylamine to yield thiohydantoins **13–18**. Each one was S-benzylated by treatment with benzyl bromide and diisopropyl ethyl amine to yield **19–24**, which also resulted to be bench-stable compounds.



Scheme 2. Preparation of N^1-acyl and N^3-aryl 2-benzylthio-3,5-dihydroimidazol-4-ones.

Reactions of N^1-acyl 2-thiobenzyl-3,5-dihydroimidazol-5-ones. To assess the viability of these substrates, their behaviour against nitroolefins under the same conditions previously reported for the N-alkyl/aryl congeners **1** was evaluated. Gratifyingly, as the brief screening in Table 1 shows, the reaction of N-acetyl **8C** with nitrostyrene **25a** to afford adduct **26Ca** proceeded at room temperature in the presence of various bifunctional Brønsted base catalysts with remarkable selectivity, whilst reactivity was more catalyst-dependent. For instance, both catalysts **C1** and **C2** were able to afford adduct **26Ca** as a 97:3 mixture of diastereomers in very high (but opposite) enantioselectivity, although no full conversion could be reached in either case after 24 h (entries 1, 5). As expected, catalyst ent-**C1** (entry 2) afforded the same enantiomer as **C2** with reproducible reactivity and selectivity compared to **C1** and was employed from this point on.

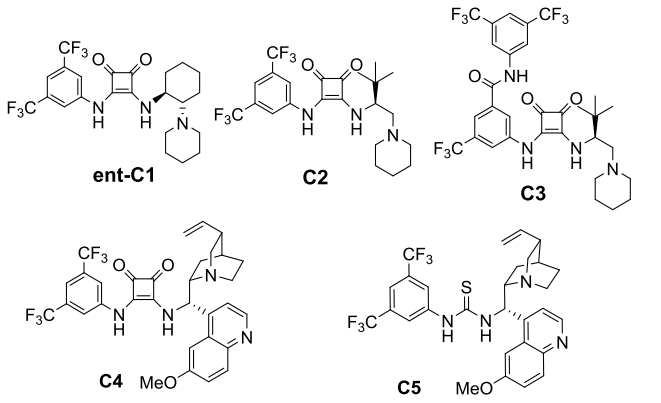
Table 1. Catalyst screening for the reaction of **8C**/**9C** with nitrostyrene **25a** (R: Ph).[a]



8C R^2: COMe
9C R^2: COPh

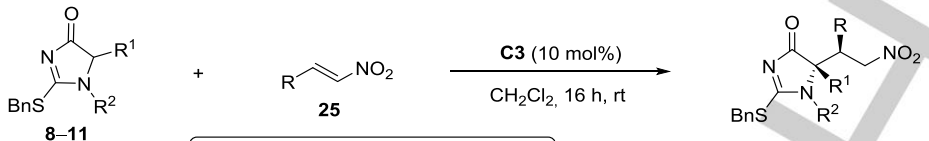
26Ca R^2: COMe
27Ca R^2: COPh

Entry	Catal.	R^2	T [ºC]	t [h]	Conv [%]	*dr*	*ee* [%]
1	**C1**	COMe	RT	24	80	97:3	–98
2	ent-**C1**	COMe	RT	24	80	97:3	98
3		COPh	RT	16	>98	>98:2	98
4			–20	96	NR	--	--
5	**C2**	COMe	RT	24	50	97:3	98
6		COPh	RT	16	>98	>98:2	97
7			–20	96	65	>98:2	98
8	**C3**	COMe	RT	16	90	98:2	99
9		COPh	RT	4	>98	98:2	99
10			–20	48	>98	>98:2	98
11	**C4**	COMe	RT	16	95	90:10	99
12	**C5**	COMe	RT	16	60	80:20	90

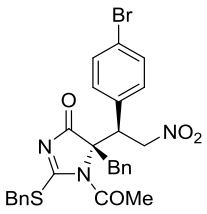


[a] The reactions were performed using 0.3 mmol of **8C**/**9C**, 0.6 mmol of nitrostyrene and 10 mol% catalyst in 0.6 mL CH_2Cl_2. *Ee* of major diastereomer as determined by HPLC

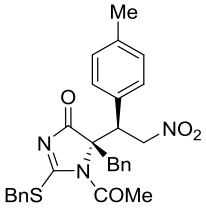
Table 2. Scope of the reaction of *N*[1]-acyl 2-benzylthio-3,5-dihydroimidazol-4-ones **8**–**11** with nitroalkenes **25**.[a]



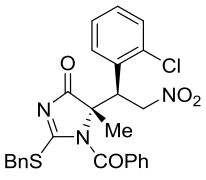
a	R: Ph	**h**	R: 4-$MeOC_6H_4$
b	R: 4-BrC_6H_4	**i**	R: 3-$MeOC_6H_4$
c	R: 4-ClC_6H_4	**j**	R: 2-$MeOC_6H_4$
d	R: 3-ClC_6H_4	**k**	R: 4-$Me_2NC_6H_4$
e	R: 2-ClC_6H_4	**l**	R: 2-furyl
f	R: 4-CNC_6H_4	**m**	R: *i*-Bu
g	R: 4-MeC_6H_4	**n**	R: *n*-Pr



