Enantioselective Construction of Tetrasubstituted Carbons through Brønsted Base Catalyzed Michael Reactions: α'-Hydroxy Enones as Key Enoate Equivalent

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ABSTRACT: Catalytic and asymmetric Michael reactions constitute very powerful tools for the construction of new *C–C* bonds in synthesis, but most of the reports claiming high selectivity are limited to some specific combinations of nucleophile/electrophile compound types, and only few successful methods deal with the generation of all-carbon quaternary stereocenters. A contribution to solve this gap is presented here based on chiral bifunctional Brønsted base (BB) catalysis and the use of α'-oxy enones as enabling Michael acceptors with ambivalent H-bond acceptor/donor character, a yet unreported design element for bidentate enoate equivalents. It is found that the Michael addition of a range of enolizable carbonyl compounds that have previously demonstrated challenging (i.e. α-substituted 2-oxindoles, cyanoesters, oxazolones, thiazolones and azlactones) to α'-oxy enones can afford the corresponding tetrasubstituted carbon stereocenters in high diastereo- and enantioselectivity in the presence of standard BB catalysts. Experiments show that the α'-oxy ketone moiety plays a key role in the above realizations, as parallel reactions under identical conditions but using the parent α,β-unsaturated ketones or esters instead proceed sluggish and/or with poor stereoselectivity. A series of trivial chemical manipulations of the ketol moiety in adducts can produce the corresponding carboxy, aldehyde, and ketone compounds under very mild conditions, giving access to a variety of enantioenriched densely functionalized building-blocks containing a fully substituted carbon stereocenter. A computational investigation to rationalize the mode of substrate activation and the reaction stereochemistry is also provided, and the proposed models are compared with related systems in the literature.

■INTRODUCTION

Catalytic asymmetric conjugate addition reactions account as one of the most useful and atom economic approaches for the construction of new *C–C* and *C–X* bonds stereoselectively.[1] Major advances in the field have been triggered by the design and discovery of new chiral catalysts, both metal catalysts and organocatalysts, often in conjunction with the development of appropriate Michael acceptor templates.[2] The templates should not only provide gained chemical versatility to the resulting conjugate addition adducts, but also should contribute to attain optimal performance by the intervening catalyst in terms of reactivity and stereoselectivity. Ideally, strongly biased achiral templates may override otherwise observed substrate-dependent catalyst behaviour thus attenuating undesired fluctuations on the catalyst efficiency. This aid from properly design templates may result instrumental when difficult transformations, such as the enantioselective generation of tetrasubstituted carbon stereocenters, are pursued.

Among several categories of Michael acceptors, α,β-unsaturated carbonyl compounds are of prime synthetic significance. Adducts resulting from the conjugate addition of a nucleophilic reagent to α,β-unsaturated aldehydes, ketones, or carboxylic acid derivatives have all found a myriad of applications. In particular, certain carboxylic acid derivatives may aftermaths be converted into the corresponding aldehyde or ketone derivatives smoothly, making the former very versatile compounds. However, while both the addition reaction to α,β-unsaturated aldehydes and to ketones are well suited for iminium ion activation catalysis,[3] conjugate addition to the corresponding carboxylic acids and their derivatives is not. In this latter case, the most common activation mechanism relies upon coordination of the carbonyl group of the α,β-unsaturated carboxylic acid derivative to a Lewis acid (metal catalysis) or a H-bond donor species (organocatalysis). In this context, several two-point binding enoyl templates bearing an additional coordinating site (X, Figure 1a) tethered to the enoyl system have been developed. Compared with monodentate templates, which may lead to two degenerate C=O···metal complex geometries, thus complicating stereocontrol, bidentate templates can form chelates upon coordination to the metal as key organizational/activation element.[4] Similarly, bidentate enoyl templates may perform superior in conjugate addition reactions triggered by bifunctional Brønsted base–H-bond catalysts, because of the likely occurrence of double H-bond interactions between the substrate and the catalyst (Figure 1a).[1, 5] This type of Brønsted base catalysis has emerged as very advantageous, not only because many Brønsted bases (BB) are commercially available and/or readily accessible, but also because the pronucleophilic reagent (NuH) do not generally need to be preactivated in a separate step.[6] However, successful BB-catalyzed enantioselective *C–C* bond forming conjugate addition reactions are often limited to certain inherently reactive nucleophiles (particularly 1,3-dicarbonyl compounds) and/or electrophiles (particularly nitroalkenes),[7]

whilst in many other instances –α,β-unsaturated esters being a notable example– sluggish reactivity or poor enantiocontrol is achieved. This situation becomes more problematic when generation of all-carbon quaternary stereocenters is pursued.[8] Both reactivity attenuation by steric constraints and difficulties in controlling face selectivity in prostereogenic trisubstituted trigonal centers make this goal to be a hot topic yet.

In this study we describe a new enoyl template model for asymmetric organocatalysis in which the bidentate substrate might engage as either H-bond donor or acceptor or both (ambivalency) during activation by the bifunctional catalyst (Figure 1b). As representatives of such a model, we show that α'-hydroxy enones perform exceedingly well in the Brønsted base-catalyzed asymmetric conjugate addition of a range of soft *C*-nucleophiles leading to tetrasubstituted carbon stereocenters in very high enantioselectivity. The chemical versatility of thus obtained adducts is also illustrated and a theoretical interpretation of the results provided.

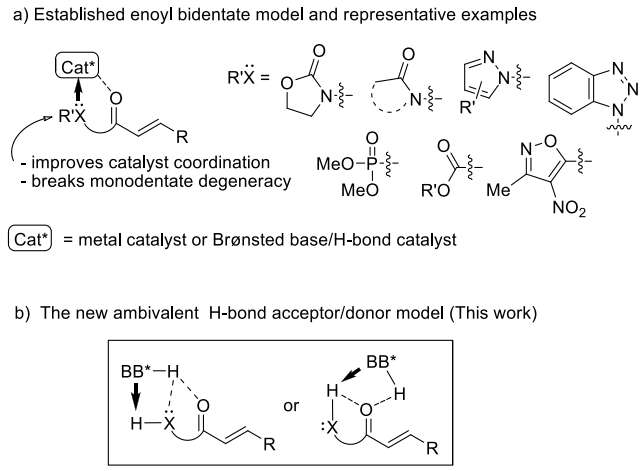


Figure 1. Bidentate enoyl templates for asymmetric catalysis: (a) previously established, and (b) the new proposal. (BB*= chiral Brønsted base).

■RESULTS AND DISCUSSION

Background and working hypothesis. While being a prominent synthetic operation towards 1,5-dicarbonyl frameworks, successful catalytic and asymmetric methods for the constructive assembly of all-carbon quaternary centers from monodentate α,β-enones are usually restricted to 1,3-dicarbonyl substrates and related active pronucleophiles. In this context, metal-catalyzed[9] enantioselective conjugate addition of 1,3-diketones, β-ketoesters and α-aryl cyanoesters to acrolein or vinyl ketones (mainly methyl vinyl ketone) as the Michael acceptor have been reported by the groups of Ito,[10] Shibasaki,[11] Sodeoka[12] and Jacobsen,[13] among others.[9]

In concurrent efforts under metal-free conditions, chiral Brønsted base-catalyzed conjugate additions of enolizable carbonyl compounds have also been explored after the pioneering work by Wynberg.[6,14] Deng has reported conjugate additions of α-substituted β-dicarbonyl compounds and α-aryl

