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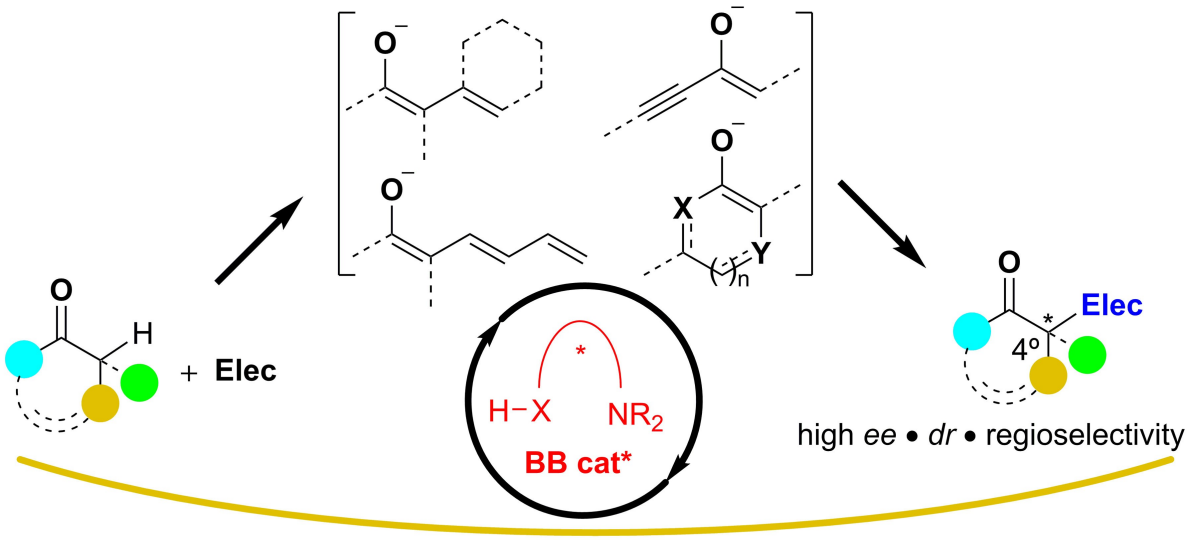
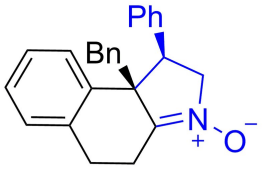
Brønsted Base-Catalyzed Enantioselective α-Functionalization of Carbonyl Compounds Involving π-Extended Enolates

Mikel Oiarbide* and Claudio Palomo*[a]

Dedicated to Prof. Keiji Maruoka on the occasion of his 70th birthday





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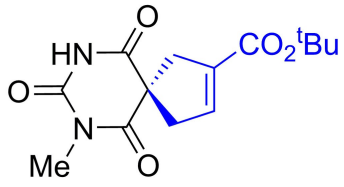

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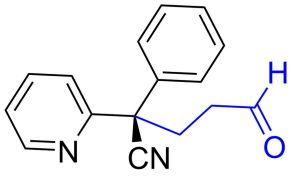

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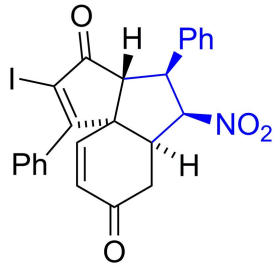

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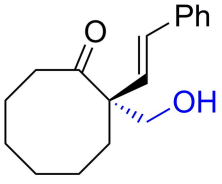

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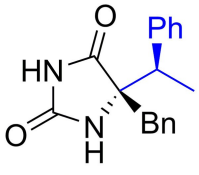

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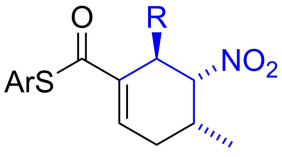

tetrasubstituted cyclohexenes

Abstract: Chiral Brønsted base (BB) catalyzed asymmetric transformations constitute an important tool for synthesis. A meaningful fraction of these transformations proceeds through transiently generated enolate intermediates, which display quite versatile reactivity against a variety of electrophiles. Some years ago, our group became interested in developing BB-catalyzed asymmetric reactions of enolizable carbonyl substrates that involve π-extended enolates in which, besides control of reaction diastereo and enantioselectivity, the site-selectivity control is an additional issue in most cases. In the examples covered in this account the opportunities deployed, and the challenges posed, by these methods are illustrated, with a focus on the generation of quaternary carbon stereocenters. In the way, new bifunctional BB catalysts as well as achiral templates were developed that may find further applications.

Keywords: asymmetric catalysis, bifunctional catalysis, extended enolates, quaternary stereocenters, regioselectivity

1. Introduction

Enolizable carbonyl compounds encompass a large variety of substructures, both cyclic and acyclic, and functional groups. Deprotonation of enolizable carbonyl compounds by Brønsted bases (BB) constitutes a major entry to enolates, which upon in situ coupling with, or addition to, an electrophilic reaction partner may lead to molecules with increasing structural and stereochemical complexity.[1] In this context, soft enolization procedures relying on the use of weak chiral organobases, particularly tertiary amines bearing one or more hydrogen-bonding (HB) donor groups attached, have been investigated extensively, enabling the development of catalyst-controlled enantioselective addition reaction of active enolizable carbonyl compounds to a range of suitable electrophiles.[2] The overwhelming majority of reported examples involve enolizable carbonyl substrates having attached at Cα an additional heteroatom-based functional group. This requirement, while considerably narrows the pool of substrates available for this type of catalytic activation, is ascribed to two main factors: (i) the necessity of threshold Cα carbon acidity of the pronucleophilic substrate for weak base-promoted deprotonation,[3] and (ii) the advantages of two-point catalyst coordination as critical element of transition state rigidification for attaining practical conversion and efficient chirality transfer.[4]

Recently, new catalyst systems based on chiral stronger Brønsted bases (sBB) capable of deprotonating, inter alia, simple enolizable carbonyl compounds have appeared.[5] Whereas the sBB approach may help to surmount the problem (i), the development of methods based on this approach progresses with paucity. In order to expand the chemical space accessible for asymmetric BB/HB bifunctional catalysis, exploring enolizable pronucleophiles incorporating either cyclic or acyclic chain unsaturation in the close vicinity of the carbonyl group bears particular interest. The presence of a double C=C (or triple C≡C) bond nearby the carbonyl in the enolizable substrate might not only facilitate deprotonation (increasing acidity) but might also modify critically the reactivity of the transiently formed enolate species, opening new opportunities for exploration.

Structures **A**-**D** depicted in Figure 1 represent various patterns of unsaturated enolizable carbonyl compounds. Deprotonation of these pronucleophiles by a base, as first step of a catalytic process, may render reactive species **A'**-**D'** capable of reacting with suitable electrophiles giving access to a variety of synthetically useful building-blocks. Some time ago, our group became interested in studying asymmetric BB-catalyzed C–C bond forming reactions involving various classes of π-extended enolates of cyclic and acyclic chain structure, e.g. structures **A'**-**D'**, as transient species. Especial attention was paid to the stereocontrolled formation of new tetrasubstituted carbon stereocenters, which remain a hot subject in asymmet-

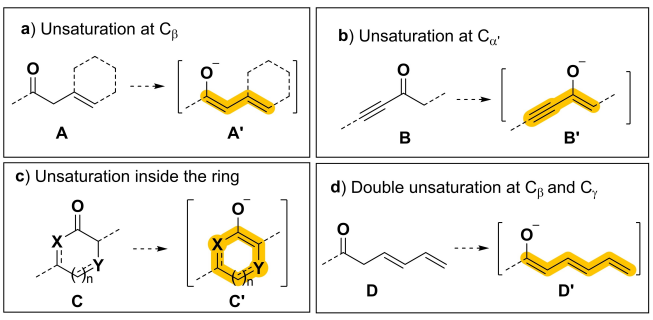

Figure 1. Unsaturated enolizable substructures leading to π-extended enolates considered in this account.

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ric catalysis.[6] In this personal account, we present our findings in this area, embracing from the development of improved BB/HB type catalysts and new reaction regioselectivity preferences to new opportunities for sequential, one-pot multi-bond forming catalytic processes. These studies ultimately provided new catalytic and enantioselective entries to access some molecular scaffolds relevant to medicinal chemistry, inter alia, 2-oxindoles, thiazolones, imidazolones, (thio)hydantoins, barbiturates, *N*-alkyl α-amino acids, and *o*-pyridyl acetonitriles, often bearing a quaternary carbon stereocenter.

2. BB-Catalyzed α-Functionalization of Unsaturated Lactam Heterocycles

Five-membered lactam heterocycles are widespread substructures within natural products, bioactive ingredients and advanced synthetic materials. A logical construction of such heterocycles with tridimensional architecture in enantioselective manner consists of the stereocontrolled α-functionalization of the enolizable parent lactam. As shown in Figure 2, partially unsaturated lactams bearing an additional O, S or N heteroatom in the ring may undergo deprotonation by weakly basic catalysts, such as tertiary amines, driven by the aromatic character of the formed enolate **I-1**. Then coupling with an electrophilic reagent would install the new group at Cα while generating a quaternary carbon stereocenter. Many catalytic methods have been reported for the α-functionalization of these heterocycles, including addition methods based on chiral Brønsted base catalysts. However, when α-substituted substrates are employed, enantioface discrimination across the trisubstituted enolate becomes challenging. To this end, the protonated catalyst must fit perfectly and interact simultaneously with the allegedly formed enolate and the approaching electrophile through multiple H-bonds mainly.

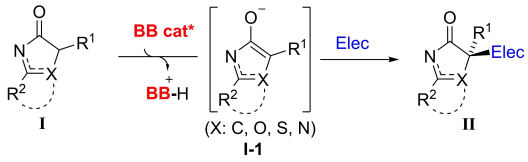

Figure 2. General depiction of 5-member enolizable lactam heterocycles and their BB-catalyzed α-functionalization via aromatic enolate intermediates.

2.1. α-Functionalization of Thiazolones, Oxazolones, Azlactones and 2-Oxindoles

First study in this area from our laboratory dealt with the catalytic conjugate addition of α-substituted 5*H*-thiazol-4-ones to nitroolefins. 5*H*-thiazol-4-ones may be viewed as surrogates of α-mercapto carboxylic acids and the enantioselective construction of these frameworks bearing a tetrasubstituted stereogenic center remains problematic.[7] In our hands, the reaction catalyzed by common urea- and thiourea-tertiary amine bifunctional catalysts[8] proceeded slowly at −60 °C and with diastero- and enantioselectivities from low to moderate. Inspired by the discovery of ureidopeptides as designed synthetic peptidomimetics in which a peptide bond is replaced with the ureido group,[9] it was wondered whether the additional NH moiety in the ureido-aminals **C1** would impart better catalytic efficiency than the parent ureas and thioureas. In this catalyst modification, an additional stereocenter is also incorporated as another element of structural tuning. The ureido-aminals such as **C1**/**C2** are easy to prepare from the corresponding *N*-protected amino acid through Curtius rearrangement and ulterior coupling of the resulting isocyanate with a chiral amine. Gratifyingly, the above addition reaction in the presence of these newly designed bifunctional catalysts proceeded comparatively faster and with higher stereoselectivity (Scheme 1).[10] Screening of various carbamate residues and chiral amine units led to identify **C1** as the optimum catalyst