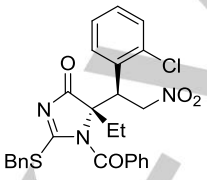
26Cb, 73%
>98:2 *dr*, 99% *ee*



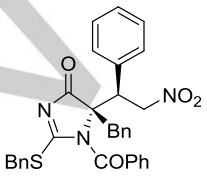
26Cg, 76%
95:5 *dr*, 97% *ee*



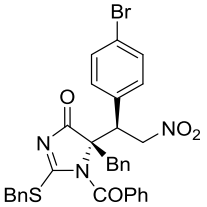
27Ae, 72%[b]
97:3 *dr*, 96% *ee*



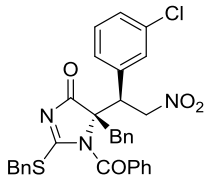
27Be, 70%[b]
97:3 *dr*, 98% *ee*



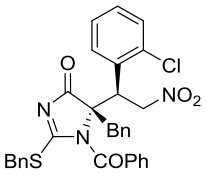
27Ca, 76%
>98:2 *dr*, 98% *ee*



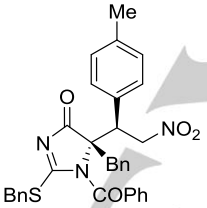
27Cb, 78%
>98:2 *dr*, 98% *ee*



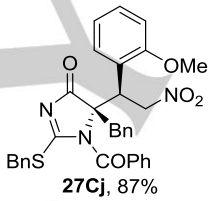
27Cd, 80%
74:26 *dr*, 98% *ee*



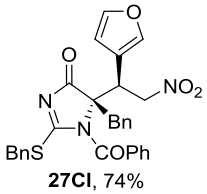
27Ce, 89%
96:4 *dr*, 98% *ee*



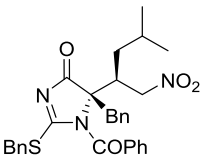
27Cg, 75%
>98:2 *dr*, 94% *ee*



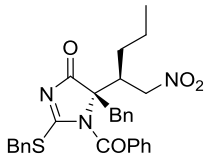
27Cj, 87%
>98:2 *dr*, 98% *ee*



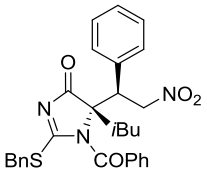
27Cl, 74%
85:15 *dr*, 98% *ee*



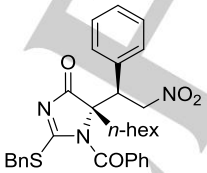
27Cm, 53%[b,c]
>98:2 *dr*, 92% *ee*



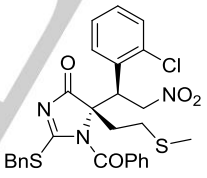
27Cn, 40%[b,c]
>98:2 *dr*, 90% *ee*



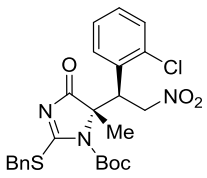
27Da, 88%
98:2 *dr*, 92% *ee*



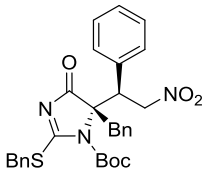
27Ea, 73%
>98:2 *dr*, 97% *ee*



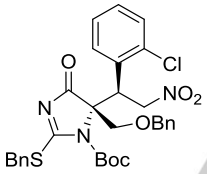
27Ge, 73%
>98:2 *dr*, 98% *ee*



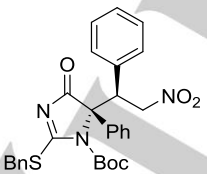
28Ae, 83%
91:9 *dr*, 99% *ee*



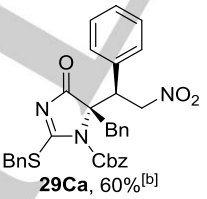
28Ca, 70%
>98:2 *dr*, 99% *ee*



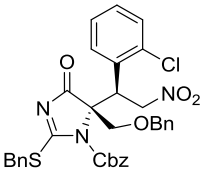
28Fe, 84%
94:6 *dr*, 99% *ee*



28Ia, 69%[d]
92:8 *dr*, 90% *ee*



29Ca, 60%[b]
>98:2 *dr*, 99% *ee*



29Fe, 91%
95:5 *dr*, 98% *ee*

[a] Reaction conditions: dihydroimidazolones **8**–**11** (1 eq, 0.2 mmol), nitroolefins **25** (2 equiv, 0.4 mmol), and **C3** (10 mol %) were stirred at 20 °C in 1.0 mL of CH_2Cl_2 for 16 h unless otherwise stated. Diastereomeric ratios and *ee* were determined by HPLC. [b] Reaction run for 48 h. [c] Reaction performed in deoxygenated dimethoxyethane at 50 °C using 5 equiv. of nitroalkene and 20 mol% catalyst. [d] Reaction run for 72 h.

The newly developed catalyst **C3**[30] was more active, leading to essentially full conversion after 24 h (90% conversion after 16 h) with nearly the same degree of diastereo- and enantiocontrol (entry 8). Regardless the catalyst employed, the N-benzoyl analog **9C** proved to be more reactive than the N-acetyl derivative **8C** and upon reaction with nitrostyrene afforded the