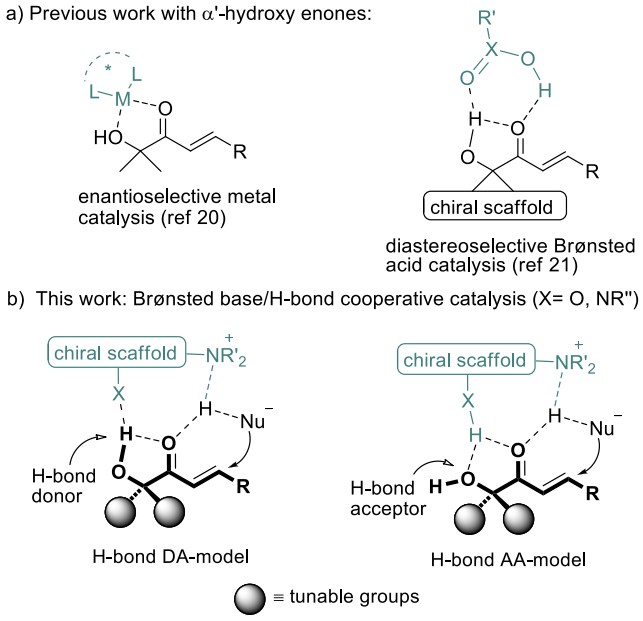


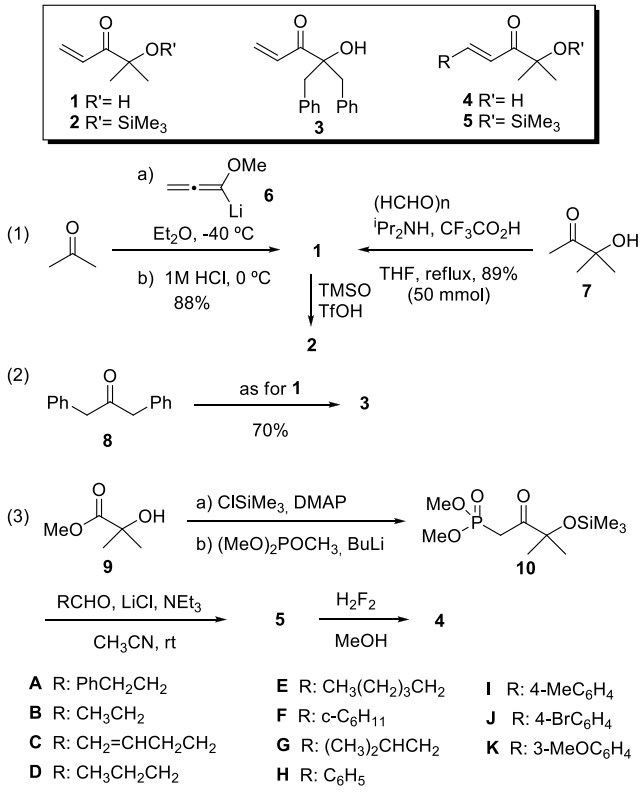
Figure 2. Two point binding α'-hydroxy enone templates for asymmetric catalysis.

cyanoacetates to acrolein or methyl vinyl ketone promoted by a bifunctional Cinchona based catalyst,[15,16] while Jørgensen documented the reaction of cyclic β-keto esters with both acrolein and methyl vinyl ketone using a non-biaryl atropisomeric Cinchona-based catalyst.[17] More recently, Rodriguez and Constantieux[18] extended the Brønsted base catalysis approach to cyclic β-ketoamides as nucleophiles against methyl vinyl ketone. Notwithstanding these achievements, the realization of BB-catalyzed asymmetric conjugate additions involving more reluctant substrate combinations, such as less reactive enolizable carbonyl compounds and acryloyl equivalents, remains challenging. Thus, whilst some ester surrogates have been applied to Brønsted base-catalyzed conjugate addition reactions,[5] to the best of our knowledge, only in three cases the generation of all-carbon quaternary centers has been documented. In a significant work, Dixon[5m] described highly enantioselective conjugate additions of cyclic β-keto esters to naphthyl thioacrylate and *N*-acryloyl pyrrol, respectively, using a modified cinchona alkaloid as bifunctional Brønsted base catalyst. When acyclic keto esters were used as nucleophiles, yields and selectivity diminished, a limitation also noticed by Bartoli and Melchiorre[5n] who used maleimides as competent Michael acceptors. Also, β,γ-unsaturated acyl phosphonates[5f] have been reported to be effective enoate surrogates against reactive pronucleophiles including azlactones and 1,3-dicarbonyl compounds.

In the early 80´s Heathcock demonstrated that α'-hydroxy ketones are convenient enoate equivalents in the context of aldol addition reactions,[19] since oxidative cleavage of the ketol moiety in the corresponding aldol adducts affords β-hydroxy carboxylic acids. Focused on this observation, research from these laboratories has led to the development of metal-catalyzed conjugate addition and cycloaddition reactions of simple α'-hydroxy enones,[20] as well as Brønsted acid-catalyzed Diels-Alder reactions of chiral α'-hydroxy enones, [21,22] methods that provide, after cleavage of the ketol moiety, products in the carboxylic acid oxidation state. In these developments the ability of

the ketol moiety for both 1,4-metal and 1,4-proton binding (Figure 2a)[23] revealed to be critical for success. Based on these precedents, we hypothesized that the H–bonding ability of the ketol moiety in α'-hydroxy enones may decisively influence reactions initiated by a proton-transfer event, such as the BB-catalyzed Michael reactions (Figure 2b).[24] Specifically, the substrate α'-hydroxy enone might participate as a two-point H-bond donor/acceptor (DA-model) or acceptor/acceptor (AA-model) partner in the transition state, a diverting design element that is lacking in previous enoyl templates.[5] To the best of our knowledge, α'-hydroxy enones have not been studied within the context of organocatalytic asymmetric bond-construction processes.[25,26]

***Scheme 1*. Preparation of α'-hydroxy enones. TMSO: *N*-(trimethylsilyl)-oxazolidin-2-one.**



Preparation of α'-hydroxy enones. The α-oxy enones **1** and **3** were readily prepared[27] from the addition of lithium methoxyallene **6** to acetone and 1,3-diphenylacetone **8**, respectively, and subsequent smooth one-pot hydrolysis of the resulting intermediates, as shown in Scheme 1. Alternatively, enone **1** could also be prepared by the method of Connell,[28] starting from the commercially available α-hydroxy ketone **7**. In both cases compound **1** was obtained in yields between the range 80-90% at 50 mmol scale. Preparation of **2** from **1** is straightforward and quantitative by silylation with commercial N-trimethylsilyl oxazolidin-2-one (TMSO). For β-substituted enones **5**, the classical Horner-Wadsworth-Emmons olefination protocol from the β-keto phosphonate **10** was used.

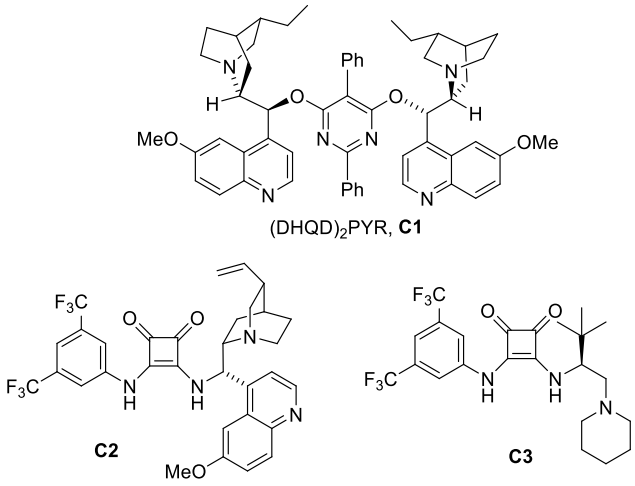
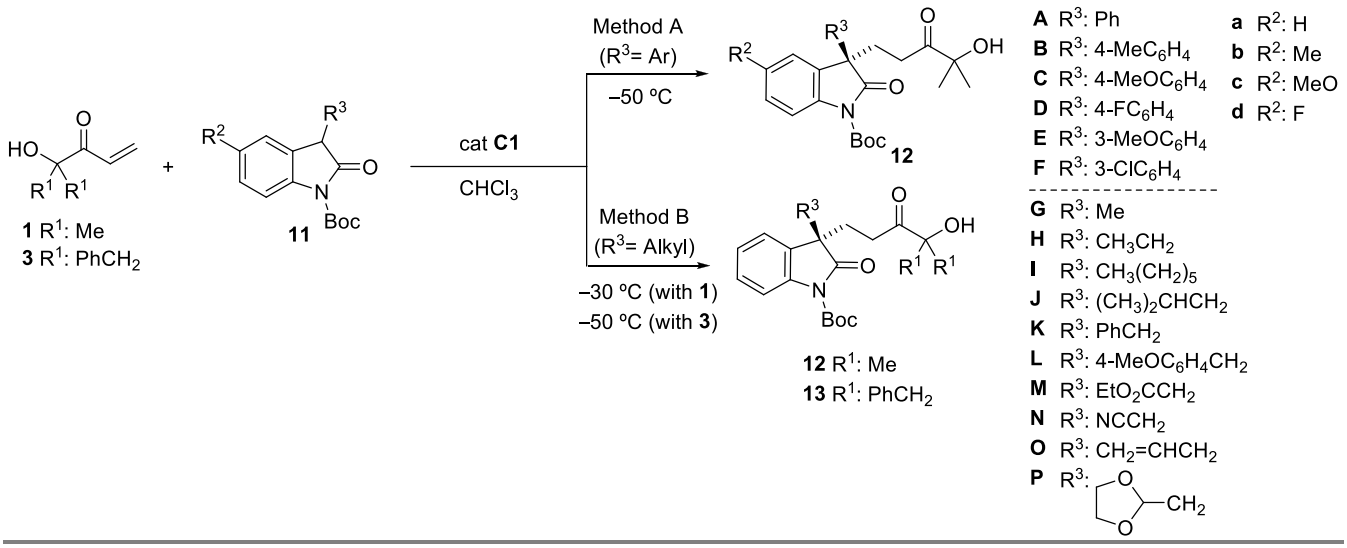