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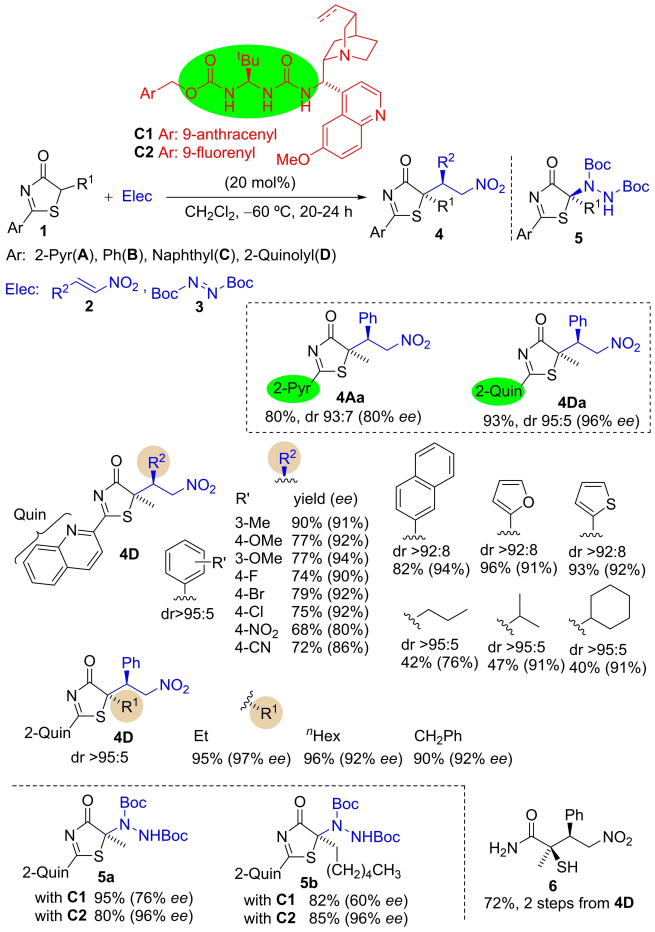
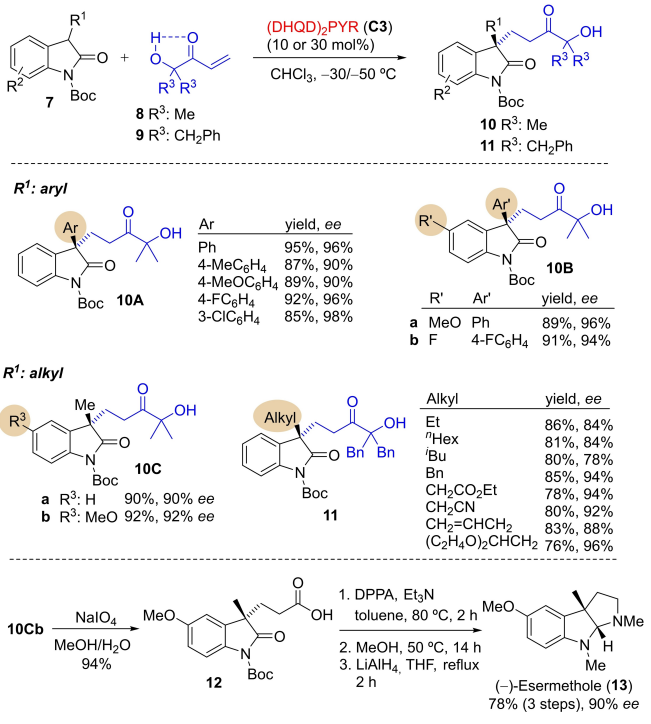
Mikel Oiarbide obtained his PhD from the University of the Basque Country UPV/EHU (Spain) in 1991 working with Prof. C. Palomo and J.M. Aizpurua on tributyltin hydride mediated transformations. He then spent two years as a PDRA with Prof. H. Rapoport at UC Berkeley (USA) working on the synthesis of N-glycosides pentostatin and coformycin. In 1994, he took up a tenure position at UPV/EHU and was promoted to Professor in 2003.



Scheme 1. Ureidoaminal/tertiary amine catalyzed addition of thiazolones **1** to nitroolefins and diazocompounds. Enantioselective generation of tetrasubstituted C–S stereocenters.

for the above reaction, affording product **4Aa** in 80% yield, 93:7 diastereomeric ratio and 80% *ee* for the major isomer. Importantly, the nature of the Ar group linked to the 5*H*-thiazol-4-one C_2 has an impact on the reaction outcome. Thus the reaction using quinolyl-substituted thiazolone **1D** resulted the most reactive and selective, affording adduct **4 Da** in 93% yield, 95:5 diastereomeric ratio and 96% *ee*. This catalytic addition reaction was extensible to 5*H*-thiazol-4-ones bearing ethyl or larger alkyl substituents at Cα, and a range of aryl nitroolefins were well tolerated. This reactivity pattern was extensible to the addition of **1** to diazocompounds, yielding the corresponding α-hydrazination adducts **5** in high yields and somehow attenuated enantioseletivity. Treatment of adducts **4** with 6 *N* HCl in dioxane at 45 °C and subsequently with 2 *N* NaOH afforded the corresponding α-mercapto carboxylic amides, such as **6**.

In connection to BB-catalyzed methodologies the realization of the Michael-type addition to acrylic systems, including acrylates, acrylamides, alkyl-vinyl ketones and acrolein, progresses slowly as compared with the addition to more reactive Michael acceptors such as nitroolefins and doubly activated systems.[11] In this context we introduced α'-hydroxy enones as an effective bidentate acrylic surrogate that may engage in H-bonding networks with the catalyst.[12] Since the ketol moiety in adducts may be easily converted into ester, alkyl ketone and aldehyde functions equally, the process would represent formally a uniform approach to addition to various acrylic systems. Among the useful nucleophilic reaction partners, π-extended enolates derivable from some heterocyclic lactams proved suitable in the presence of various types of chiral BB catalysts. For instance, the addition of α-aryl 2-oxindoles[13] **7** to α'-hydroxy enone **8** proceeded smoothly in the presence of 20 mol% (DHQD)PYR (**C3**) to afford quaternary carbon-bearing Michael adducts **10** in high yields and enantioselectivities (Scheme 2). Under these conditions, the enantioselectivity of the addition reaction of α-alkyl 2-oxindoles other than α-methyl to enone **8** was significantly lower. Fortunately, high selectivities were obtained when the *gem*-dibenzyl analog **9** was employed instead. Ulterior oxidative cleavage of the ketol moiety allowed access to the corresponding carboxylic acids ($NaIO_4$), aldehydes (BH_3 then $NaIO_4$) and ketones (R'MgBr then $NaIO_4$), respectively. For instance, treatment of **10Cb** with $NaIO_4$ afforded acid **12** in 94%, which could be



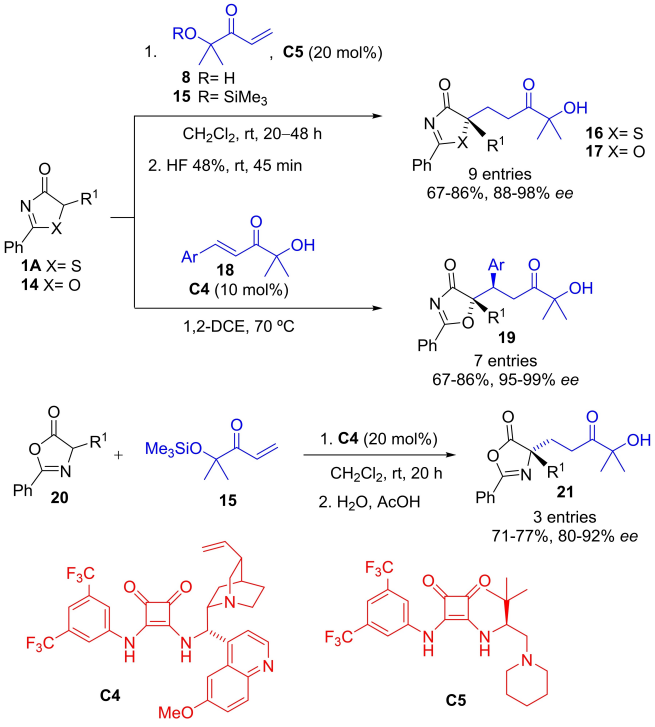
Scheme 2. Enantioselective α-functionalization of α-substituted 2-oxindoles.

transformed into esermethole **13**, a (−)-physostigmine precursor, in 78 % over three steps and 90 % *ee*.

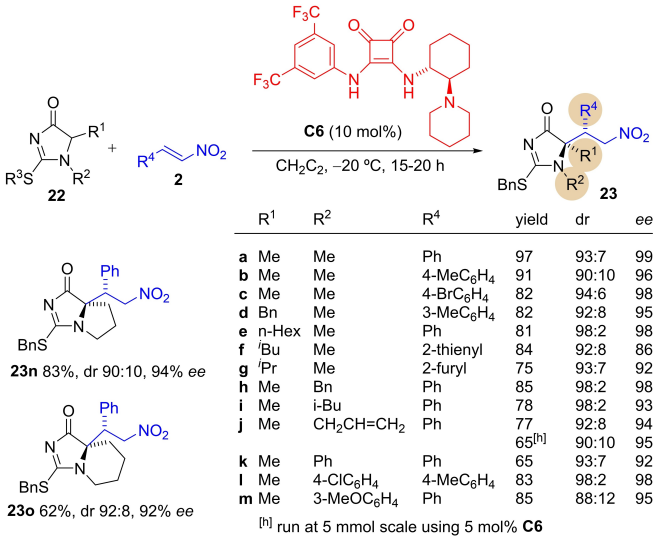
Enantioselective, catalytic conjugate additions of transiently generated π-extended enolates derived from related heterocyclic lactams and lactones, i. e. oxazolones, thiazolones and azlactones,[14] were also feasible. However, for optimum results with these enolizable heterocycles adjustment of the α-oxy enone template and/or the chiral BB catalyst was necessary. In particular, the addition of these enolizable heterocycles to the O-silyl protected analog **15** proceeded with higher enantioselectivity than the additions to the parent hydroxy enone **8** usually. As shown in Scheme 3, α-substituted thiazolones **1A** and oxazolones **14** reacted with **15** smoothly in dichloromethane at room temperature in the presence of squaramide **C5**[15] to afford, after in situ desilylation with HF, adducts **16** and **17** in yields in the range 67–86 % and 88–98 % *ee*, respectively. Similarly, azlactones **20** afforded adducts **21** in good yields and enantioselectivity with **C4**[16] as optimum catalyst. Oxazolones **14** also participated in the reaction with β-aryl substituted hydroxyenones **18** with generation of adjacent tertiary/quaternary stereogenic centers[6g] in good selectivity. The reaction involving the β-alkyl substituted hydroxyenone congeners **17** of **18** was unproductive. The high variability of the reaction outcomes depending on the particular combination of above donor/acceptor substrate combinations suggests that strong steric interactions may operate during the reactants approaching.

2.2. α-Functionalization of Imidazolones

In subsequent work we focused on the enolizable lactam heterocycles **22**. These structures, 2-thio substituted 1*H*-imidazol-4(5*H*)-ones, may be viewed as masked forms of α-amino acid derivatives,[17] in general, and (thio)hydantoins,[18] in particular, both relevant substructures among biologically active compounds. Despite this potential, to the best of our knowledge these pronucleophiles were unprecedented in asymmetric catalytic transformations. Heterocycles **22** can be prepared in gram-scale in two steps from the respective thiohydantoins. As shown in Scheme 4, soft deprotonation of **22** upon exposure to Rawal's chiral tertiary amine catalyst **C6**[19] and subsequent reaction with active Michael acceptors like nitroolefins was feasible, giving rise to adducts **23** smoothly (CH_2Cl_2, RT or −20 °C).[20] It is noticeable that, regardless the nature of the R^1 group in the π-extended enolate intermediate **I-2 I-1**, adducts from the α-carbon reaction were observed exclusively. In related heterocyclic systems, particularly azlactones, substrate-dependent regiodivergent α- and γ-addition product formation has been reported.[21] While various alkyl groups at sulfur other than benzyl, such as methyl and ethyl, were also well tolerated in **22**, the chemical yield of the catalytic reaction diminished slightly. Alkyl-substituted nitroolefins were also tolerated but, as expected, the yields and especially selectivity with these acceptors decreased. Imidazolones with various substituents at both the C_5 and N_1 position were equally competent, including bicyclic ones leading to



Scheme 3. Enantioselective additions of thiazolones, oxazolones and azlactones to an acrylate equivalent using squaramide/tertiary amine catalysts.