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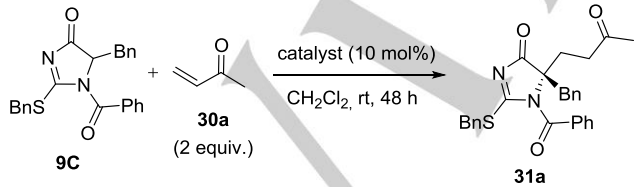
corresponding adduct **27Ca**, again, in essentially perfect diastereo- and enantioselectivity (entries 3, 6 and 9). This same order of catalyst activity, namely ent-**C1** < **C2** < **C3**, was observed at subzero temperatures, despite the fact that ent-**C1** is perfectly soluble, while both **C2** and **C3** were only partially soluble. Thus, whilst ent-**C1** was completely unactive at –20 °C, **C2** (entry 7) and specially catalyst **C3** (entry 10), did promote the reaction between **9C** and nitrostyrene at that temperature, affording compound **27Ca** in very high stereoselectivity. It was also observed that cinchona-based squaramide catalyst **C4**[31] was equally active, albeit less selective (dr 90:10, entry 10), whilst the corresponding thiourea analog **C5**[32] was both less active and selective (entry 11). In their turn, quinine and $(DHQD)_2PYR$ were completely ineffective catalyst for this reaction. With these initial results in hand, the scope of the reaction was explored using catalyst **C3**, albeit ent-**C1** and **C2** could be employed with almost equal effectiveness. As the data in Table 2 show, the reactions were performed at room temperature and worked uniformly well for N-acyl heterocycles **8**/**9** bearing a variety of substituents at the **C5** position of the heterocycle (benzyl, short and large linear alkyl, branched alkyl, heteroalkyl). A range of 5,5-disubstituted cycloadducts **26**/**27** were isolated in very high yields and enantioselectivities, and in dr generally ≥94:6, adduct **27Cd** (dr=74:26) being an exception. The reactions involving the more problematic aliphatic nitroolefins did also proceed with very good diastereo- and enantioselectivity (adducts **27Cj** and **27Ck**). However, these latter substrates resulted comparatively less reactive than the aromatic congeners and required 5 equiv. of nitroalkene and 20 mol% catalyst in DME at 50 ºC for practical reaction conversions. Under these conditions, deoxygenated solvent was optimal to prevent α-hydroxylation reaction. Dihydroimidazolone templates with N-Boc and N-Cbz groups (**10** and **11**) were also competent substrates for this reaction, affording adducts **28** and **29** with essentially perfect stereoselectivity and good yields. As formation of product **28Ia** in 69% yield and high selectivity proves, the method is also suitable for templates with an aryl group at the **C5** position. It should be mentioned that in some instances and under extended reaction times the formation of small amounts (~5%) of overaddition of the initially formed adduct to a second molecule of nitroolefin was observed. Adjusting the reaction time was generally enough to minimize or even cancel this undesired side reaction properly.

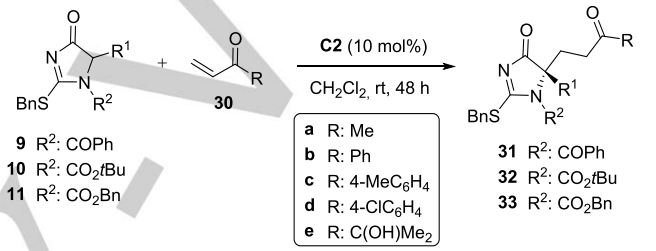


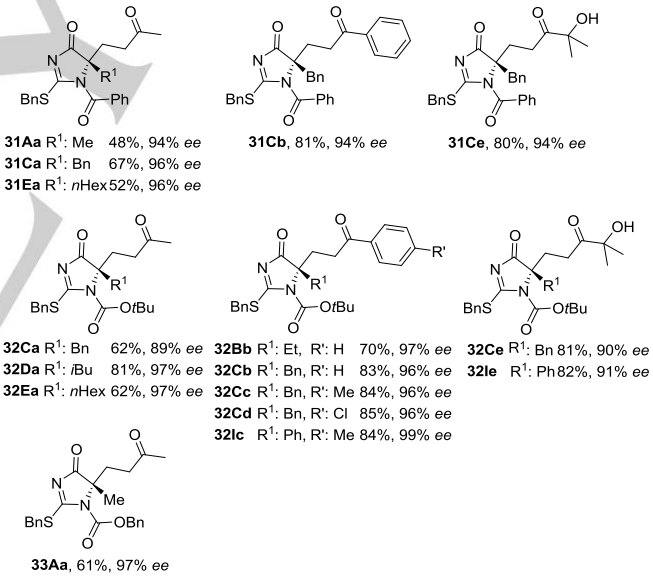
Catalyst	conv. (%)	*ee* (%)
ent-C1	50	72
C2	85	96
C3	70	95

Scheme 3. Catalyst screening for the reaction of **9C** with methyl vinyl ketone **30a**.

At this stage, the efficacy of this catalytic system against simple vinyl ketones, a less active but yet relevant Michael acceptor category, was explored. Initial screening of catalysts for the reaction of **9C** with methyl vinyl ketone **30a** as representative reaction model (Scheme 3), showed a trend in catalyst activity and selectivity similar to that observed with nitroalkenes. Thus, ent-**C1** could promote the addition of **9C** to **30a**, although the reaction progressed slowly and with suboptimal enantioselectivity. In contrast, catalyst **C3** and, especially, **C2** resulted comparatively more active (reaction conversion after 48 h at room temperature, 70% and 85%, respectively) and led to *ee*'s of 95% and 96%.

Table 3. Reaction of N-acyl 2-benzylthioimidazolones **9**–**11** with vinyl ketones **30**.[a]



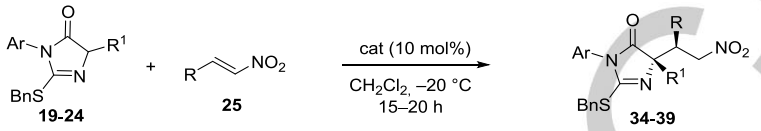


[a] The reactions were performed using 0.3 mmol of **9**-**11**, 0.6 mmol of vinyl ketone **30** and 10 mol% catalyst **C2** in 0.6 mL CH_2Cl_2. *Ee* determined by HPLC.