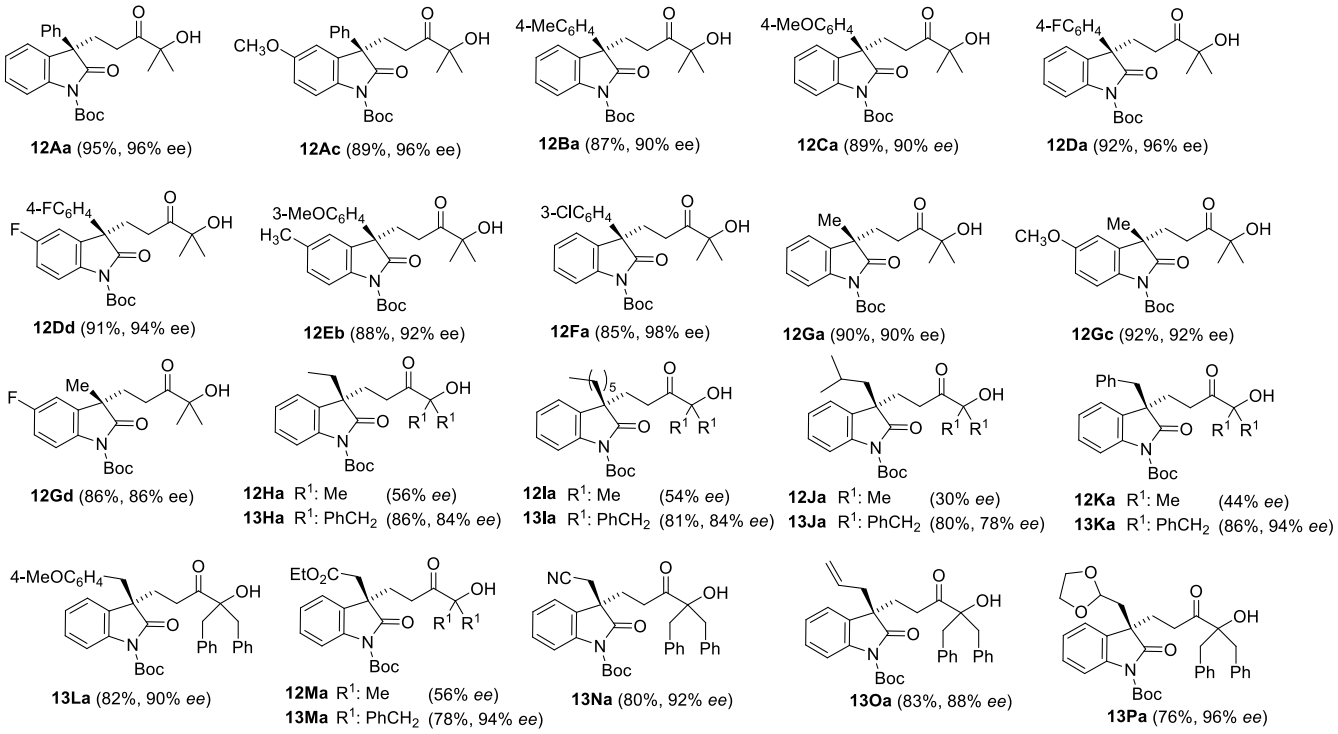
Figure 3. Catalysts employed within this work.

This phosphonate was in its turn prepared from commercial hydroxyester **9**.[29] Likewise, for β-aryl substituted α–hydroxy enones **4** (R=Ar), an aldol condensation of **7** with benzaldehydes may also be employed.[27]

Conjugate additions of 3-substituted oxindoles. To assess the reactivity profile of these α'-hydroxy enones in Brønsted base catalysis, our study was initiated with the reaction of α'–hydroxy enone **1** and 3-substituted oxindoles. The oxindole structural motif is widely present within natural and synthetic bioactive molecules,[30] however, Brønsted base promoted reaction of 3–substituted oxindoles with alkyl vinyl ketones has met with limited success so far.[31,32] For example, it has been reported that methyl vinyl ketone (MVK),[31a,b] ethyl vinyl ketone [31a] and phenyl vinyl ketone [31a] all provided *ee´*s between the range of 60%–70% in the reactions with 3-aryl oxindoles; the reactions with 3-methyl-, 3-isobutyl-, and 3-allyl oxindoles proceed with even lower *ee´*s (of about 55%).[31c] In addressing these issues, and after screening several Brønsted base catalysts,[27] we were gratifying to find that the above addition reactions using **1**, conducted in the presence of 10 mol% $(DHQD)_2PYR$ (**C1**), afforded the corresponding adducts **12** in excellent yields and enantioselectivities. As the data in Table 1 show, under these conditions (–50 ºC in $CHCl_3$ as solvent) oxindoles **11A-F** bearing 3-aryl substituents with either electron donating or electron withdrawing groups are tolerated with almost equal efficiency. Oxindoles with substitution at the aromatic ring also provided adducts with excellent chemical and stereochemical results. Likewise, the 3-methyl oxindoles **11Ga**, **11Gc**, and **11Gd**, which are valuable precursors of natural products, *vide infra*, were competent reaction partners to give the respective adducts **12Ga**, **12Gc** and **12Gd** in good yields and enantioselectivities, typically 90% *ee*. Nevertheless, attempts to further expand this reaction to oxindoles bearing larger alkyl chains at the *C*3 position failed. Oxindoles **11H**, **11I**, **11J**, **11K** and **11M**, all provided the corresponding adducts **12** with poor enantioselectivity, typically 50% *ee*. Whilst these results seem to be quite common for reactions involving 3-alkyl substituted oxindoles, very few attempts to address this deficiency have resulted with success.[32] In fact, few catalytic systems work well for both aryl- and alkyl-substituted oxindoles.[32d] Given the ready

Table 1. Conjugate additions of 3-substituted oxindoles to α'-hydroxy enones 1 and 3.[a]