	R^1	R^2	R^4	yield	dr	ee
a	Me	Me	Ph	97	93:7	99
b	Me	Me	4-MeC_6H_4	91	90:10	96
c	Me	Me	4-BrC_6H_4	82	94:6	98
d	Bn	Me	3-MeC_6H_4	82	92:8	95
e	n-Hex	Me	Ph	81	98:2	98
f	^{t}Bu	Me	2-thienyl	84	92:8	86
g	^{i}Pr	Me	2-furyl	75	93:7	92
h	Me	Bn	Ph	85	98:2	98
i	Me	i-Bu	Ph	78	98:2	93
j	Me	$CH_2CH{=}CH_2$	Ph	77	92:8	94
				65[h]	90:10	95
k	Me	Ph	Ph	65	93:7	92
l	Me	4-ClC_6H_4	4-MeC_6H_4	83	98:2	98
m	Me	3-MeOC_6H_4	Ph	85	88:12	95

[h] run at 5 mmol scale using 5 mol% **C6**

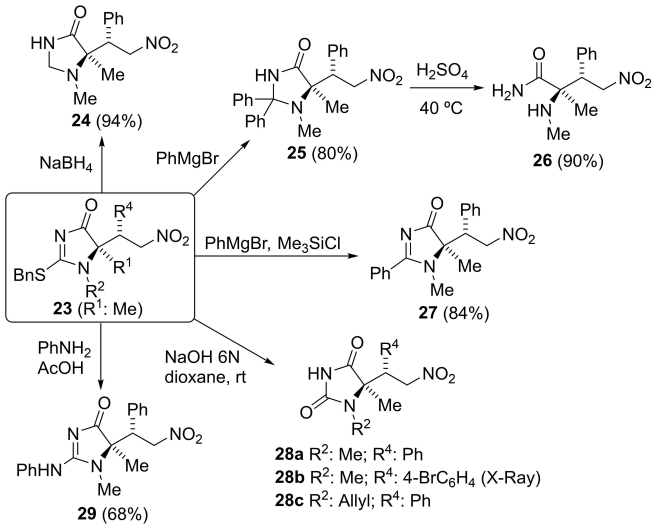
Scheme 4. C6-Catalyzed addition of 2-alkylthioimidazolones **22** to nitroolefins

adducts **23n** and **23o**. Using catalyst **C5** similar levels of stereoselectivity was attained, but in favor of the opposite enantiomer.

The resulting adducts could be elaborated in a number of ways using simple protocols, Scheme 5, to give access to imidazolidinones such as **24**, **25** and **27**; *N*-methyl α-amino amides (**26**); hydantoins (**28**); and guanidines (**29**).

To explain the observed reaction outcomes we proposed a Papai-type[22] transition state model **TS1** (Figure 3) in which the extended enolate and the incoming nitroolefin would approach through their *Re/Re* faces. In support of this TS model, we found that the chemical shift of the *ortho*-ArH in the catalyst is considerably affected ($\Delta\delta = +0.11$ ppm) by addition of 1 equivalent of imidazolone **22a** (R^1,R^2: Me, R^3: Bn), whereas it remains unaffected by addition of nitrostyrene **2** (R^4: Ph). This observation also suggests that the polarized aromatic *ortho* protons in this type of catalysts contribute to TS stabilization. However, the alternative, Takemoto-type[23] approach as in **TS2** could not be fully discarded.

Further studies[24] demonstrated that not only the *N*-alkyl/aryl derivatives **22A** but also the related *N*-acyl imidazolones **22B** and the isomeric **30** (Figure 4) were effective enolizable pronucleophiles for the BB-catalyzed addition reactions, and that the pool of suitable electrophilic partners could be broadened to other Michael acceptors and aldehydes. However, it was necessary to find the best fitting bifunctional catalyst for each substrate combination. For example, as indicated in Scheme 6, newly developed catalyst **C7**, bearing a tethered amide unit capable for an additional H-bonding interaction,[8m] was more active than the parent catalysts **C5** or **C6** in promoting the addition of **22B** to nitroolefins. Thus, while the **C5**-catalyzed addition of **22B** (R^1: Bn; R^2: COPh) to β-nitrostyrene at room temperature required 16 hours for full conversion, the same reaction in the presence of **C7** was over in 4 hours, both providing the corresponding adduct **31**



Scheme 5. Chemical elaboration of the 2-alkylthioimidazolone addition adducts **23** into enantioenriched amine-containing building-blocks.

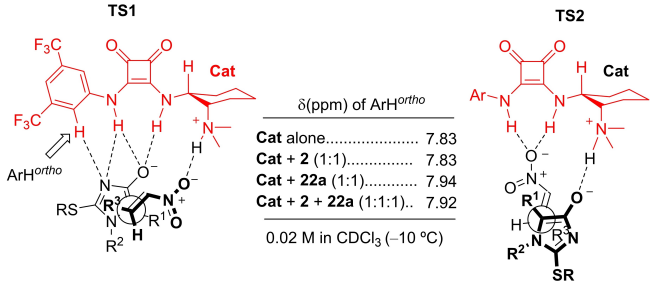


Figure 3. Plausible TS models and selected ^{1}H NMR data.

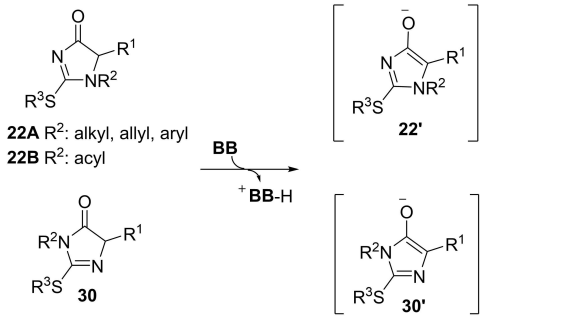
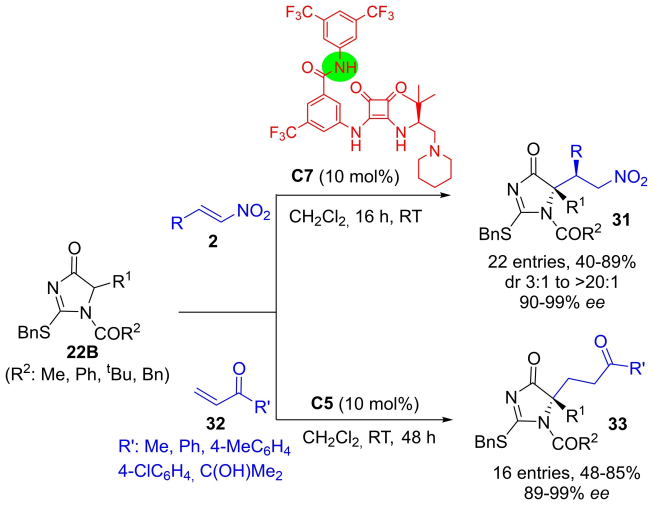


Figure 4. Base-catalyzed enolization of various 2-alkylthioimidazolone structures yielding π-extended "aromatic" enolates.



Scheme 6. Reaction of 2-benzylthiodihydroimidazolones **22B** with nitroolefins and vinyl kenones.

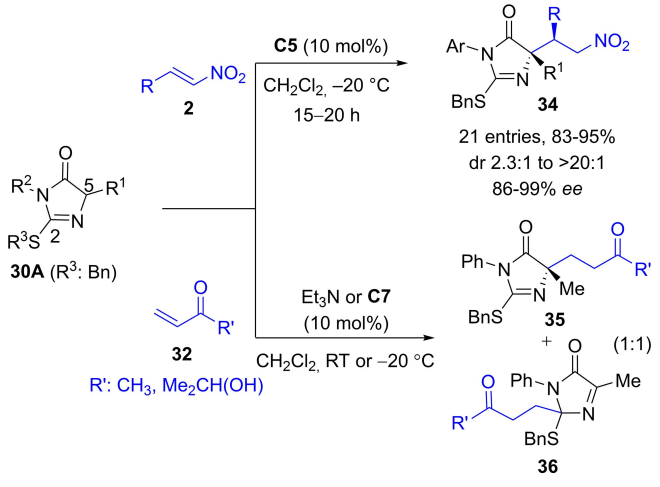
in 97% and 98% *ee* as essentially single diastereomer. The reaction catalyzed by **C7** proved to be quite general, providing various *N*-acyl derivatives **31** in yields above 70% for most entries, d.r. up to >98:2 and very high enantioselectivity (Scheme 6). Aliphatic nitroolefins also led to high selectivities, but eroded isolated yields (R: ^{i}Bu 53%, R: ^{n}Pr 40%) under these conditions.

In this context enones **32** demonstrated to be competent electrophilic reaction partners and the corresponding adducts **33** were obtained in high yields and very high enantioselectivity, with few exceptions (Scheme 6).

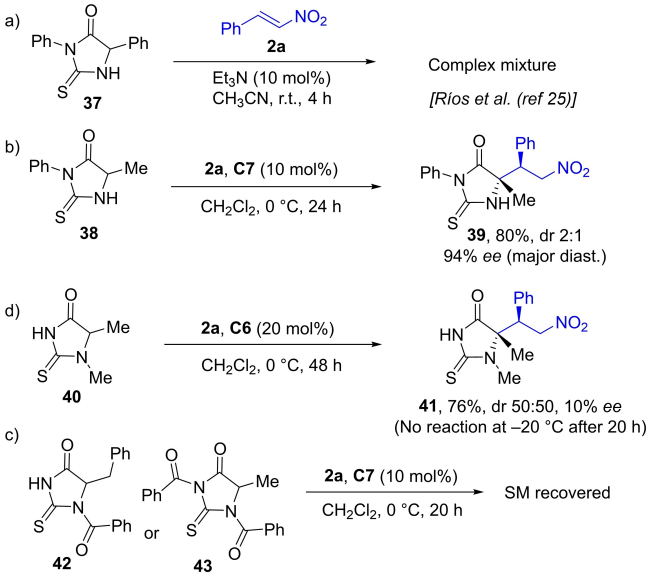
As noted above, N^3-substituted 2-benzylthioimidazolones **30A** could also be functionalized by BB/HB-catalyzed addition reactions to electrophiles. However, the behavior of these heterocycles was electrophile-dependent. Thus, with nitroolefins the α-addition adducts **34** were obtained cleanly and for most examples in high yields, diastereo- and enantioselectivities (Scheme 7). However, when reacted with vinyl ketones **32** two divergent reaction pathways were observed producing, respectively, the 5-addition products **35** and the 3-addition products **36**. Configuration of products **36** was not determined and that of products **35** was assigned by assuming a uniform reaction mechanism. Attempts to favor either reaction pathway were unsuccessful and, regardless the type of mono- or bifunctional BB catalysts and the reaction temperature, a quasi-equimolar ratio of both regioisomeric products was formed in the studied cases. Formation of regioisomeric mixtures was previously reported in BB-catalyzed addition reactions involving azlactones as the nucleophile.[21]

In the aforementioned examples readily accessible and partially unsaturated 2-benzylthio imidazolones **22** and **30** showed to be quite active and selective in BB/HB-catalyzed addition reactions. In sharp contrast, the related saturated heterocyclic (thio)hydantoin pronucleophiles shown in Scheme 8 displayed comparatively poorer reactivity and/or selectivity. For example, it was reported[25] that the base-catalyzed reaction of thiohydantoin **37** with nitroolefins led to complex reaction mixtures. In our hand, the similar reaction of the N_3- and N_1-substituted thiohydantoins **38** and **40** afforded the corresponding α-addition adducts **39** and **41**, respectively, but with poor diastereoselectivity or/and enantioselectivity. Finally, both mono- and dibenzoylated compounds **42** and **43** proved to be unreactive under the present catalytic conditions.