Then the reactions of **9**, **10** and **11** with vinyl ketones **30** were explored, using **C2** as the catalyst. As data in Table 3 show, independently of the substitution pattern, each vinyl ketone **30a**-**d** was equally competent reaction partner giving rise to the respective Michael adducts **31**-**33** in generally good yields and selectivities. On the other hand, intrinsically less reactive Michael acceptors, such as α,β-unsaturated esters and, in particular, acrylates, were not competent reaction partners. However, this deficiency may be surmounted in part by using the α-hydroxy

enone **30e**, an acrylate equivalent (vide infra) very easy to prepare from acetone or commercially available 3-hydroxy-3-methyl-2-butanone in two steps.[33] Thus, adducts like **31Ce**, **32Ce** and **32Ie** were obtained in good yield and selectivity, and, as will be shown later, could be converted into the corresponding carboxylic acid product through conventional ketol cleavage.

Table 4. Scope of the catalytic reaction of N^3-substituted 2-benzylthio-3,5-dihydroimidazol-4-ones with nitroolefins.[a]

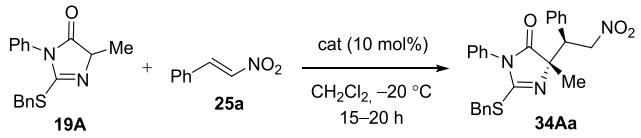


Entry	Ar	R^1	R	Product	Catalyst	Yield [%]	*dr*	*ee* [%]
1	Ph	Me	4-BrC_6H_4	**34Ab**	**C2**	95	>98:2	99
2	Ph	Me	4-ClC_6H_4	**34Ac**	**C2**	94	>98:2	99
3	Ph	Me	3-ClC_6H_4	**34Ad**	**C2**	86	>98:2	99
4	Ph	Me	2-ClC_6H_4	**34Ae**	**C2**	90	>98:2	99
5	Ph	Me	4-NCC_6H_4	**34Af**	**C2**	88	>98:2	96
6	Ph	Me	4-MeC_6H_4	**34Ag**	**C2**	87	>98:2	97
7	Ph	Me	4-MeC_6H_4	**34Ag**	**C3**	83	84:16	96
8	Ph	Me	4-$MeOC_6H_4$	**34Ah**	**C2**	85	95:5	90
9	Ph	Me	4-$MeOC_6H_4$	**34Ah**	**C3**	86	70:30	90
10	Ph	Me	3-$MeOC_6H_4$	**34Ai**	**C2**	94	>98:2	98
11	Ph	Me	4-$Me_2NC_6H_4$	**34Ak**	**C2**	92	>98:2	99
12	Ph	Bn	Ph	**34Ca**	**C2**	90	93:7	98
13	Ph	Bn	Ph	**34Ca**	**C3**	92	91:9	99
14	Ph	$(CH_3)_2CHCH_2$	Ph	**34Da**	**C2**	90	>98:2	99
15	Ph	$MeSCH_2CH_2$	Ph	**34Ga**	**C2**	85	>98:2	86
16	Ph	$MeO_2CCH_2CH_2$	Ph	**34Ha**	**C2**	90	>98:2	99
17	4-MeC_6H_4	Me	Ph	**35Aa**	**C2**	89	93:7	97
18	4-ClC_6H_4	Me	Ph	**36Aa**	**C2**	90	>98:2	94
19	4-BrC_6H_4	Me	Ph	**37Aa**	**C2**	86	>98:2	99
20	4-$MeOC_6H_4$	Me	2-ClC_6H_4	**38Ae**	**C2**	91	>98:2	94
21	3-ClC_6H_4	Me	4-$MeOC_6H_4$	**39Ah**	**C2**	90	>98:2	87

[a] Reaction conditions: **19**–**24** (1 eq, 0.3 mmol), **25** (2 equiv, 0.6 mmol), catalyst (10 mol %) were stirred at –20 °C for 15–20 h in 0.6 mL of CH_2Cl_2. Diastereomeric ratio and *ee* for the major diastereomer were determined by HPLC.

Reactions of N^3-aryl 2-thiobenzyl-3,5-dihydroimidazol-4-ones 19–24 with nitroolefins. In all examples shown the masked hydantoins of type **I/II** were used exclusively. Accordingly, the hydrolysis of the isothiourea moiety of the resulting adducts would deliver a route to N^3-unsubstituted hydantoins (see below). In order to develop a similar catalytic approach useful for the synthesis of the complementary N^3-protected N_1-unsubstituted hydantoins, we next studied the behaviour of 2-benzylthio-dihydroimidazolones **19**–**24**. While it was expected that these compounds would also provide an extended pseudoaromatic enolate species **III'** upon enolization in the presence of a bifunctional Brønsted base catalyst (Fig 4), whether or not these latter would react as efficiently as **I'/II'** was unanswered yet. To begin the study, the reaction of **19A** with β-nitrostyrene **25a** was carried out in the presence of a base catalyst. As the results in Scheme 4 show for the titled reaction, catalyst ent-**C1** was able to promote the formation of the contiguous quaternary and tertiary carbon stereocenters of **34Aa** with good isolated yield, moderate diastereoselectivity (62:38) and very high enantioselectivity for the major isomer. Under such smooth reaction conditions, among the catalyst examined, both catalysts **C2** and **C3** were, once again, the best in affording product **34Aa** in nearly quantitative yield, diastereoselectivities higher than 95:5 and excellent enantioselectivity (96% and 95% *ee*, respectively, for the almost exclusive diastereomer).