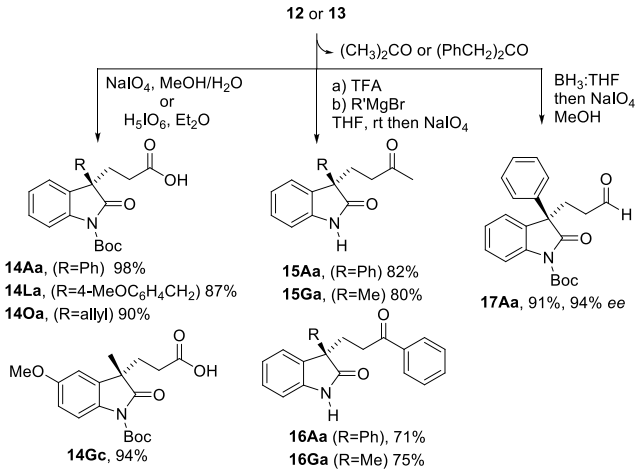


a The reactions were generally performed on a 0.30 mmol (for R^3= Ar or Me) or 0.1 mmol (for R^3= Alkyl) scale in $CHCl_3$ (1.5 mL/mmol) using enone **1** (1.5 equiv.) or **3** (3 equiv.) and catalyst **C1** (10 mol% for **1**; 30 mol% for **3**). Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

availability of α'-hydroxy enones we focused on the α'-disubstitution pattern as an additional element for steric tuning. We were gratifying to observe that the enantioselectivity was notably increased, typically from 50% *ee* up to 90% *ee*, by using α'-hydroxy enone **3**. As the results in Table 1 show, the reactions were tolerant with oxindoles bearing short, large, and ramified alkyl chains as well as alkyl chains with functional groups. These results are of special interest in that diverse functionality may be generated from a single common adduct. Thus, treatment of adducts **12Aa** and **12Gc** with $NaIO_4$ in $MeOH/H_2O$ provided the corresponding carboxylic acids **14** in yields of 98% and 94%, respectively, along with acetone as the only organic side product formed, Scheme 2. Alternatively, oxidative cleavage of adducts **13La** and **13Oa**, by treatment with periodic acid in this case, led to acids **14La** and **14Oa** in 87% and 90% yield, along with dibenzyl ketone which could be recovered and reused. On the other hand, the addition of the corresponding Grignard reagent or reduction of the carbonyl group followed by diol cleavage as above furnished the methyl- and aryl ketones **15**/**16** and the aldehyde **17**, respectively, in good yields. Importantly, during the above manipulations configurational integrity of newly generated tetrasubstituted carbons in adducts was untouched as determined for aldehyde **17Aa** (94% *ee*) and acid **14Gc** (90% *ee* as determined in esermethole, *vide infra*). It

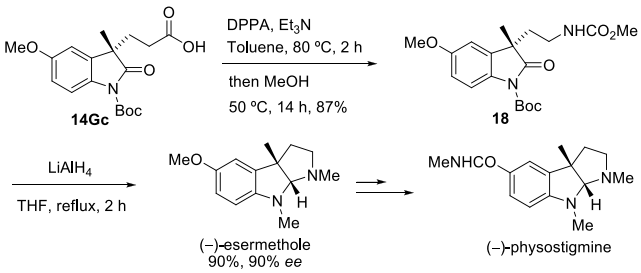
is worth of note that the present method allows preparation of ketones such as **15Ga** and **16Ga**, formally derived from the less sterically demanding methyl-sustituted oxindoles, with enantioselectivities among the best reported until now.[31]

***Scheme 2*. Ketol scission in adducts 12.**



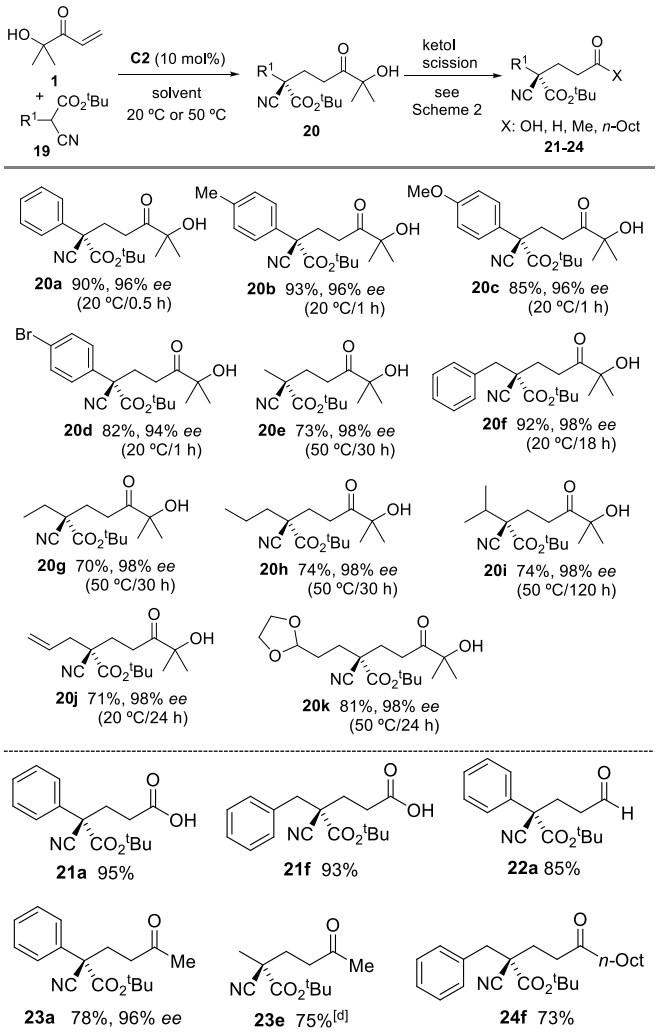
In addition, as far as we know, no asymmetric and catalytic conjugate addition of 3-substituted oxindoles to acrylate esters or their surrogates have been developed yet.[30,33] Our method may serve to remediate this deficiency by providing building-blocks that can be easily transformed into biologically active compounds such as (–)-esermethole, Scheme 3,[34] an advanced intermediate for the synthesis of (–)-physostigmine.[35] Thus, Curtius rearrangement of carboxylic acid **14Gc** afforded carbamate **18**, which upon treatment with $LiAlH_4$ underwent reductive cyclization to (–)-esermethole of 90% *ee*.

***Scheme 3*. Short enantioselective synthesis of (–)-esermethole.**



The key role played by the $(CH_3)_2COH$ fragment of the template as a traceless activating group in the above reactions was clear from competitive experiments involving both **1** and methyl vinyl ketone (MVK), a simple enone lacking any group for additional H-bond coordination. Thus, when the reaction of oxindole **11Aa** was carried out with a 1:1 mixture of **1** and MVK in the presence of **C1** (10 mol%) at –50 ºC, **12Aa** was the exclusive addition product obtained, without detecting any product from the addition reaction of **11Aa** to MVK. In another experiment, the reaction between oxindole **11Aa** and MVK run at –30 ºC in the presence of **C1** led, after 48 h, to 35% conversion only, with an isolated product of 50% *ee*.

Table 2. Conjugate addition of α-substituted *tert*-butyl cyanoacetates 19 to α'-hydroxy enone 1 promoted by C2.[a]



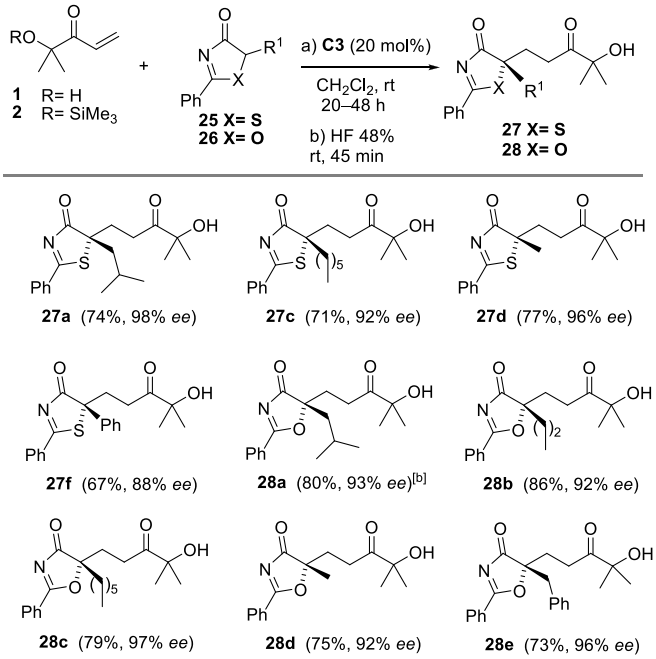
[a] The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 at 20 ºC or in $CHCl_3$ at 50 ºC. Yield of isolated major isomer after chromatography. *Ee* Determined by HPLC. [d] $[\alpha]_D^{22}$= + 3.9 (*c*= 1, $CHCl_3$); Lit.[10] $[\alpha]_D^{20}$= + 2.7 (*c*= 5, $CHCl_3$, 81% *ee*).