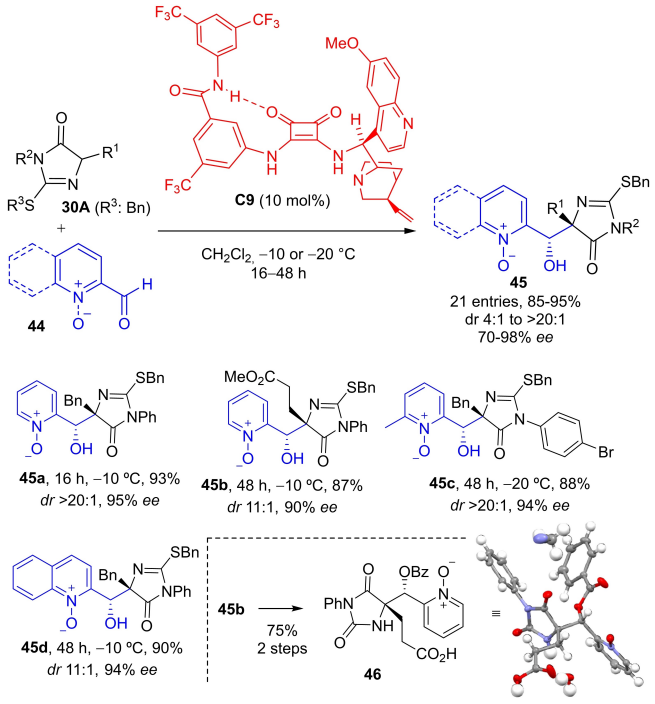
The BB-catalyzed addition reaction of these enolizable imidazolidones could be extended to additional electrophiles, including aldehydes (aldol-type reaction) and vinyl sulfones (Michael-type addition), provided that "reactive forms" of these latter species were employed.[26] For example, imidazolidones **30A** could reacted with 2-formyl pyridine *N*-oxides **44** to afford the corresponding aldol adducts **45** bearing adjacent tri- and tetrasubstituted carbon stereocenters in high diastereo- and enantioselectivity (Scheme 9).[27] Among several BB catalyst, the amide-squaramide **C9** led to the highest selectivity. This catalytic reaction showed to be quite general for differently substituted imidazolones **30A** and aldehydes **44**. Once again, the free amide NH group in **C9** proved to be crucial for attaining effective catalysis and stereoselectivity, as the reaction using the *N*-methyl analog led to poor results. The calculated structure of **C9** at B3LYP(D3)/6-31+G(d) level of theory predicted an intramolecular NH…O=C binding as depicted in Scheme 9, with the two extended arene systems at the opposite ends of the molecule showing



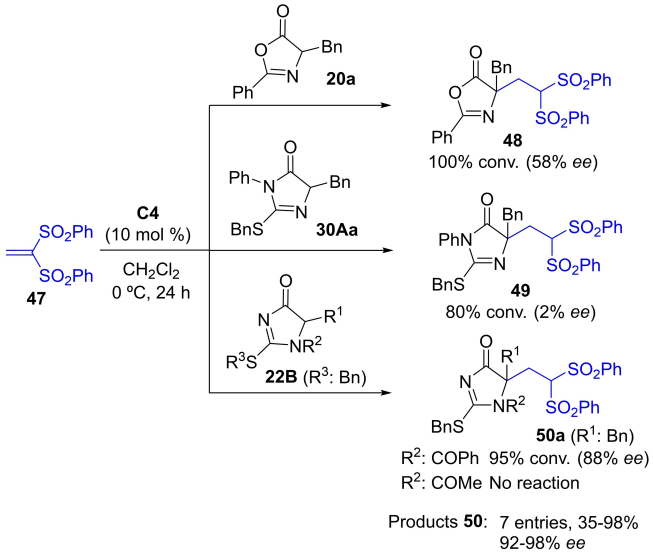
Scheme 7. Electrophile-dependent reactivity patterns in BB/HB-catalyzed additions of 2-benzylthiodihydroimidazolones **30 A** with nitroolefins and vinyl kenones, respectively.



Scheme 8. Reactivity profile of the related thiohydantoins **37**, **38**, **40**, **42** and **43**. SM: starting material.



Scheme 9. Scope of the **C9**-catalyzed aldol reaction of azaarene-2-carbaldehyde *N*-oxides **44** with hydantoin surrogates **30 A**.



Scheme 10. Comparison of various lactam pronucleophiles against the catalytic addition reactions to vinyl bis(sulfone) **47**.

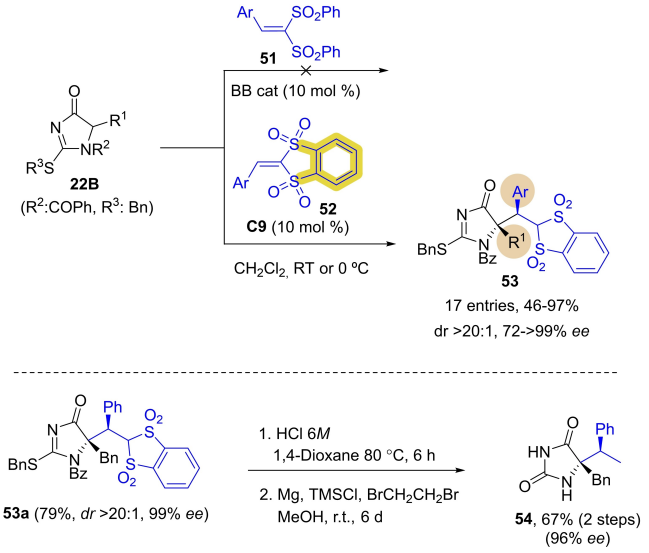
approximately perpendicular orientation one another. In this development the use of pyridine- and benzopyridine-*N*-oxide carbaldehydes proved to be crucial. The parent (benzo)pyridine carbaldehyde systems were totally inefficient, indicating threshold electrophilicity of the aldehyde is needed for this type of catalysis. Conversion of the heterocyclic template of adducts into the corresponding hydantoin, e.g. **45 b**→**46**, could be accomplished in two simple steps by first alcohol benzoylation and subsequent acid hydrolysis.

Very recently, we studied the behaviour of these enolizable lactam heterocycles **22** and **30** in the additions to vinyl sulfones using the same type of chiral BB catalyst systems.[28] It was found that in reactions involving even the most reactive unsubstituted vinyl bis(sulfone) **47**, both reactivity and selectivity are strongly dependent on the structure of the heterocyclic pronucleophile. As Scheme 10 shows, while **C4**-catalyzed reaction of **47** with azlactone **20 A** proceeded fast, the reaction enantioselectivity was suboptimal. The enantiocontrol of the addition reaction involving imidazolone **30 Aa** was even worse. More striking, when using imidazolones **22 B** radically different reactivities were observed depending on the nature of N_1 substituent. While the *N*-acetyl derivative (R^2: COMe) was totally unreactive in CH_2Cl_2 at 0 °C, the corresponding *N*-benzoyl derivative reacted smoothly to give rise product **50 a** in 95% conversion after 24 hours and a 88% *ee*. This divergent behavior was tentatively attributed to increased carbon acidity of the benzoyl derivative as compared to the acetyl derivative, with pK_a estimates, respectively, of 15 and 16 (according to Grzybowski's method) or 19.71 vs 21.15 (using Jaguar pK_a module29 in DMSO as implemented in Schrodinger 2021–0130 program suite). These conditions were applied to other α-alkyl and α-heteroalkyl substituted 2-benzylthioimidazoles **22 B** which nicely provided the corresponding adducts **50** in very high enantioselectivity.

As expected, the corresponding β-substituted vinyl sulfones **51** proved to be much more challenging acceptors due to attenuated reactivity. All attempted reactions with varying catalysts and conditions led to recovery of unmodified starting materials. Then we decided to investigate the cyclic ("rigidified") congeners **52**, which according to Mayr kinetic measurements are roughly one order of magnitude more electrophilic than the acyclic congeners.[29] Gratifyingly, the reaction of **22 B** with **52** in the presence of 10 mol% squaramide catalyst **C9** proceeded smoothly even at 0 °C to afford adducts **53** in moderate to good yields, essentially complete diastereoselectivity and usually very high enantioselectivity (Scheme 11). Among other applications, the bis(sulfone) moiety of adducts could be reductively removed in the presence of magnesium metal.[30] to achieve the formal α-alkylation products, e.g. **54** from **53 a**, which are difficult to prepare otherwise.

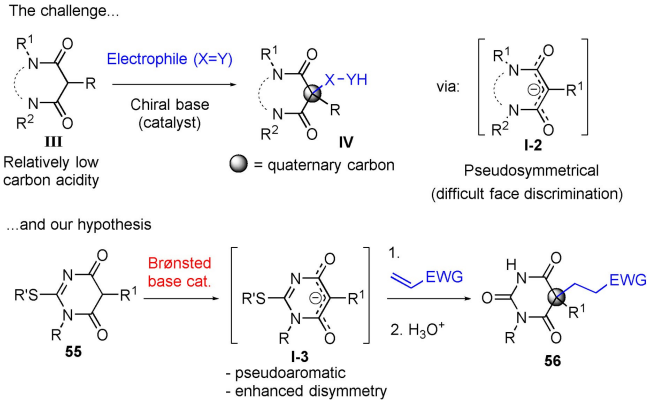
2.3. α-Functionalization of Barbituric Acid Surrogates

Barbituric acid derivatives have found applications as therapeutic agents as well as functional materials, and thousands of 5,5-disubstituted barbiturates have been synthesized and selected



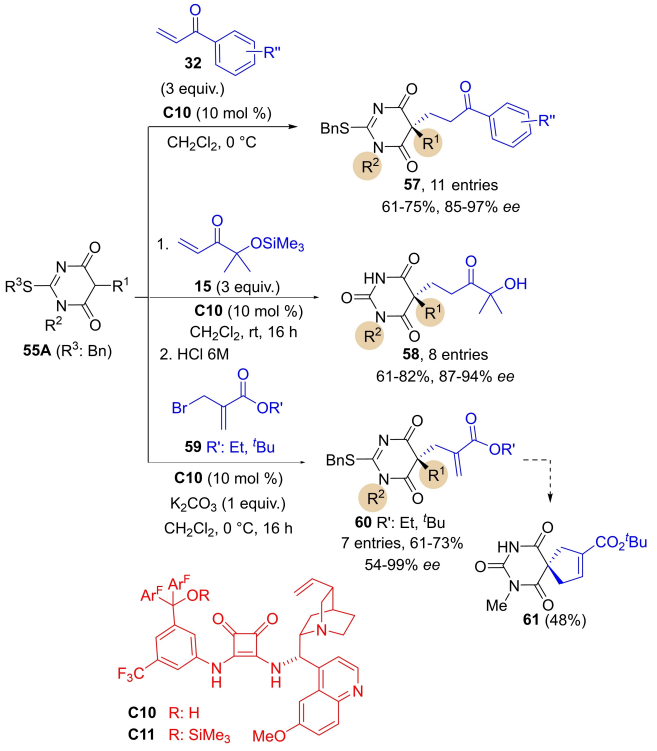
Scheme 11. The challenge of expanding the reaction scope to β-substituted vinyl bis(sulfones).

for clinical trials.[31] However, the great majority are racemic, even though pharmacological profile is known to be configuration-dependent. One reason contributing to this situation might be the lack of enantioselective methods to access the cyclic 1,3-diimide substructure with in-ring chirality,[32] which may be related to the pseudosymmetric structure of the resulting enolate intermediate **I-52** (Scheme 12). By analogy with what we previously found concerning the reactivity of enolizable five-member lactam heterocycles, it was reasoned that chiral BB catalysis may be well suited for deprotonating the corresponding unsaturated alkylthio-substituted pronucleophiles **55**. The allegedly formed extended enolate intermediate **I-63** would display enhanced dissymmetry as compared with **I-52**.