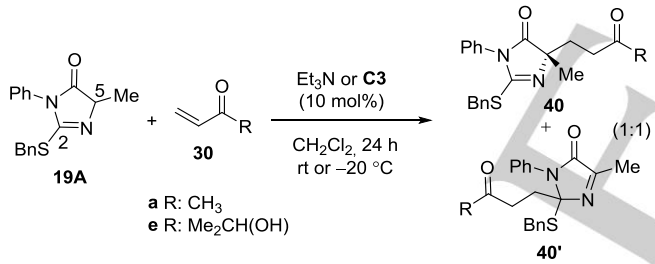
With catalyst **C2** selected for further reaction development, the robustness of the method with respect to structural variation of both reactants was explored (Table 4). As data in entries 1–11 illustrate, aryl-substituted nitroolefins **25a**-**k** with either electron-reach, neutral or poor character were equally competent reaction partners affording upon reaction with **19A** the corresponding



(ent-**C1**) 95%, dr 62:38, 94% *ee*
(**C2**) 99%, dr 97:3, 96% *ee*
(**C3**) 95%, dr 96:4, 95% *ee*
(**C4**) 99%, dr 83:17, 88% *ee*
(**C5**) 99%, dr 60:40, 75% *ee*

Scheme 4. Catalyst screening for the reaction of **19A** with nitrostyrene.

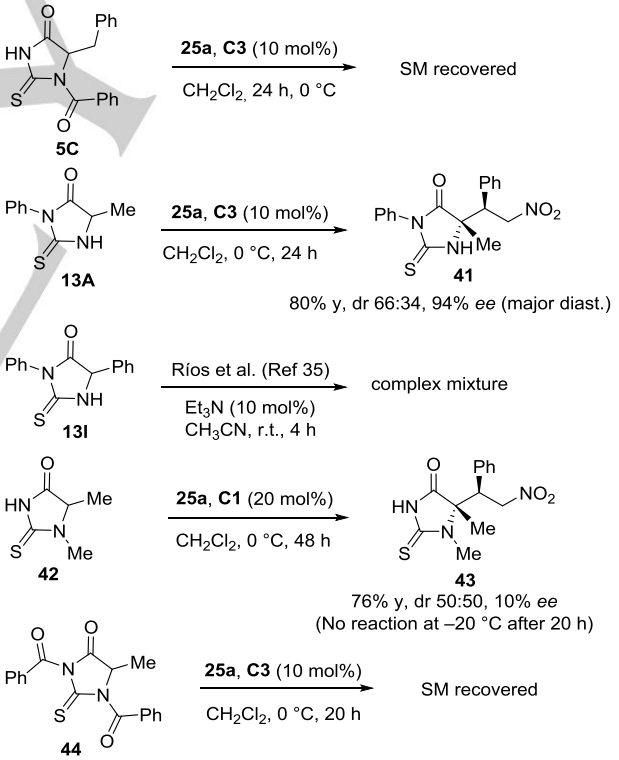
adducts **34A** in very good yields and with nearly perfect diastereo- and enantioselectivity in most cases. During this substrate screening, catalyst **C3** revealed to be less efficient than **C2**, as the inferior diastereoselectivity attained for products **34Ag** and **34Ah** indicates (compare entries 7/6 and 9/8). Variation of the R^1 substituent of the imidazolidinone substrate did not have any appreciable impact on the reaction outcome. Thus, not only methyl, but also benzyl (entries 12, 13) and other alkyl (entry 14) and functionalized chains (entries 15, 16) were tolerated at the substrate **C5** position without affecting the reaction efficiency and selectivity. On the other hand, as the results in entries 17-21 demonstrate, N^3-aryl substrates **20**-**24** bearing aryl groups other than phenyl also participate in this reaction satisfactorily.



Scheme 5. Reaction of 2-benzylthiodihydroimidazolones **19A** with vinyl kenones **30a** and **30e**.

Vinyl ketones also were competent electrophilic partners in the reactions of N^3-substituted 2-benzylthioimidazolones **19**–**24**. However, in contrast to what was observed with nitroalkenes, the reactions involving vinyl ketones followed two divergent pathways, one producing the 5-addition products **40** and the 3-addition path leading to product **40'** (Scheme 5). Configuration of products **40'** was not determined and that of products **40** was assigned by assuming a uniform reaction mechanism. Attempts to favour either reaction pathway were unsuccessful and, regardless the catalyst and reaction temperature, an essentially equimolar ratio of either product was formed for the studied cases (Scheme 5). Similar observations were previously reported in BB-catalyzed addition reactions involving azlactones as the nucleophile.[34]

Control experiments using the related thiohydantoins. To put in context the reactivity and, particularly, selectivity profiles of templates **I–III** under the present soft enolization conditions, the behavior of **5C**, **13A**, **42** and **44**, four parent thiohydantoins with comparable substitution patterns at N^1 and N^3, was explored (Scheme 6). Initial control experiments showed that, in contrast to templates **I–III** (see above), none of these four thiohydantoins reacted at all with nitrostyrene **25a** in the presence of catalyst **C3** at low temperature (experiments carried out at –20 °C). This lack of reactivity was most evident in the case of thiohydantoin **5C** which remained unchanged even after stirring the mixture for 24 h at 0 °C. We ascribe the comparatively higher reactivity of templates **I–III** to their tendency towards enolization owing to the aromatic character of the resulting enol/enolate intermediate species. At higher temperatures (0 °C) N^3-phenyl thiohydantoin **13A** reacted with nitrostyrene **25a** in the presence of catalyst **C3**, but product **41** was obtained as a 1.9:1 mixture of diastereomers. Similarly, N^1-methyl thiohydantoin **42** also reacted with nitrostyrene **25a** at 0 °C, but, again, led to a roughly equimolecular mixture of diastereomers with marginal enantioselection. In its turn, it has been reported by Rios[35] that **13I** upon treatment with nitrostyrene at room temperature gave a complex mixture. Finally, the N,N-dibenzoyl derivative **44** showed to be completely unreactive under these conditions.