Conjugate additions of cyanoacetates. Encouraged by these results, we next investigated the reaction of α'-hydroxy enones with α–substituted cyanoacetates.[36, 37] The problems experienced in achieving efficient chirality transfer in metal catalyzed conjugate additions with these pronucleophiles have been ascribed to the fact that cyanoacetates are incapable of two-point binding.[38] We reasoned that the capacity of α'–hydroxy enones for two-point binding (Figure 2) may ameliorate this deficiency. Indeed, we found that **1** was effective in the Brønsted base catalyzed reaction with not only α–aryl, but also α–alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates,[37] particularly against alkyl vinyl ketones.[37a] After evaluation of a survey of different Brønsted bases, including **C1**, the squaramide family of catalysts pioneered by Rawal[39] probed the most effective in these instances. Among them, catalyst **C2**[40] resulted optimal for the reaction between **1** and a range of both α-aryl and α-alkyl *tert*-butyl cyanoacetates **19**. In general, the reaction with α-aryl cyanoacetates **19a-d** was performed at room temperature using three equivalents of enone **1** to afford, after 1 hour, adducts **20a-**

d with excellent yields independently of the nature of the aromatic ring substitution. In contrast, most α-alkyl cyanoacetates tested showed decreased reactivity with reaction times of about 120 h required for complete conversion under the above conditions. However, by using threefold excess of the latter and rising the temperature to about 50 °C, full conversions of products **19e-k** were attained within about 30 h or less, with very high yields of isolated product and essentially perfect enantioselectivity obtained. Again, chemical manipulation of the ketol unit in adducts **20** using simple Grignard technology and/or reduction/oxidation protocols, as in Scheme 2, provided a straightforward entry to the corresponding carboxylic acids **21**, aldehydes **22** and ketones **23**/**24**. Comparison of optical rotation value of product **23e** (see Table 2, footnote d) with literature data[10] served to set the configuration of the products and hence the stereochemical course of the above catalytic reactions. As noted above enantioselective synthesis of products like **21**-**24** through direct catalytic Michael reactions remains challenging. Once more, the design enone **1** demonstrated to be instrumental in achieving these levels of reactivity and selectivity. For example, when an equimolar mixture of cyanoacetate **19a**, enone **1** and MVK was stirred at 20 ºC for 30 min in the presence of 10 mol% **C2**, a 12:1 mixture of **20a** and the addition adduct from MVK, respectively, was obtained. Likewise, parallel reactions of other typical Michael acceptor templates, i.e. *N*-acryloyl oxazolidinone or *N*-acryloyl pyrazole, with cyanoacetate **19e** under the above conditions were sluggish (less than 55% conversion after 120 h at room temperature for the two cases).

Conjugate additions of heteroatom-bearing soft carbon nucleophiles: Besides all-carbon quaternary stereocenters, tetrasubstituted carbons bearing a sulfur, oxygen or nitrogen heteroatom are also interesting yet difficult products to obtain as single enantiomers. Therefore, we decided to investigate the capacity of our template model to participate in Brønsted base-catalyzed conjugate additions of several heteroatom-bearing soft carbon nucleophiles. For this study 5*H*-thiazol-4-ones **25**[41] and 5*H*-oxazol-4-ones **26**[42, 43] were initially selected and we found that reaction of thiazolone **25a** and oxazolone **26a** with α'–hydroxy enone **1** did proceed in the presence of several Bronsted bases, including **C1** and **C2**, but with very poor enantioselectivity. Further exploration led us to examine the modified enoyl template **2**, prepared by simple silylation of the hydroxyl group in enone **1**. To our pleasure, the reaction of 5*H*-thiazol-4-ones **25** and enone **2** catalyzed by **C2** in dichloromethane at –20 ºC provided, after desilylation of the resulting intermediates, the corresponding addition products **27** in good yields and *ee*´s up to 98%. The parent 5*H*-oxazol-4-ones **26** participated with equal chemical efficiency in the reaction with enone **2**. For example, under the above conditions, **26a** provided **28a** in 85% yield albeit in 73% *ee*. This result was further improved by using catalyst **C3**,[44] and the reaction between **2** and oxazolone **26a** performed at room temperature afforded, after desilylation of the resulting intermediate, adduct **28a** in 80% yield and 93% *ee*.

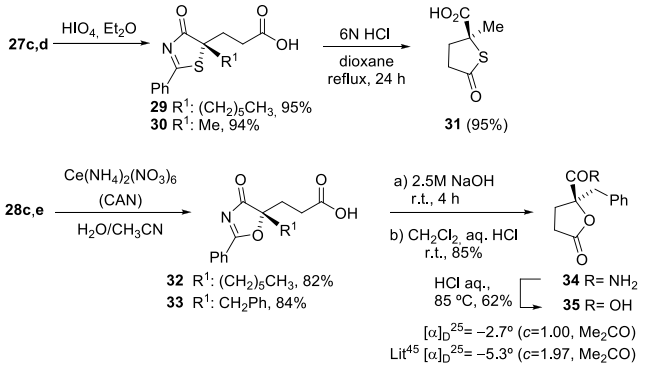
Table 3. Conjugate addition of 5*H*-thiazolones 25 and 5*H*-oxazolones 26 to α'-silyloxy enone 2.[a]



[a] The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.9 mL) using 1.5 equiv. of enone **2**. For thiazolones **25** reactions were conducted at −20ºC and for oxazolones **26** at r.t. Yields after chromatography. *Ee* determined by HPLC. [b] 73% *ee* from catalyst **C2**.

In general, excellent yields and enantioselectivities were achieved for a survey of thiazolones and oxazolones bearing either short, large, or ramified alkyl chains at the heterocyclic ring (Table 3). While these reactions were typically carried out in the presence of 20 mol% of catalyst, the catalyst loading could be reduced to 10 mol% provided the reactions were carried out at higher temperature. For example, products **28a** and **28b** were obtained in essentially same chemical yields and stereoselectivities as above when the corresponding reactions were performed in $CHCl_3$ at 40 ºC during 30–40 h. Clearly, these results show that the α'–hydroxy enone template may be easily modified to better adapt to different substrate/catalyst combinations.

***Scheme 4*. Elaboration of thiazolone and oxazolone adducts 27 and 28**.

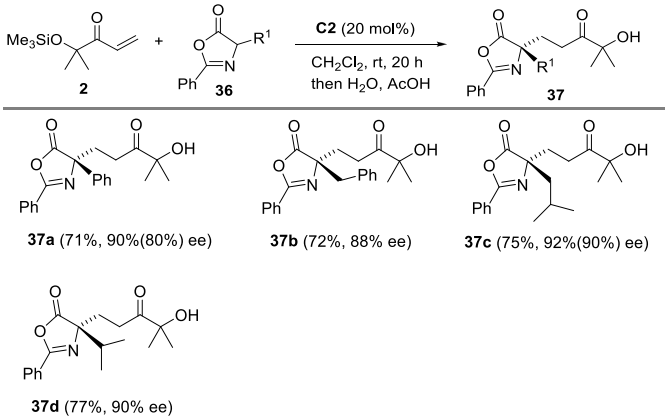


Transformation of adducts **27** and **28** into the corresponding carboxylic acids **29**, **30**, **32** and **33**, Scheme 4, was easily achieved by treatment with periodic acid in the case of thiazolone adducts **27**, and with cerium ammonium nitrate (CAN)

in the case of oxazolones **28**. Subsequent transformation of adduct **29** into the thiolactone **31**, as well as adduct **33** into the lactone derivative **34**, by simple ring opening under mild acid and/or basic conditions, illustrates the utility of the method. In addition, formation of known lactone **35**[45] from **34** served to establish the stereochemical course of the reactions. It should also be noted that both **25a** and **26a** upon treatment with either methyl acrylate or *tert*-butyl acrylate under the above conditions did not provided the corresponding Michael adducts.