Scheme 12. The challenge of generating in-ring chiral barbiturates and a template-based dissymmetry enhancement approach involving extended enolate intermediates. Adapted from ref. [33] Copyright (2017), with permission from American Chemical Society.

We started by preparing 2-benzylthio-4,6-dioxopyrimidines **55** in one step from the corresponding thio-barbiturates. Gratifyingly, the reaction between **55A** (Scheme 13) and vinyl aryl ketones could be catalyzed by bifunctional BB/HB catalysts.[33] Among the catalysts screened, the squaramide-triarylmethanol **C10** and its *O*-silyl ether **C11** provided the best selectivity, with the former being more active. Adducts **57** were obtained in good yields and enantioselectivities from high to excellent. α'-Silyloxy enone **15** was also a competent Michael acceptor in these catalytic additions. Given the easy with which the ketol group in adducts **58** can be transformed into carboxylic acid and aldehyde functions, this protocol enables access to products formally derived from the conjugate addition to acrylic esters and acrolein. Complementing these addition reactions, the coupling between **55A** and Morita-Baylis-Hillmann-type bromides **59** was also possible in the presence of K_2CO_3 as the acid scavenger, leading to the allylic alkylation products **60** in good yields and enantioselectivities from moderate to extremely high. The synthetic potential of thus obtained adducts was illustrated by the conversion of **60** (R^1: allyl) into spiranic **61** through a ring-closing metathesis



Scheme 13. Catalytic enantioselective addition of barbiturate surrogates **55 A** to Michael acceptors and Morita-Baylis-Hillmann bromides.

reaction catalyzed by Grubbs catalyst in CH_2Cl_2 at room temperature and ulterior acid hydrolysis in dioxane/water.

3. BB-Catalyzed Functionalization of β-Tetralones and Related Benzo-Fused Cycloalkanones

β-Tetralones have been employed profusely as starting scaffold for the synthesis of polycyclic carbon structures with various biological activities.[34] Asymmetric functionalization of β-tetralones via prior transformation into a chiral enamine is already established.[35] In contrast, catalyst-controlled direct methods for the enantioselective α or α'-functionalization are rare. With β-tetralones and related benzo-fused cyclic ketones, full control of the two possible ketone enolization sites becomes an issue. We anticipated that the fused aromatic ring in β-tetralones might induce preferential enolization at Cα rather than $C_{\alpha'}$, while increasing the carbon acidity as to be feasible for weak base, i.e. tertiary amine catalyst, induced deprotonation (Figure 5).

However, the above predictions were uncertain given the precedents in the literature. Thus, while BB-catalyzed α-functionalization of α-substituted cyclopentanone is reported to proceed satisfactorily, the same process appeared unpractical with α-substituted cyclohexanones.[36] We were delighted to observe that α-substituted β-tetralones **62** reacted smoothly with nitroolefins in the presence of 10 mol% squaramide-tertiary amine catalysts in CH_2Cl_2 at room temperature (Scheme 14). The α-addition adducts **63** were obtained exclusively and as a single diastereomer.[37] The reactions using catalyst **C12** proceeded with *ee*'s up to 99%. Interestingly, the α-unsubstituted β-tetralone **62** (R^2: H) also reacted cleanly in the presence of 2 mol% catalyst **C4** or **C12** to provide the monoaddition adduct **64** only. With the exception of the 2-furyl substituted β-tetralone, which led to equimolar mixture of diastereomers, the remaining examples were isolated with *dr* higher than 4:1 and perfect enantiocontrol of both isomers. These adducts were prone to base-promoted epimerization, which may explain the moderate diastereoselectivity. Nevertheless, the process could be applied to related benzo-fused cycloalkanones successfully providing a route to diverse substructures, such as **65**–**67**. In the case of starting from a benzo-fused cyclic diketone, adduct **68** was isolated as a result of a sequential, catalytic Michael-nitroaldol process.

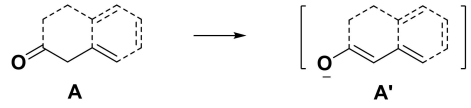
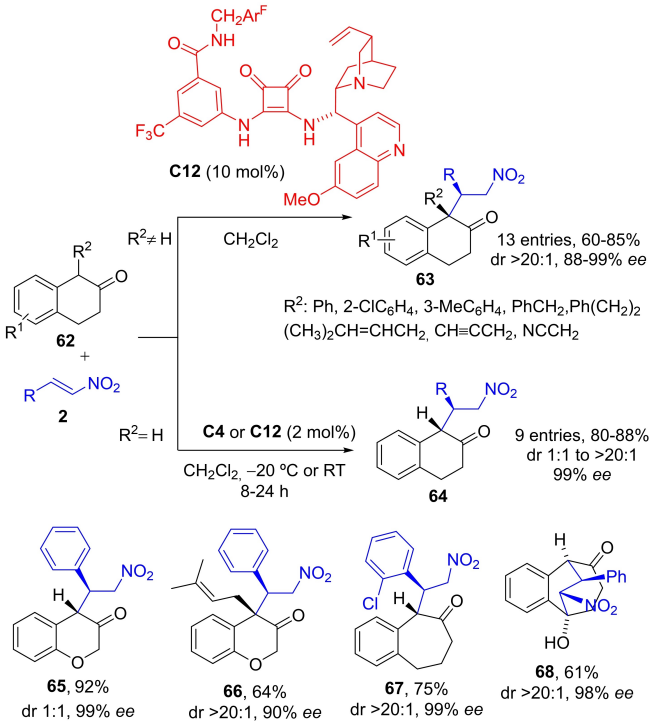


Figure 5. π-Extended enolates of type **A'**.

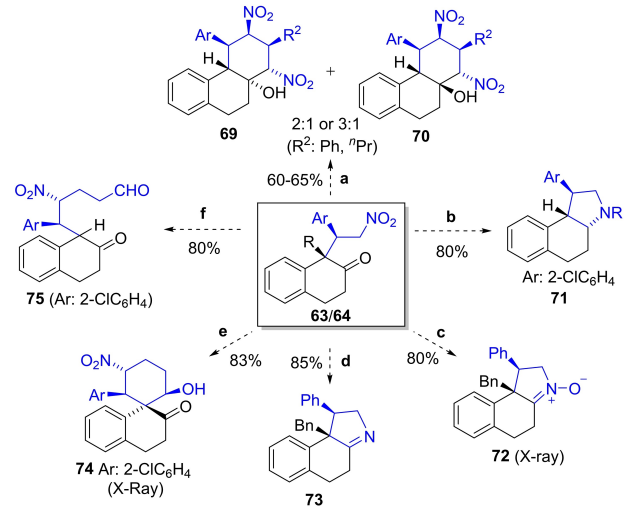


Scheme 14. BB-catalyzed enantioselective α-functionalization of β-tetralones and related benzo-fused cycloalkanones.

The structural diversity of polycyclic products within reach by applying this technology is considerably broad as examples depicted compounds **69**–**75** in Scheme 15 show, all affordable from the corresponding adduct **63** or **64** through conventional chemistry in one or maximum two synthetic steps.

4. BB-Catalyzed Functionalization of 2-Pyridyl Acetates and Acetonitriles

o-Substituted pyridine frameworks are among the most commonly used nitrogen heterocycles in FDA approved pharmaceuticals.[38] Development of catalytic, enantioselective routes to access pyridines and related azaarenes with a quaternary carbon substituent at ortho position is therefore of practical relevance. α-Deprotonation of *o*-substituted acyl pyridines may lead to mixtures of *E*- and *Z*-configured enolates **D'** aza-**A'** (Figure 6), making enantiocontrol of reactions proceeding through these intermediates difficult. In contrast, the corresponding nitriles (2-pyridyl acetonitriles) would skip such a complication. In addition, nitrile is a versatile functional group for many synthetic purposes. However, the α-carbon acidity of nitriles is relatively low.[39] In order to overcome this shortcoming, we decided to use the corresponding pyridine *N*-oxides instead, which should be comparatively



Reagents and conditions: **a**: nitroolefin, **C4** (10 mol%), CH_2Cl_2, RT, 48 h; **b**: H_2 (45 atm), Pd/C, MeOH, 80 °C, 20 h; **c**: H_2 (1 atm), Pd/C, MeOH, RT, 72 h; **d**: Zn, HCl_{aq}, EtOH, 40 °C; **e**: acrolein, pyrrolidine (10 mol%) **f**: acrolein, **C4** (10 mol%).

Scheme 15. Diverse transformations of adducts into highly functionalized (poly)cyclic molecules.

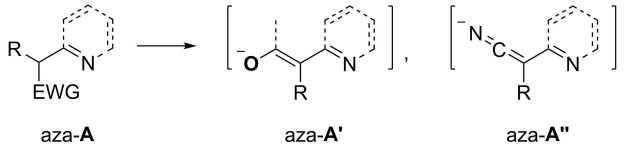
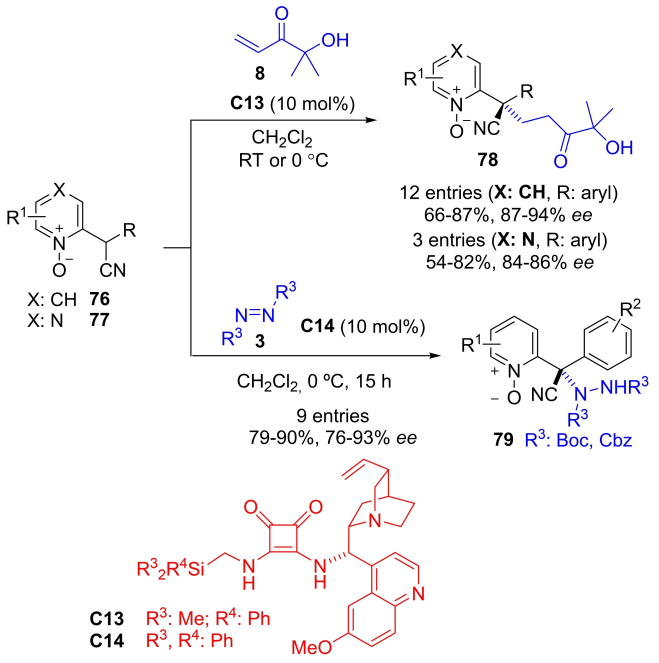


Figure 6. π-Extended enolates of type **D'**aza-**A'** and the related nitrile analogs **D"**aza-**A"**.



Scheme 16. BB-catalyzed asymmetric α-functionalization of *o*-cyanoalkyl pyridine/pyrazine *N*-oxides..

more acidic and thus more active substrates for BB-catalyzed α-functionalization. Moreover, the *N*-oxide group may provide an additional site for catalyst coordination, and be reductively converted into the parent pyridine if desired.