Scheme 6. Reactivity profile of the related thiohydantoins **5C**, **13A**, **13I**, **42** and **44**. SM: starting material.

Hydrolysis of adducts into 5,5-disubstituted hydantoins. Removal of the benzylthio adjuvant from adducts obtained through these series of catalytic conjugate addition reactions

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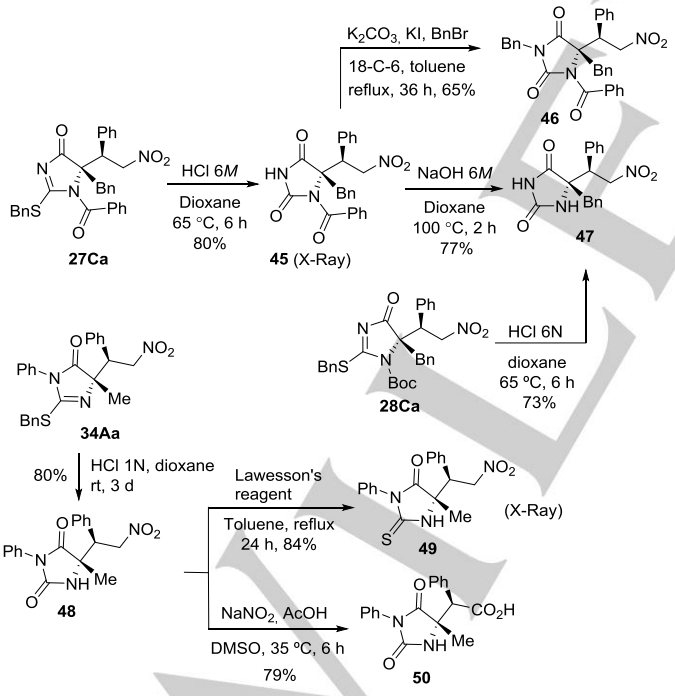
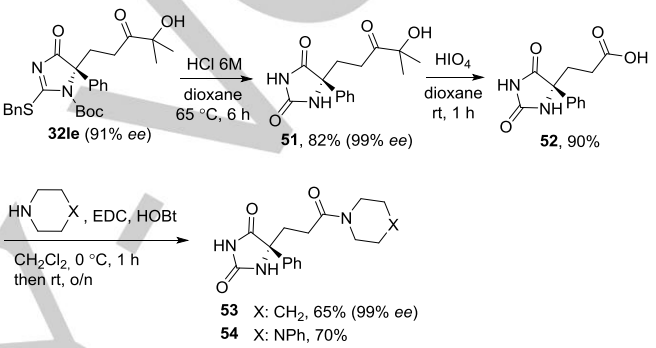
could be carried out by hydrolysis under various convenient conditions. As shown in Scheme 7, treatment of N_1-benzoyl adduct **27Ca** with HCl 6M in dioxane at 65 °C for 6 hours gave rise to the corresponding N-acyl hydantoin **45** in 80% yield. Subsequent treatment of **45** with NaOH 6M at 100 °C produced the free hydantoins **47** in 77% yield. On the other hand, the same acid hydrolytic conditions applied to N-Boc adduct **28Ca** induced concomitant deprotection of Boc group affording hydantoin **47**. Interestingly, alkylation of imide nitrogen in product **45** under standard Williamson conditions allowed access to the corresponding N-benzyl adduct **46** in good yield. In its turn, hydrolysis of N^3-phenylthio-4,5-dihydroimidazol-4-one **34Aa** to the respective hydantoin **48** could be carried out by treatment with HCl 1M at room temperature. Temperature control for this reaction is important for clean hydrolysis. The same reaction carried out at more forcing conditions (65 °C) led to a 1:1 mixture of compounds **48** and the thio-analog **49**. In any event, the resulting adduct **48** could be fully converted into its thiohydantoin analog **49** applying Lawesson's reagent, which served to establish the compound identity and configuration by X-ray analysis. On the other hand, Nef type oxidation of the nitro group in **48** under Mioskowski conditions[36] proceeded smoothly to furnish the carboxylic acid **50** in 79% isolated yield. Configurational integrity of adducts was not affected during all these transformations and the final products were obtained as essentially single enantiomer (≥99% *ee*).



Scheme 7. Hydrolysis of cycloadducts to 5,5-disubstituted hydantoins and further elaborations.

Scheme 8 shows a specific application to the synthesis of pharmacologically active constituents based on a three-step sequence. Both amides **53** and **54** have been reported to present significant inhibitory activity as ADAMTS (A disintegrin and metalloproteinase inhibitors).[37] Starting from adduct **32Ie** (Table 2, 82%, 91% *ee*), an acid hydrolysis of the S-benzylisothiourea moiety in dioxane at 65 °C, followed by ketol oxidative scission with HIO_4, provided carboxylic acid **52** in 74% yield over two steps. Final coupling of acid **52** with piperidine and N-phenyl piperazine using EDC/HOBt coupling reagent led to amides **53** and **54** in 65% and 70% yield, respectively. These examples show that adducts can be manipulated easily, with minimum production of waste organic materials (e.g. acetone is obtained as byproduct in the **51**→**52** transformation) and, most important, with preserved configurational integrity.



Scheme 8. Synthesis of ADAMTS (A disintegrin and metalloproteinase) inhibitors **53** and **54**.

Mechanistic insights. Several experiments were carried out in order to get insights on the reaction mechanism. In a first set of experiments (Figure 5), the conversion for the reaction between **10C** and **25a** was measured as a function of time, maintaining the concentration of **25a** pseudoconstant (15 equiv.) and in the presence of 10 mol% of catalyst **C3**. The plotting in of $-\ln([\mathbf{10C}]/[\mathbf{10C}]_o)$ versus time gave a straight line (R^2=0.996) which indicates first-order dependence in the nucleophile.