Further exploration of the broad scope of α-silyloxy enone **2** showed that α-substituted azlactones, 4*H*-oxazol-5-ones, also fit well. For example, Table 4, the reaction between azlactones **36** and enone **2** in the presence of the catalyst **C2** or **C3** led, after desilylation of the intermediate adducts, to the corresponding products **37** with good yields and *ee*'s. In each case, reactions proceeded with high site selectivity and no products from reaction at the C_2-position of the azlactone ring were observed.[46]

Table 4. Conjugate addition of azlactones.[a]



[a] The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.6 mL) using 3.0 equiv. of enone **2**. Yield of isolated products after chromatography. *Ee* determined by HPLC. In parentheses *ee*'s from catalyst **C3** (10 mol%).

***Scheme 5*. Elaboration of adducts to α,α-disubstituted glutamic acid derivatives.**

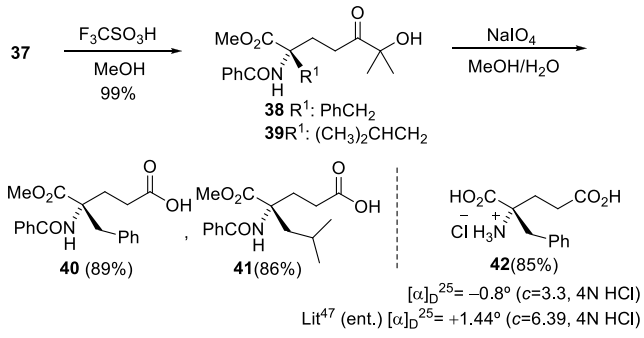
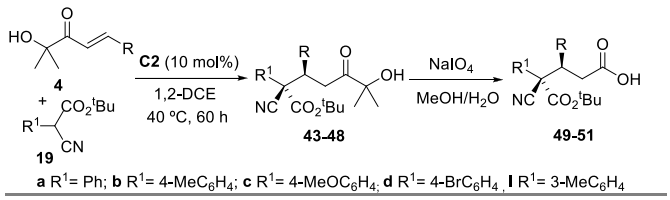
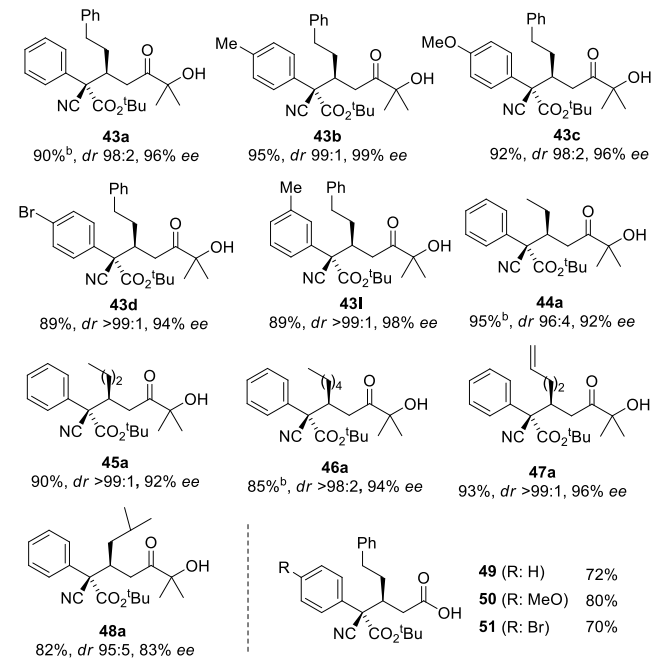


Table 5. Conjugate addition of cyanoacetates to β-substituted α-hydroxy enones [a]





[a] The reactions were performed on a 0.30 mmol scale in 1,2-DCE (1.2 mL) using 3.0 equiv. of enone **4**, at 40 °C otherwise stated. Yield of isolated products after chromatography. *ee* determined by HPLC. *dr* determined by ^{1}H-NMR or HPLC. [b] Reaction carried out at 50 °C.

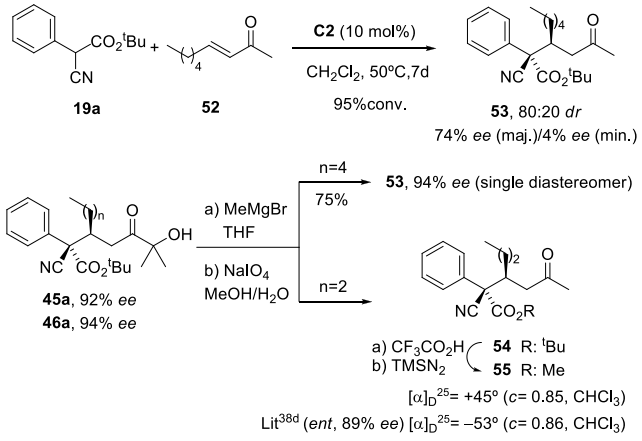
Elaboration of thus obtained azlactone adducts afforded useful building-blocks. For instance, Scheme 5, azlactone ring opening in **37b**,**c** to afford the corresponding compounds **38** and **39**, and subsequent ketol elaboration, provided acids **40** and **41**, respectively. The former was then transformed into the known glutamic acid derivative **42**[47] as a proof of the stereochemical course of the catalytic reaction.

Reactions with β-substituted α–oxy enones: Generation of adjacent quaternary/tertiary stereocenters. Given the results attained with the α-oxy vinyl ketones **1** and **2**, we wondered whether this template model would be effective to generate a quaternary carbon adjacent to a tertiary stereogenic center, a synthetic task that generally presents added difficulties. To this end we selected the reaction of α–substituted cyanoacetates owing to the inherent challenges associated with this kind of pronucleophiles, *vide supra*. In this context, Peters has recently addressed this issue and provided a solution to the case of reactions involving cyclic enones, i.e. cyclohexenone, using metal catalysis.[38a] On the other hand, only one example of Michael reaction of α-substituted cyanoacetates with β-substituted alicyclic enones has been documented, based on salen complex catalysis.[38d]

We were gratifying to observe that α-aryl cyanoacetates **19a-d** and **19l** reacted with β-alkyl substituted α–hydroxy enones **4A-E** to furnish adducts **43-47** in good yields, Table 5. The reactions were carried out in 1,2-dichloroethane at 40 °C and generally essentially

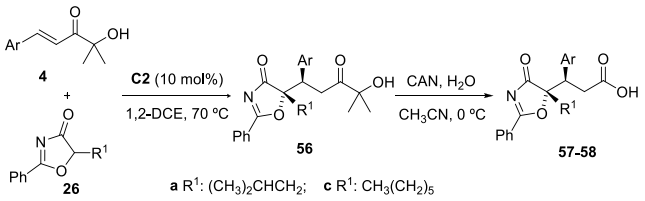
one diastereomer was produced in excellent enantiomeric excess. As exceptions, β-substituted enones **4F** and **4H**, bearing the cyclohexyl and phenyl groups, respectively, were ineffective under these conditions, whilst **4G** provided **48a** in good yield but diminished stereoselectivity. On the other hand, α-alkyl cyanoacetates were unreactive and did not provide the corresponding adducts. Despite these limitations, which, in their turn, confirm the difficulties associated with these problematic pronucleophiles, the method represents the first Michael addition of α-substituted cyanoacetates to β-alkyl enones catalyzed by a chiral Bronsted base, and confirms once more the excellent behaviour of α′–hydroxy enones as Michael acceptors. In this respect, whilst no reaction was observed from **19a**, **19c** and **19d** with methyl 5-phenylpent-2-enoate in the presence of **C2**, oxidative cleavage of **43a**, **43c** and **43d** provided the desired carboxylic acids **49**-**51**. We also examined the **C2** catalyzed reaction between cyanoacetate **19a** and trans-3-nonen-2-one **52**, which lacks the α′–hydroxy group (Scheme 6). The reaction proceeded, but required seven days to reach 95% of conversion and the product was formed as an 80:20 mixture of diastereomers with only modest enantioselectivity for the major isomer **53**. In sharp contrast, the reaction between **19a** and α′–hydroxy enone **4E**, as mentioned above, gave **46a** as essentially single diastereomer in 94% *ee* (Table 5), which enables an alternative and highly stereoselective entry to product **53** via usual alkylation and oxidative scission. Similarly, **45a** could be converted into the methyl ketone **54** and, upon subsequent transesterification, the corresponding methyl ester **55**, which exhibited essentially identical ^{1}H and ^{13}C NMR spectra to those reported in the literature,[38d] but opposite optical activity, thus confirming the stereochemical assignments for the adducts.