Our initial attempts using *o*-cyanomethylpyridine and enone **8** as an active Michael acceptor in the presence of various typical BB/HB bifunctional catalysts led to very low conversions and selectivities, even using 20 mol% catalyst loading. The reactivity increased considerably by using the corresponding *N*-oxide derivative **76** and after 2 days at 40 °C conversions near 90 % were achieved with typical squaramide-tertiary amine catalysts. Then we decided to test the related squaramides bearing an alkyl-aryl silyl group appendage, e. g. **C13**, speculating with the possibility of Si···O stabilizing interactions in the substrate-catalyst complex. With this latter catalyst total conversion was reached in about 24 h at 40 °C. Further optimization of reaction conditions allowed to obtain enantioselectivities above 90 % by running the reaction at RT or 0 °C, with 10 mol catalyst loading with still acceptable reaction times. As Scheme 16 illustrates, the catalytic reaction tolerates a variety of 2-pyridyl acetonitrile *N*-oxides **76** bearing Cl, Br or Me substituents at the pyridine ring and either electron-poor or electron-rich aryl substituents at Cα. Substrates with alkyl substituents at Cα were also tolerated, but gave poorer conversion and selectivity. Eventually, the related pyrazine N-oxides **77** were also competent pronucleophiles. Importantly, among various additional transformations of thus obtained adducts, the *N*-oxide product could be transformed into the corresponding parent pyridine by treatment with $(Bpin)_2$ in warm acetonitrile in yields typically in the 75–80 % range.[40]

Several control experiments were carried out to quantify the effect on the reactivity and/or enantioselectivity of: (i) the substrate *o*-, *m*- and *p*-substitution pattern, (ii) using the *N*-oxide analogs as compared to the parent pyridines, and (iii) the noncatalyzed vs. the catalyzed reaction. As the data in Figure 7 show, the *N*-oxide group and its *ortho*-relationship to the cyanoalkyl substituent are key for optimal reaction outcome. As a general trend, for the three positional isomers *ortho*, *meta* and *para*, the corresponding pyridine *N*-oxide showed to be more reactive than the parent pyridine in both the catalyzed and uncatalyzed reactions. In fact, among the six experiments involving cyanoalkylpyridines, only that using *p*-cyanoalkylpyridine in the presence of **C13** provided practical conversion after 24 h, leading to racemic product. Equally important is the position of the *N*-oxide group relative to the cyanoalkyl substituent on the ring. Among the three cyanoalkylpyridine *N*-oxides, the *meta* and *para* isomers showed to be inherently

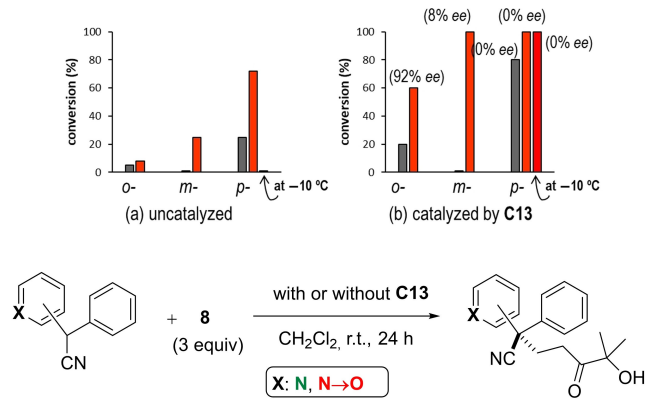
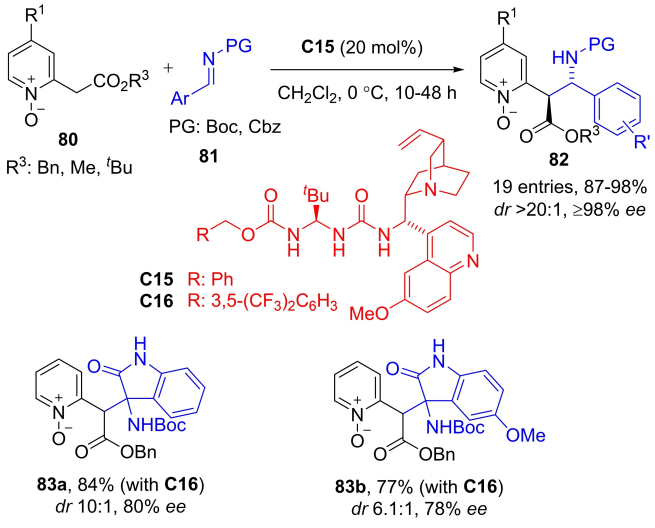


Figure 7. Comparison of various *o*-, *m*-, and *p*-substituted pyridinylacetonitriles vs. their *N*-oxide analogues for the noncatalyzed and catalyzed reactions. Adapted from ref. [40] Copyright (2016), with permission from American Chemical Society.

more reactive than the *ortho* isomer, also in the presence of cat **C13**, although both led to essentially racemic product. In contrast, the ortho isomer led to 92% *ee*. Under similar conditions and using the triphenylsilyl analog **C14** as optimum catalyst, the α-hydrazination reaction leading to adducts **79** could be carried out satisfactorily.

Further investigations showed that the *N*-oxides of 2-azaaryl acetate esters **80** are also competent pronucleophiles and their BB-catalyzed α-functionalization could be successfully applied.[41] In this latter case (Scheme 17), however, the silyl group-bearing catalysts, e.g. **C13**, proved suboptimal. In particular, the Mannich-type addition reaction of acetate esters **80** with *N*-Boc and *N*-Cbz aldimines **81** was best performed



Scheme 17. Catalytic Mannich reaction of 2-pyridylacetate *N*-oxides **80** with aldimines and ketimines **81** to afford adducts **82** and **83**, respectively.

using urea-aminal catalysts, e.g. **C15**, and products **82** were formed in very good yields and excellent diastereo- and enantioselectivity. The catalytic addition reaction involving isatin-derived imines as active ketimines, did also work well to provide adducts like **83a** and **83b**, although with attenuated enantioselectivity.

5. BB-Catalyzed Functionalization of Unsaturated Ketones and Thioesters via Di- and Trienolates

Upon exposure to base, enolizable carbonyl compounds displaying β,γ-chain-unsaturation may lead to formation of dienolates **A'**, or even trienolates **D'** (Figure 8). Dienolates are ambidentate nucleophiles and may react through α- or γ-carbon, while trienolates may react even through the ε-carbon. This makes control of the reaction site-selectivity an issue, beyond the problems of reaction diastereo- and enantiocontrol.[42]

Regarding site-selectivity, the majority of catalyst-controlled asymmetric reactions of transiently generated vinylogous enolates and enolate equivalents, including dienamines, tend to proceed through Cγ.[43] This pathway implies π-conjugation is preserved along the reaction coordinate. In contrast, attack from Cα would imply disruption of conjugation. Examples belonging to this latter reactivity pattern are uncommon and might require steric shielding of the γ-position.[44] We found that allylic ketones and thioesters, in the presence of bifunctional BB/HB catalysts, may react through the α-position preferentially against conjugated (1,4-addition) and nonconjugated (1,2-addition) carbon electrophiles.[45] For instance, Scheme 18, the addition of allyl-alkyl ketones **84** to nitroolefins catalyzed by **C17** provided the Michael-type adducts **85** as exclusive reaction products. The reaction tolerates a variety of aryl-substituted nitroolefins and ketones bearing aryl, alkyl or alkenyl side-chains all participated equally, affording adducts **85** in diastereoselectivities from moderate to excellent and high enantioselectivity. Under these conditions, neither double addition products nor epimerization were observed. A simple hydrogenation of the olefinic residue in the resulting adducts **85** allowed to access products, e.g. **86**, from a formal side-selective, diastereo- and enantioselective alkylation of nonsymmetrical alkyl-alkyl ketones, a yet unsolved transformation using direct methodologies.

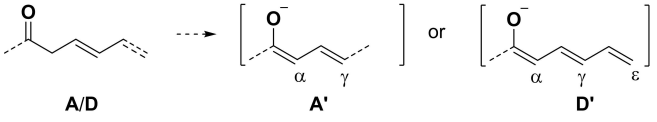
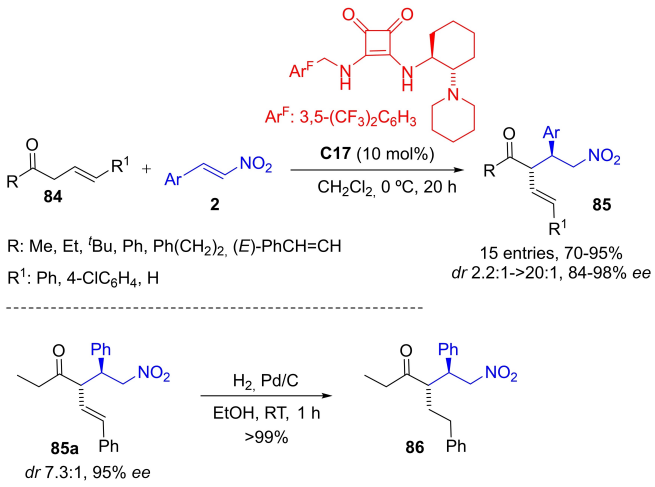
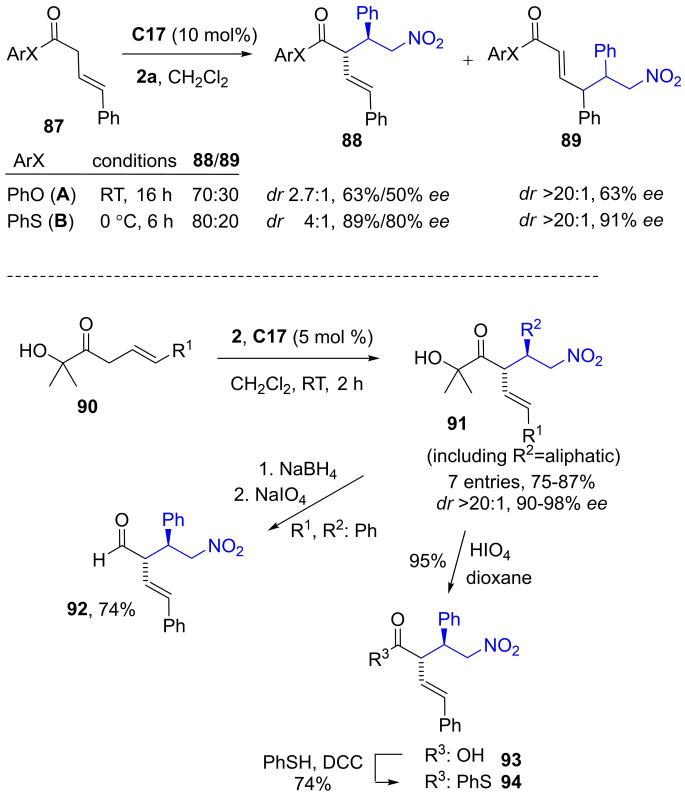


Figure 8. Generation of di- and trienolates from deprotonation of (doubly) unsaturated enolizable pronucleophiles.



Scheme 18. The BB/HB-catalyzed α-selective addition of allylic ketones to nitroolefins via transient dienolate.

Submitted to similar reaction conditions and type of catalysts, the corresponding allylic esters **87 A** and thioesters **87 B** were less selective than ketones, and mixtures of the α- and γ-addition adducts **88**/**89** were obtained (Scheme 19, top). This deficiency could be surmounted using hydroxyketones as masked ester/aldehyde equivalents. Thus, the corresponding α'-hydroxy ketones **90** reacted with both aryl- and alkyl-substituted nitroolefins to give adducts **91** in very high selectivity. Ulterior oxidative ketol/diol scission provided an indirect access to the target ester and aldehyde α-addition products, e. g. **92**–**94**.

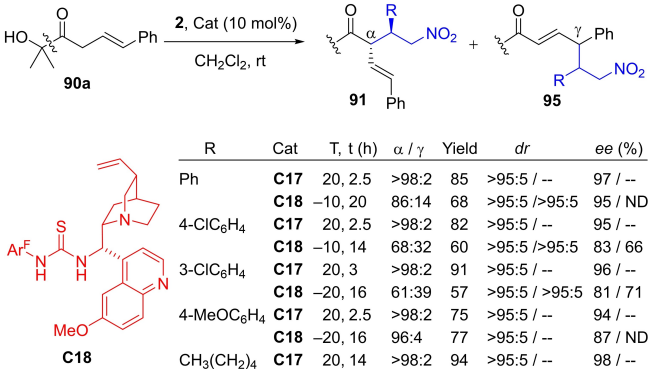


Scheme 19. The side-selectivity problem with ester and thioester pronucleophiles and an indirect solution employing hydroxy ketones instead.