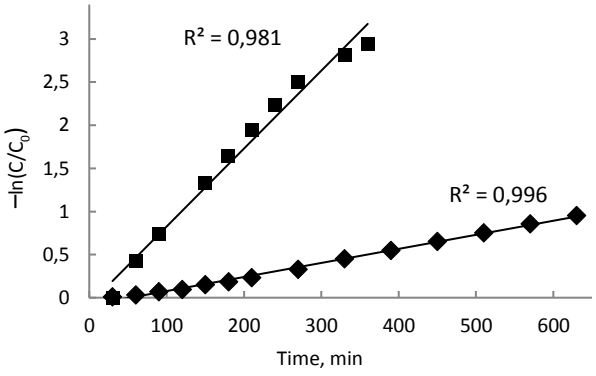


Figure 5. Plot of reaction conversion vs. time for the **C3**-catalyzed reaction between **10C** and **25a** under pseudoconstant concentration of **25a** (♦) and **10C** (■).

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The reaction order in the electrophilic component was determined similarly by measuring the reaction conversion as a function of time under pseudoconstant concentration of nucleophile **10C** (15 mol equiv.) and in the presence of 10 mol% of catalyst **C3**. In this instance, plotting ln([**25a**]/[**25a**]$_0$) versus time afforded again a straight line (R^2=0.9815) indicating first-order reaction with respect to the acceptor component too. Unfortunately, the reaction order in the catalyst could not be determined by this means due to the limited solubility of the catalyst.

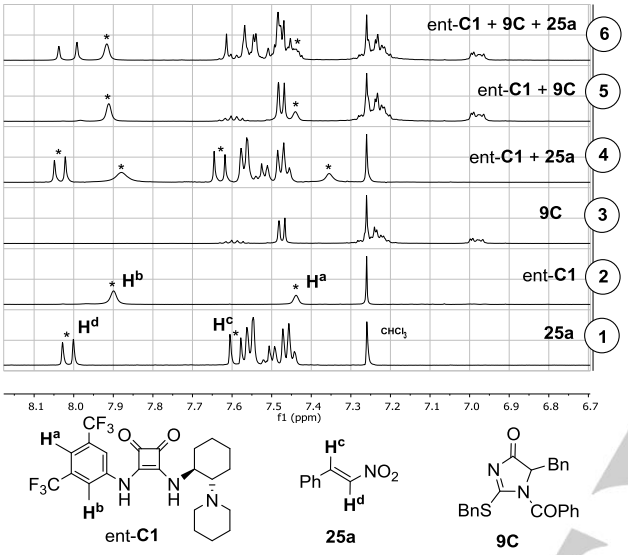

Figure 6. Insets of ^{1}H NMR spectra corresponding to individual samples of **9C**, **25a**, ent-**C1**, and three 1:1 combinations of them taken in $CDCl_3$ at rt (concentration ~0.1 M).

On the other hand, the collective experimental data shown in Tables 1–4 reveal the unique reactivity profile of templates **I**–**III**, as opposite to the variable results attained with the parent thiohydantoins (see Scheme 6). An interesting aspect of this high reactivity is that it appears quite general regardless the catalyst employed, and therefore it should be ascribed to an inherent feature of the template design. As shown in the introductory section (Fig 4), the pseudoaromatic character of the enolic forms **I'**–**III'** would facilitate the enolization process, but this effect alone would not necessarily justify the subsequent reactivity against the electrophilic acceptor. In order to get additional insights in this respect, and more specifically with regard to the affinity of the templates for these type of bifunctional catalysts, we performed competitive ^{1}H NMR experiments involving template **9C**, nitroolefin **25a** and catalyst ent-**C1** (Figure 6). Catalyst ent-**C1** was chosen because its complete solubility in halogenated solvents as noted above. As the comparison of spectra 1, 2 and 4 shows, admixing **25a** and ent-**C1** caused a slight downfield shift of the olefinic protons H^c/H^d of **25a** along with an upfield shift of H^a and H^b of ent-**C1**, quite significant ($\Delta\delta \approx 0.1$ ppm) in the former case, clearly indicating some degree of molecular recognition between nitrostyrene **25a** and the catalyst. In its turn, variation of the chemical shifts when admixing the template **9C** and the catalyst (compare spectra 2, 3 and 5) seemed to be less pronounced, with only a slight downfield shift of H^b. However, spectrum 6, in which both substrates **25a** and **9C** must compete for best catalyst binding, reveals that the molecular affinity between **9C** and ent-**C1** is relatively high. Indeed, the chemical shift pattern of ent-**C1** in 6, in particular the chemical shifts of both H^a and H^b, remained essentially that of spectrum 5 and distinct from spectrum 4. These observations reinforce the idea that the new hydantoin template upon enolization would remain tightly bound to the catalyst during the key C–C bond-forming event, allowing an efficient transfer of chiral information.

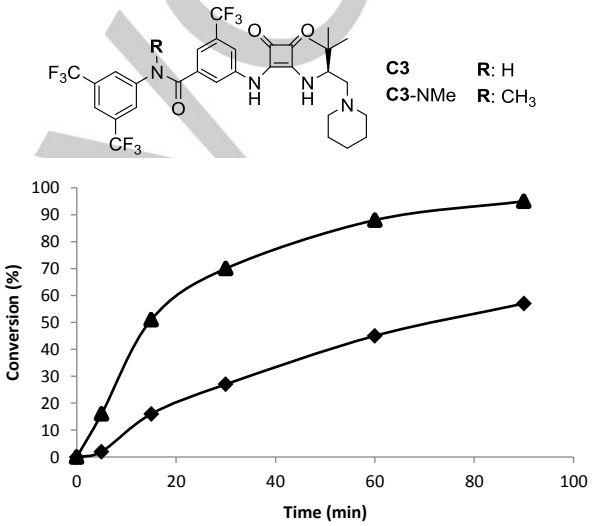

Figure 7. Conversions for the reaction between **9C** and **25a** catalyzed by **C3** (▲) and its *N*-Me derivative (♦), respectively, under standard conditions.