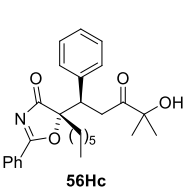
***Scheme 6*. Conjugate addition of α-substituted cyanoacetates to simple enones and an indirect solution to the low inherent stereoselectivity.**

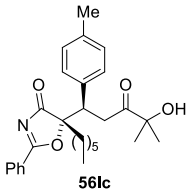


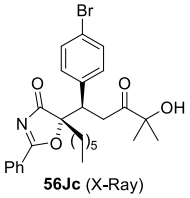
Oxazolones **26** also participated in the reaction with β-substituted enones **4** to give the corresponding α,α-disubstituted α-hydroxy acid precursors with an adjacent tertiary stereocenter, Table 6. However, in contrast to the case of cyanoacetates noted above, the reactions of oxazolones **26** worked well only with β-aryl enones to afford the corresponding addition products **56**. The reactions with β–alkyl enones were unproductive and the starting materials could be recovered unchanged. From these results, it is clear that for these types of substrate combinations leading to adjacent quaternary/tertiary stereocenters, there might be strong steric interactions that may justify the observed variability. Configuration of adduct **56Jc** was established by a single crystal X-ray analysis and that of the remaining adducts by assuming a uniform reaction mechanism. Additionally, conversion of **56** into the carboxylic acids **57** and **58** could be accomplished by using CAN as the optimum oxidant.

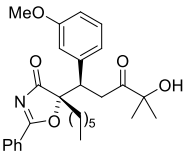
Table 6. Conjugate addition of oxazolones to β-substituted α-hydroxy enones.[a]

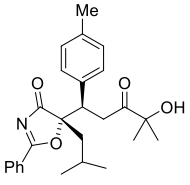


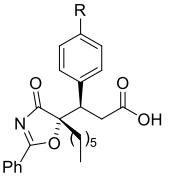












The reactions were performed at 70 ºC on a 0.15 mmol scale in dichloroethane (0.45 mL) using 3.0 equiv. of enone **4**. Yield of isolated products after chromatography. Diastereomeric ratios determined by ^{1}H NMR (300MHz) on the crude reaction products and confirmed by HPLC. *ee* determined by chiral HPLC (for compounds **57** and **58**, after derivatization to their methyl esters).

Computational studies. With these experimental data in hand, it seemed clear that α'–oxy enones exhibit some unique reactivity as compared with ordinary enones, i.e. MVK. Both higher reactivity and improved levels of enantioselectivity are observed in the BB-catalyzed reactions studied. Similarly, our experimental results indicate a distinct behaviour of α'–oxy enones as compared with other typical enoyl templates previously reported for the BB-catalyzed enantioselective generation of quaternary stereogenic carbon centers. More specifically, the catalyst-controlled conjugate addition of α-substituted cyanoacetates is, as mentioned before, sluggish with the majority of Michael acceptors, whilst it works well with α'–oxy enones. With the aim to bring some light on such distinguishing behavior, we decided to study computationally[48] the case of the conjugate addition reactions of cyanoacetates. MVK and the two α'-oxy enones **1** and **59** were selected as the model Michael acceptors, and the relationship between their reactivity and structure was examined first. In agreement with our working hypothesis, calculations show that the intramolecular H-bond activation in **1** and **59** induces a change in a series of electronic parameters (Figure 4), explaining their higher reactivity in comparison with MVK. In particular, the electrophilicity index ω[49] for both **1**/**59** (2.0 eV) is higher than that for MVK (ω = 1.6 eV), which is consistent with the lower energy of LUMO for **1** and **59** (–1.9 eV) as compared with the LUMO of MVK (–1.5 eV),

and also the more positive character of the β-carbon of **1** (NPA charge of –0.31) than the corresponding β-carbon of MVK (–0.34). These values correlate well with the Wiberg bond index for **1** (1.90) and MVK (1.92), respectively, indicating the diminished double bond character of the enone C=C bond in **1**.

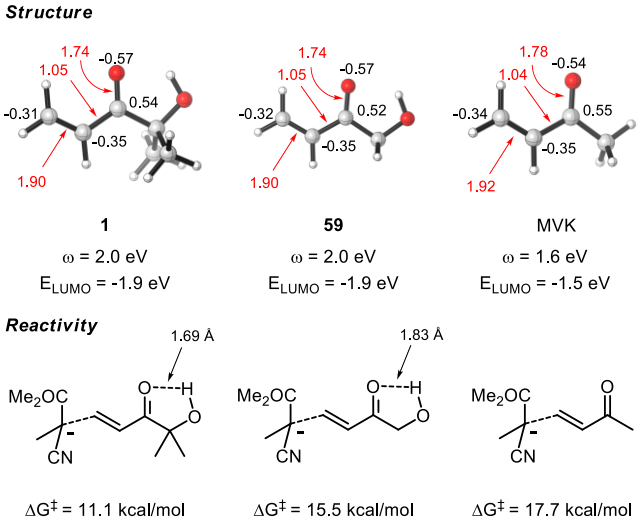


Figure 4. Structure/reactivity relationship

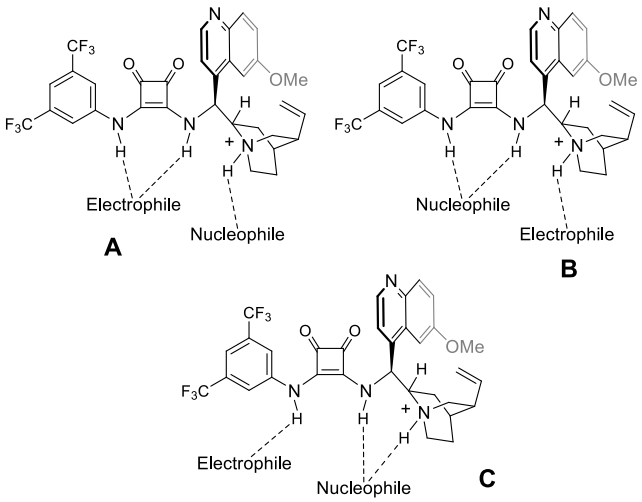


Figure 5. Three alternative substrate-catalyst combinations.

Subsequently, the activation energy of the reaction of these three Michael acceptors with methyl α-methylcyanoacetate was computed. This barrier resulted significantly lower for α'-hydroxy enone **1** (11.1 kcal/mol) than for MVK (17.7 kcal/mol). On the other hand, although the electronic parameters of both α'-hydroxy enones **1** and **59** do not differ significantly one another (see above), the reaction involving the latter presents an activation energy 4.4 kcal/mol higher than the reaction with **1**. This additional stabilization of the transition state (TS) for the reaction with **1** as compared with **59** is consistent with the shorter intramolecular hydrogen bond in the former case (1.69 Å *vs* 1.83 Å, Figure 1) and might be ascribed to a favorable Thorpe-Ingold effect[50] imparted by the two geminal methyl substituents in **1**.