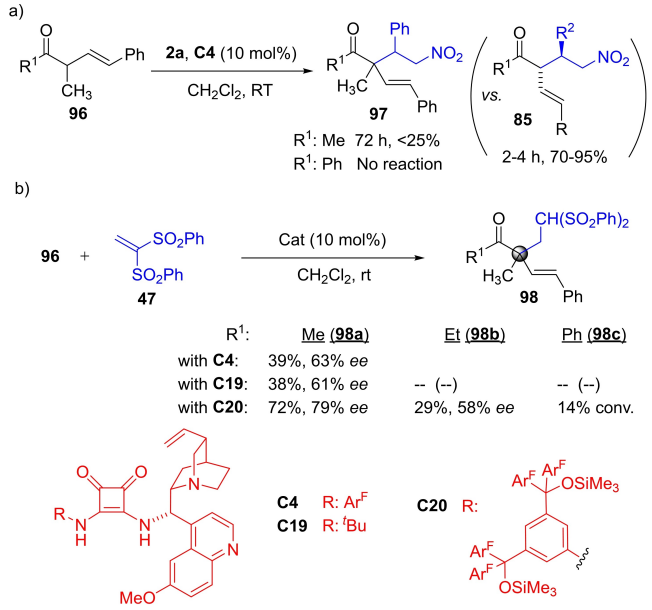
It should be noted that in certain cases the nature of the bifunctional BB/HB catalyst may modulate, or even override, the substrates innate regio-selectivity trend. As the data in Scheme 20 indicate, while mixtures of both α and γ-addition products **91**/**95** were obtained using the thiourea/tertiary amine catalyst **C18**,[46] essentially perfect regioselectivity was observed using catalyst **C17** instead.[47]

The catalytic, enantioselective α-functionalization of α-branched allylic ketones represents an unmet challenge so far. In this type of transformation exquisite stereocontrol during formation of a new quaternary α-carbon is necessary. Moreover, inducing the intermediate dienolate to react through the α-carbon rather than the less sterically shielded γ-carbon seemed a difficult task. Initial experiments aimed at reacting the α-branched methyl ketone **96** with nitrostyrene to produce **97** (less than 25% yield after 72 hours at RT) demonstrated the attenuated reactivity of **96** as compared with the parent α-unsubstituted ketones (Scheme 21).[48] Additional control experiments showed that this limited reactivity is even more dramatic for the corresponding α-branched phenyl ketone **96c**. As expected, using reactive, sterically less demanding Michael acceptors, such as vinyl bis(sulfone) **47**, some reactivity is gained, but still larger alkyl (ethyl) and aryl ketones remain unpractical, while the enantioselectivity remained poor.

We hypothesized that cyclic α-branched allylic ketones may show better reactivity and selectivity profiles in these catalytic transformations. The usually higher nucleophilicity of cyclic vs. acyclic parent substrates[49] and the less conformational disorder of the former might be key factors for threshold

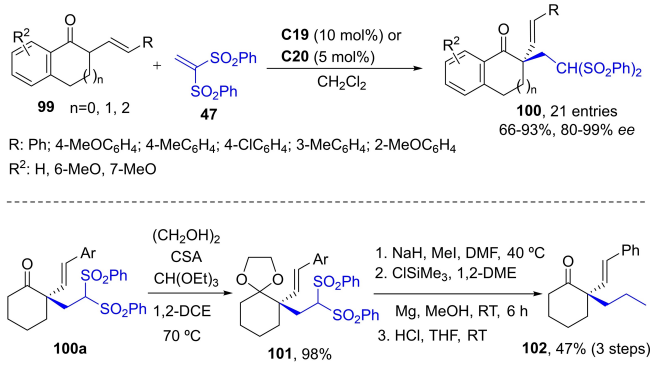


Scheme 20. Catalyst-dependent tuning of the regioselectivity of addition reactions of ketone dienolates to nitroolefins.



Scheme 21. Initial attempts for the asymmetric BB/HB-catalyzed α-functionalization of α-branched allylic ketones.

reactivity of cyclic systems. In addition, chirality transfer from the catalyst to the product might be secured as there is not *E*/*Z* configurational ambiguity of the intermediate dienolate in cyclic systems. Gratifyingly, the reaction between cycloalkanones **99** and vinyl bis(sulfone) **47** proceeded at 0 °C within 16 h smoothly in the presence of either catalyst **C19** or **C20** to give products **100** in very good yields and high enantioselectivity for most cases (Scheme 22).[48] As before, desulfonylation of adducts yielded products derived from a formal alkylation process, e.g. **102**. Not only monocyclic 5, 6, 7 and 8-membered cycloalkanones were compatible, but also benzo-fused cycloalkanones were excellent substrates for this catalytic



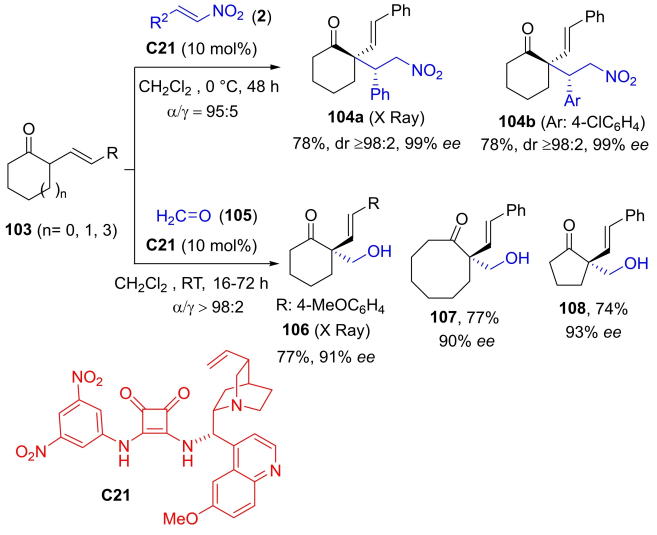
Scheme 22. Scope of the BB/HB-catalyzed enantioselective α-addition of α-branched allylic cycloalkanones **99** to vinyl bis(sulfone) and adduct elaboration.

addition affording the α-quaternary products in very high enantioselectivity. Control experiments demonstrated that both common Brønsted acid catalysts (i.e. (*R*)- or (*S*)-TRIP) and primary amine-thioureas were less efficient catalysts for this reaction.

As the examples in Scheme 23 show, these α-branched cycloalkanones may also react with nitroalkenes and formaldehyde to afford in high selectivity the corresponding 1,4- and 1,2-addition adducts **104** and **106–108**, respectively, using **C21** as a catalyst.[50]

The most probable transition states for both Re-face and Si-face approaches in these addition reactions according to DFT calculations would be **TS3** and **TS4** (Figure 9).

We also studied the likelihood for catalytic, enantioselective α-functionalization of doubly unsaturated skipped ketone and thioester systems **109** and **114** which would involve trienolate formation. In initial attempts using the aryl thioester **109** and nitrostyrene as reaction partner, up to four different



Scheme 23. The **C21**-catalyzed addition of α-branched allylic cycloalkanones to nitrostyrenes and formaldehyde.

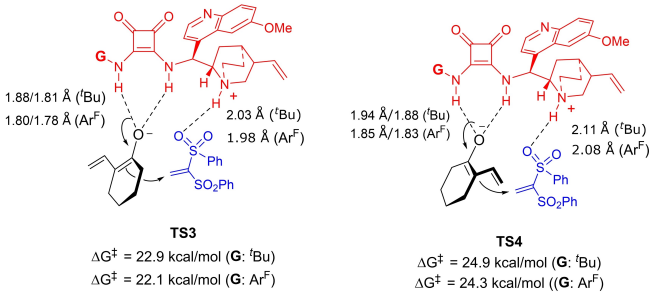
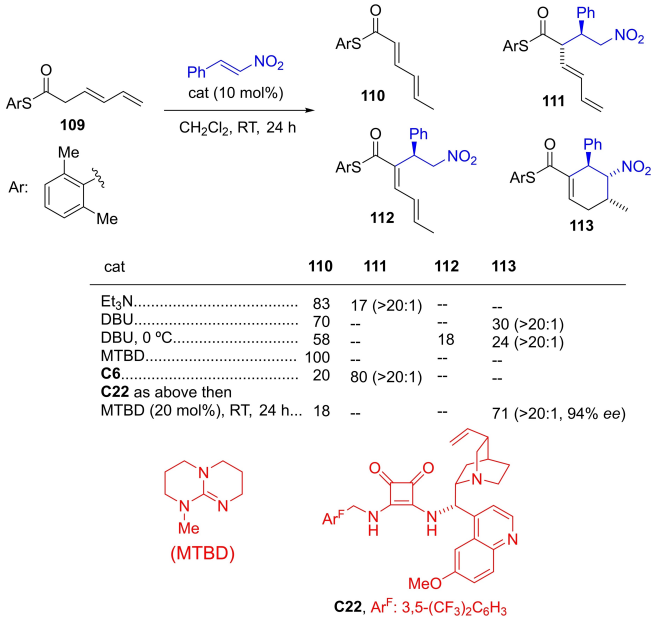


Figure 9. The less energetic TS for the addition of allylic cyclohexanone to vinyl bis(sulfone) and the $\delta_{O\text{-}H}$ hydrogen-bond distances.

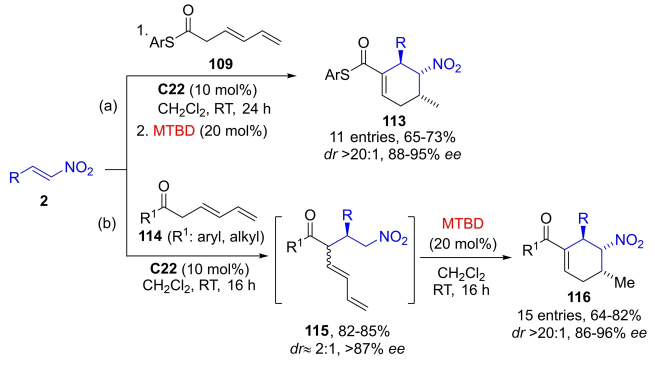
products **110–113** were isolated, with the strength of the base catalyst used being determinant on product distribution (Scheme 24). Upon optimization of the catalyst and conditions, formation of cyclohexene product **113** could be maximized using **C22**[19] as the initial catalyst (10 mol%) and then adding MTBD (20 mol%) to promote the isomerization/intramolecular addition reaction cascade process.[51]

Under optimized conditions, that consist of a two-step one-pot process involving first stirring of aryl thioesters **109** and nitroolefins **2** (R: aryl) in the presence of 10 mol% **C22** for 24 hours at room temperature and then addition of 20 mol% MTBD and stirring for an additional 16 hours,



cat	110	111	112	113
Et_3N	83	17 (>20:1)	--	--
DBU	70	--	--	30 (>20:1)
DBU, 0 °C	58	--	18	24 (>20:1)
MTBD	100	--	--	--
C6	20	80 (>20:1)	--	--
C22 as above then MTBD (20 mol%), RT, 24 h	18	--	--	71 (>20:1, 94% *ee*)

Scheme 24. Screning of basic catalysts for the reaction between doubly unsaturated thioesters **109** and nitrostyrene, and products formed.

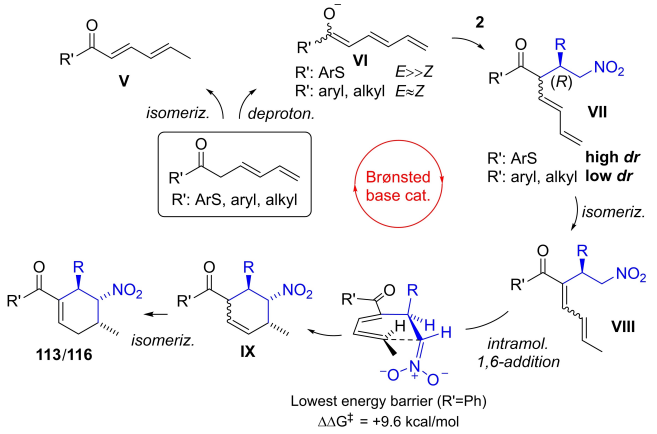


Scheme 25. Scope of the BB-catalyzed tandem reaction involving, respectively: (a, top) doubly unsaturated thioesters and (b, bottom) doubly unsaturated ketones.

cycloadducts **113** were isolated in good yields as single diastereomer and high enantioselectivity (Scheme 25a). Extension of this catalytic method to doubly unsaturated skipped ketones **114** was straightforward (Scheme 25b). In this case, the initially formed α-addition adducts **115** could be isolated, if desired, before subsequent MTBD-catalyzed transformation into cycloadducts **116**. Interestingly, while analysis of the open-chain adducts **115** showed a mixture of diastereomers in a ratio of ca. 2:1, the final products **116** were isolated as essentially single diastereomers, which would be compatible with a kinetic resolution of diastereomers.