In order to get more insights on the structural/functional requirements of these catalysts for optimal activity and selectivity, the performances of catalyst **C3**, featuring a free NH amide, and its N-Me derivative were compared. As the conversion profiles in Figure 7 show for the reaction between **9C** and **25a**, catalyst **C3** resulted significantly more active than its N-methylated form. For instance, with **C3** the reaction conversion was over 70% after 30 min at RT (over 90% after 1 h), whilst with **C3**-NMe barely reached 27% after 30 min (45% after 1 h). While erosion of the stereoselectivity was less important (**C3**, dr=98:2, 99% *ee*, Table 1, entry 9; **C3**-NMe, dr>98:2, 90% *ee*), the difference in catalyst activity is significant, especially considering that, unlike **C3**, **C3**-NMe is completely soluble, and may be attributable to the ability of the free amide in **C3** for additional H-bonding. Although the number of individual H-bond interactions within the substrate-catalyst complex in the transition state, and their precise orientation, are unknown yet, and based on previous studies in the literature for related catalytic systems,[38] a simultaneous activation of both reactants as in stereomodels **A**/**A'** (Figure 8) may be proposed tentatively for the reactions catalyzed by **C3**. The free amide NH would be H-bonded internally as in **A**, to assist

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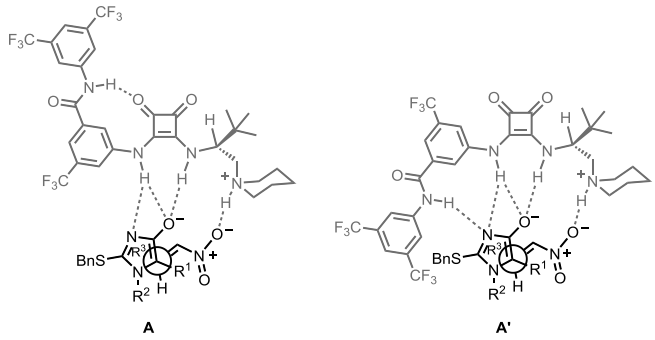
catalyst preorganization, or intermolecularly as in **A'** to better fix one of the approaching reactants. Similar models are conceivable for the remaining templates and catalysts in which the approaching trajectory of both reactants correctly explains the observed configuration, both relative and absolute, of adducts.



A **A'**

Figure 8. Plausible TS stereomodels for the **C3**-catalyzed reaction between templates **II** and nitroolefins.

Conclusions

A new, quick entry to the enantioselective synthesis of 5,5-disubstituted hydantoins has been developed based on an organocatalytic Michael reaction approach using easy to prepare and handle 2-benzylthio-3,5-dihydroimidazol-4-ones as key 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 (linear/branched alkyl, aryl) positions of the resulting hydantoins and affords essentially single diastereomeric products with enantioselectivities higher than 95% *ee* in most cases. These hydantoin surrogates demonstrate to be clearly superior to the parent thiohydantoins which were inefficient in terms of reactivity and/or selectivity under similar catalytic conditions. Among the catalysts examined, **C2** and the newly prepared squaramide-tertiary amine catalyst **C3** provided the highest selectivity in the reactions with either nitroolefins or vinyl ketones as the acceptor component. One designing advantage of **C3** is its adaptability to particular reaction needs owing to the easy modification of the carboxamide unit. Kinetic studies of these catalytic Michael reactions support a first order rate dependence on both donor and acceptor reactants. On the other hand, ^{1}H NMR monitoring of mixtures of donor template, acceptor and catalyst suggest that the good reactivity, and high fidelity of chirality transfer with, these templates is bound to the unique capacity of the benzylthiodihydroimidazolone system for catalyst binding. Since the adducts obtained through the present method may display a tetrasubstituted stereogenic center adjacent to a tertiary one and can be chemically manipulated in many ways, new perspectives are opened in the field of hydantoin chemistry. The potential of the method is illustrated with an expeditious synthesis of ADAMTS inhibitors **53** and **54**. Further applications of templates **I-III** as pronucleophiles in related catalytic settings can be foreseen.

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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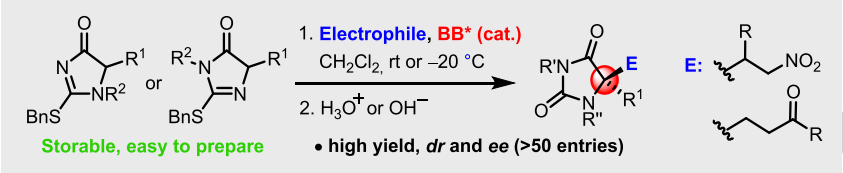

Hydantoins made easy: a general, catalytic and asymmetric procedure to access 5,5-disubstituted (quaternary) hydantoins is developed relying on the Brønsted base catalyzed enantioselective C-functionalization of a design dihydroimidazolone template with Michael acceptors.

Joseba Izquierdo, Julen Etxabe, Eider Duñabeitia, Aitor Landa, Mikel Oiarbide, Claudio Palomo**

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Enantioselective Synthesis of 5,5-Disubstituted Hydantoins via Brønsted Base Catalyzed Michael Reactions of a Design Template.