The origin of the stereoselectivity in the **C2**-catalyzed reaction between hydroxy enone **1** and α-cyanoacetates was addressed next, and the first question to elucidate was the preferred H-bond pattern formed between the catalyst and both substrates in the TS corresponding to the *C–C* bond-forming step. In this respect, up to –at least– three different ternary complexes (**A**-**C**, Figure 5) have been proposed for reactions involving non covalent cooperative activation of the intervening nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)-tertiary amine catalyst.[51] Therefore, the question of whether or not a unified H-bond network model (**A**, **B**, **C**, other) could be applied to different reactions within this catalysis category seems to be still open and more data are desirable. In our case, we computed the reaction leading to adduct **20e** (Table 2), and despite much effort we were unable to find any plausible transition structure of type **B** among the several H-bond combinations studied.[52] From a look to the geometries of the resulting complexes, it seemed that once cyanoacetate is H-bonded to the catalyst there is not space available for the electrophile to interact with the same catalyst molecule. Thus, the structure closest to **B** we could find involves attack of the H-bonded cyanoacetate anion to the non complexed enone.[53] On the other hand, a single structure similar to model **C** was also found; however, it was predicted to be unrealistic due to its high activation energy.

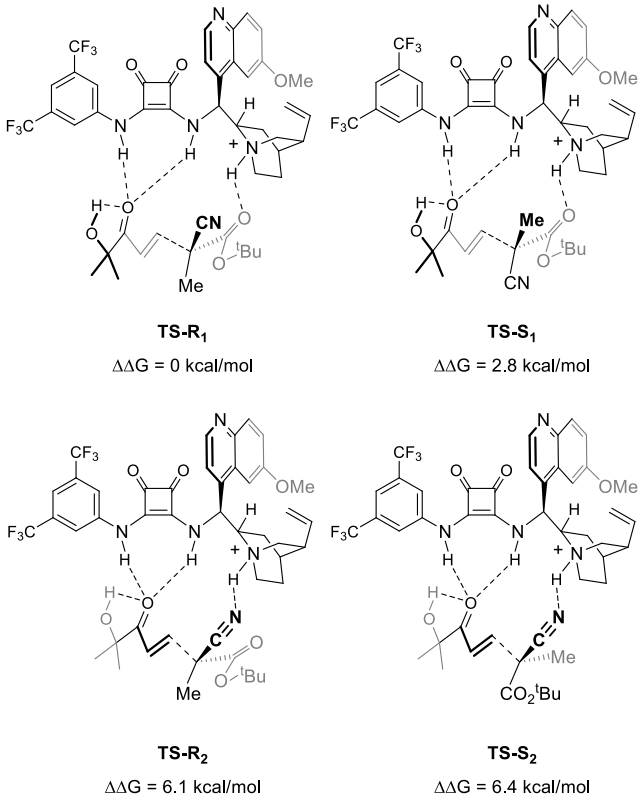


Figure 6. Located TS's for the catalytic addition reaction.

In its turn, four feasible structures of type **A** (**TS-R**$_1$, **TS-S**$_1$, **TS-R**$_2$, **TS-S**$_2$, Figure 6) were located, in which the α'-hydroxy enone carbonyl is double H-bonded to the squaramide NH groups, while the protonated quinuclidine NH$^+$ might bind to either the CN or the ester group of the cyanoacetate moiety. **TS-R**$_1$ is the lowest in energy and correctly explains the formation of the major isomer observed experimentally.[54] The next most feasible structure is **TS-S**$_1$. The energy difference between these

two structures is 2.8 kcal/mol at M06-2X/6-311+G** computational level.[55] Interestingly, in both cases the $CO_2{}^tBu$ is involved in H-bonding with the catalyst NH+ moiety. The remaining two structures, **TS-R$_2$** and **TS-S$_2$**, both involving a $NH^+\cdots NC$ interaction, lye 6.1 and 6.4 kcal/mol higher in energy than **TS-R$_1$**, respectively. From these results, some tentative conclusions may be drafted: (i) in the studied catalytic reactions, the ketol moiety of the acceptor α'-hydroxy enone plays a key role in both decreasing reaction energy barrier; (ii) among the several possible H-bond combinations for the ternary nucleophile-catalyst-electrophile complex, type **A**[51a-e] is preferred, with the squaramide group interacting with the α'-hydroxy enone (electrophile activation), and the protonated quinuclidine interacting with the cyanoacetate anion (nucleophile activation); (iii) given previous data in the literature in favor of models of type **B**[51f-k] and **C**[51l] for related catalytic reactions, we believe that a unified model cannot accommodate well for all reactions falling within this type of non covalent bifunctional catalysis, and case to case analysis is required; (iv) calculations for our system confirms that H-bond with a nitrile group contributes poorly to TS stabilization as compared with H-bond to ester group, probably due to the fact that linear arrangements, as in $C\equiv N\cdots HX$, are more difficult to fit in the TS than angular arrangements, as in $C=O\cdots HX$.[56]

Eventually, the combination of these factors leads to the highly stereoselective formation of the new quaternary stereocenter in **20e**.

■CONCLUSIONS

In summary, the highly stereoselective generation of tetrasubstituted carbons, including *C–N*, *C–O*, *C–S* and all-carbon quaternary stereocenters, has been realized via bifunctional Brønsted base catalyzed Michael reaction of various types of hitherto challenging pro-stereogenic *C*-nucleophiles and α'–oxy enones as key enoate surrogates. Competitive and parallel experiments using simple enones (or esters) and the respective α'–oxy enones, indicate that the α–oxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity. The ability of α'–hydroxy enones to engage in H-bond networks as either donor or acceptor component (or both) was unknown in previous bidentate enoyl templates, and may in the future be exploited as new design element in other organocatalytic asymmetric transformations. An additional noteworthy aspect of this design is that the *gem*-dialkylcarbinol framework of the template can be easily modified at both the carbon and oxygen sites, thus enabling easy template tuning for optimal performance. The resulting α–oxy ketone adducts can smoothly be converted into the corresponding aldehyde, ketone or carboxylic acid derivatives through simple oxidative cleavage of the ketol unit. The present methodology thus provides access to synthetically relevant building-blocks bearing a fully substituted carbon atom which were hitherto difficult to prepare in enantioenriched form. Studies towards broadening this methodology are currently underway.

ASSOCIATED CONTENT

Supporting Information. Full experimental details and characterization of compounds including NMR spectra, HPLC chromatograms, and X-ray ORTEP, as well as Cartesian coordinates of all computed stationary points, relative and absolute activation energies for all reactions and complete reference 48 are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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[54] Extrapolation of this TS model to the case of the reaction between β-substituted enones **4** and cyanoacetates **19** would also correctly predict the (*S*,*S*) relative configuration of adducts obtained in Table 5. In contrast, the structure closest to **B** we could find predicts products of wrong relative stereochemistry upon a similar extrapolation.

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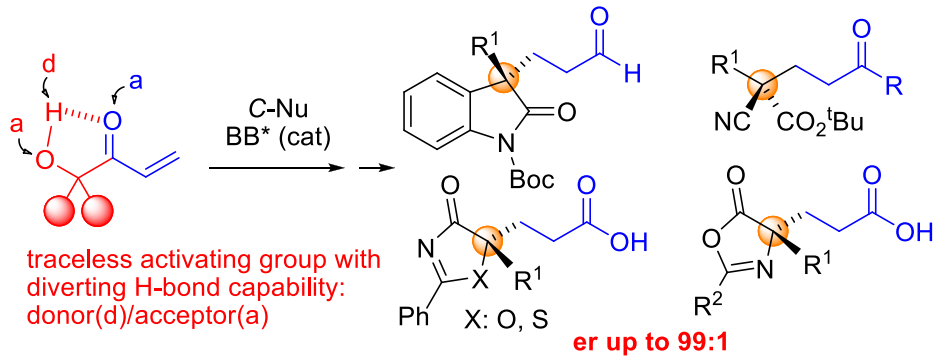

traceless activating group with diverting H-bond capability: donor(d)/acceptor(a)

er up to 99:1