As shown in Scheme 26, the above results could be explained by assuming a concatenation of base-catalysed deprotonation-addition-isomerization events, including: (i) deprotonation of the unsaturated ketone/thioester with formation of trienolate **VI**, which would react with nitroolefin through Cα preferentially, (ii) isomerization of the double bonds in **VII** leading to conjugate diene-thioester/ketone **VIII**, (iii) base-promoted carbocyclization of **VIII** via intramolecular 1,6-addition, and (iv) base-catalyzed isomerization to conjugated cyclohexene products **113/116**.

In this reaction scheme, among the four possible isomeric products in step (i), DFT calculations carried out on a model reaction correctly predict formation of **VII** featuring an (*R*)-configured β-carbon as major isomer. Here, isomerization of **VII** to **VIII** (step ii) makes the actual configuration of Cα stereocenter in **VII** irrelevant. In addition, none of the chiral amine catalysts tested is able to promote the **VII**→**VIII** isomerization nor the subsequent conversion of **VIII** to **IX** (step iii). Instead, achiral stronger base is needed. Therefore, the carbocyclization step appears to be fully substrate-controlled. This assumption was also supported by the calculated energy barriers for the four possible nitronate-dienone approaching combinations, with the *re*,*re* approach



Scheme 26. The proposed mechanism for the BB-catalyzed, trienolate mediated cascade process leading to tetrasubstituted cyclohexene products.

(9.6 kcal/mol barrier) lying about 2 kcal/mol lower than the other three possible approaches. Finally, isomerization of starting thioesters/ketones **109**/**114** into the conjugated **V** would be a dead-end for the system.

6. BB-Catalyzed Functionalization of Conjugated Ynones

Enolizable alkynyl ketones (conjugated ynones) represent a distinguished subset of ketones with some unique reactivity profile in BB catalyzed transformations. In contrast to the previous examples which involve linearly extended di(tri)-enolates, deprotonation of alkynyl ketones **B** would produce crossed π-systems **B'**/**B"** (Figure 10). We and others[52] have observed that the alkynyl moiety in these systems, while facilitating enolate formation, influences the reactivity trends of transiently formed (di)enolates as well as the stability of the resulting adducts.

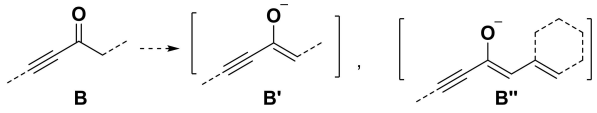
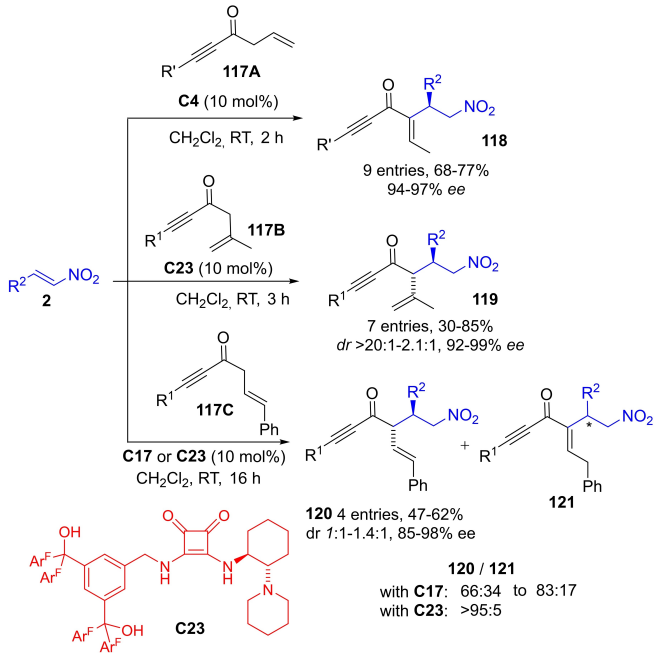


Figure 10. Formation of alkynyl crossed (di)enolates from deprotonation of ynones.

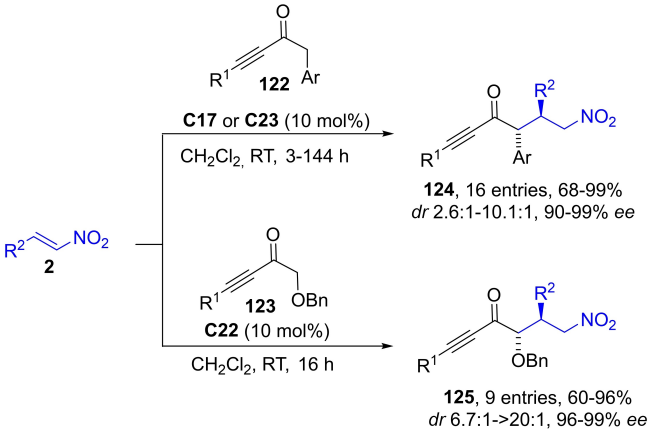


Scheme 27. Substitution pattern-dependent reaction outcomes of BB/HB-catalyzed Michael addition reactions involving alkynyl dienolates.

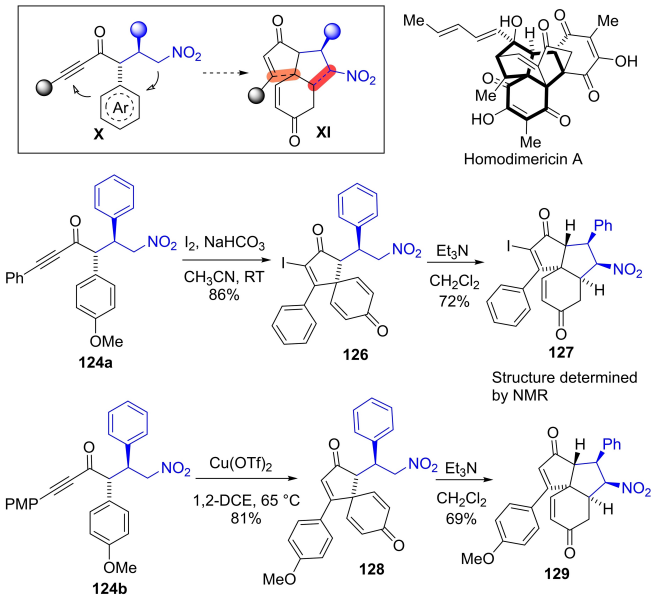
For example, allylic ynones showed to react with nitro-olefins under the presence of bifunctional BB/HB catalysts following diverting pathways that depend on the substitution pattern on the olefinic residue. Thus (Scheme 27), simple allyl ynones **117A** invariably yielded the corresponding α-addition/isomerization adducts **118**, with **C4** being the best catalysts.[45] In contrast, the β-methylsubstituted congeners **117B** provided the α-addition adducts **119** without ulterior isomerization, regardless the catalyst employed. Finally, the γ-substituted ynones **117C** provided a mixture of both types of products, the ratio of which is catalyst-dependent. With the new catalyst **C23** the α-addition product could be isolated in high enantioselectivity as a mixture of diastereomers.[53]

The activation effect imparted by the alkynyl sidearm on the ketones α-reactivity goes beyond allylic ynones. Thus, we found that arylmethyl ynones **122** and alkoxymethyl ynones **123** both display gained reactivity as compared with the parent alkyl or aryl ketones in BB-catalyzed transformations.[53] For example, Scheme 28, the reaction with nitroolefins at room temperature using 10 mol% catalyst **C17**, **C22** or **C23** afforded the respective addition products **124** and **125** in isolated yields from moderate to very high and useful stereoselectivities. In sharp contrast, under these conditions simple arylmethyl or alkoxymethyl ketones are completely unreactive.

Importantly, the alkyne moiety in the resulting adducts is a versatile platform for further chemical elaboration. As illustrated in Scheme 29, this aspect could be capitalized via intramolecular carbofunctionalizations of species **X** to construct polycyclic structures like **XI**. For example, applying Larock's ipso-halocyclisation[54] to adduct **124a** the spirocycle **126** was furnished in 86% yield. Then trimethylamine promoted intramolecular Michael reaction afforded product **127** in 72% yield. Similarly, heating adduct **124b** at 65 °C in the presence of copper(II) triflate, according to the method of



Scheme 28. Unlike simple α-aryl- and α-alkoxy ketones, the corresponding ynones smoothly react with nitroolefins under BB/HB catalysis.



Scheme 29. Easy gain of structural complexity via carbofunctionalizations of adducts resulting from BB/HB-catalyzed α-functionalizations of ynones.

Taylor and Unsworth,[55] led to the spirocycle **128** (81%), which allowed easy transformation into tricycle **129** in 69% isolated yield. The resulting tricyclic carbon skeletons of **127** and **129** resemble the core structure present in homodimericin A, a structurally intricate compound whose enantioselective chemical synthesis is still pending.

7. Conclusions

Catalyst-controlled direct, asymmetric α-functionalization of enolizable substrates is a powerful strategy to access synthetically relevant building-blocks in enantioenriched form.

Among the several activation strategies, methods based on Brønsted base catalyst-promoted deprotonation of the carbonyl pronucleophile has proven mild and practical. In this context, enolizable substrates incorporating a chain-unsaturation nearby the carbonyl group result especially attractive because the adducts resulting from their addition to, or coupling with, an electrophilic reagent will display additional carbon-carbon double or triple bonds available for ulterior synthetic manipulation. In the past recent years, our group has investigated how to exploit these opportunities to expand the chemical space of enantioenriched building-block available, with a focus on the generation of quaternary carbon stereocenters. During this exercise several difficulties were encountered concerning either the lack of threshold reactivity, insufficient stereoselectivity or chemo- and site-selectivity complications. In general, we found that enolization of many types of "benzylic" and allylic (skipped) ketones and thioesters, including ynones and α-branched examples, is feasible using bifunctional tertiary amine/HB donor catalysts, and that they may react with a sort of electrophilic reaction partners, including nitroolefins, vinyl sulfones, enones, aldehydes, imines or diazocompounds leading to products in high chemo-, site-, diastereo- and enantioselectivities in most cases. Eventually, an unexpected tandem process to afford isomerically pure tetrasubstituted cyclohexene compounds was uncovered. In this context, it was also found that heterocyclic lactams, including newly designed alkylthio-substituted imidazolones and pyrimidinediones, may work as efficient masked forms of (thio)hydantoins, α-amino amides and barbituric acid derivatives, allowing new enantioselective entries to the respective target compounds bearing a quaternary α-stereocenter. In our experience, each reaction development required careful screening of both the optimum reaction conditions and organocatalyst. Given the variety of substrates, both nucleophilic and electrophilic, and reaction types explored, there was no universal bifunctional catalyst identified. Instead, well-established or even commercial (thio)urea- and squaramide-based aminocatalysts were sufficient occasionally. In other instances, new catalysts were developed that incorporate either additional H-bond donor sites (ureido-aminals, NH amides, phenols), enhanced steric constrains (tertiary carbinol ethers), a trialkylsilyl side-arm or combinations of these designing elements. In several of the examples illustrated, additional insights on the activation mechanisms and the course of reaction site- and stereoselectivity were investigated by means of computational methods. Finally, while this investigation has provided a variety of new procedures to access synthetically relevant building-blocks in enantioenriched form through operationally simple protocols, new or not-so-well understood problems as well as yet unmet challenges were also uncovered that will deserve further efforts in the area.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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