α-Branched Ketone Dienolates: Base-Catalyzed Generation and Regio- and Enantioselective Addition Reactions.

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Abstract: In this study, the unique capacity of bifunctional Brønsted bases to generate α-branched ketone dienolates and control both site- and stereoselectivity of their addition reactions to representative classes of carbon electrophiles (i.e. vinyl sulfones, nitroolefins, formaldehyde) is documented. We demonstrate that using selected chiral tertiary amine/squaramide catalysts the reactions of β,γ–unsaturated cycloalkanones proceed through the dienolate Cα almost exclusively and provide all-carbon quaternary cyclic ketone adducts in good yields and very high enantioselectivities. Minor amount (<5%) of γ-addition is observed when nitroolefins are used as electrophiles. The parent acyclic ketone dienolates resulted less reactive under these conditions, constituting a yet challenging substrate category. Quantum calculations correctly predict these differences in reactivity and explain the observed site- and enantioselectivity

Introduction

Over the years the production of, and the reactions with, ketone enolates and their equivalents have been basic operations in organic chemistry.[1] One of the most significant advances in this field has been the development of catalytic methods to control their generation and reactions outcomes.[2] In this context, ketone dienolates and their equivalents pose some unique challenges: while of great synthetic value since they lead to adducts with a strategically positioned C=C double bond, dienolates may react through either the α or the γ nucleophilic carbon thus demanding stringent reaction control. To date, the overwhelming majority of catalytic methods involving dienolate or equivalent intermediates deal with α-unsubstituted ones, and proceed mainly through the γ carbon (vinylogous reactivity, Figure 1a).[3] These methods include catalyst-promoted addition reactions of preformed silyl dienol ethers (X: OSiR'$_3$)[4] as well as direct approaches based on metallic catalysis (X: O$^-$M$^+$),[5] dienamine activation (X: NR'$_2$),[6] and Brønsted acid[7] and base[8] catalysis activations. The γ-attack pathway seems kinetically favourable because it involves no disruption of the π-conjugation along the reaction coordinate.

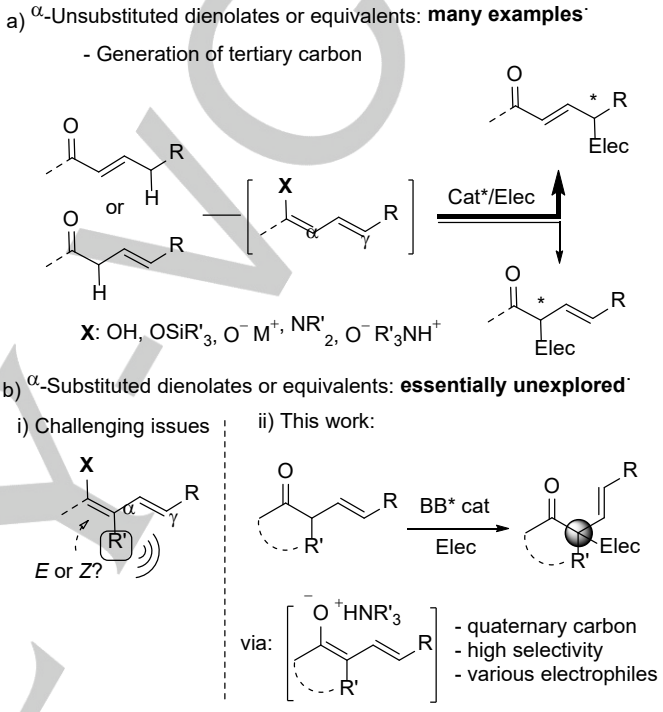

Figure 1. Divergent reaction pathways of dienolates or equivalents and the challenge to control reactions involving α-branched dienolates to obtain α-quaternary products.

Exceptions to this mainstream γ-selectivity involve concomitant isomerization of the C=C double bond to yield Morita-Baylis-Hilmann type adducts (no α-stereocenter is formed),[9] require restricted substrate categories[10] or substrates with strong steric bias,[11] or lead to moderate enantioselectivity.[12] In addition, none of these α-selective methods have been revealed useful for enantioselective generation of α-quaternary ketone (or related carbonyl) products[13], a process that would necessarily involve as intermediates α-substituted dienolates or equivalents (Figure 1b, i). Such a realization would not only require a stringent control over the *E*/*Z* enolate geometry and the face selectivity, but should also retain sufficient α-reactivity despite the steric congestion at Cα. This problem has recently been addressed by Toste via Brønsted acid catalysis[14] and as far as we know, no other solutions have been reported. Moreover, while Brønsted acid activation approach is well suited for α-aminations,[14a] apparently shows limitations with common carbon electrophiles such as conjugated olefins, with allenamides being a notable exception.[14b] Herein we report another solution to this problem by documenting the first carbon-carbon bond forming reactions

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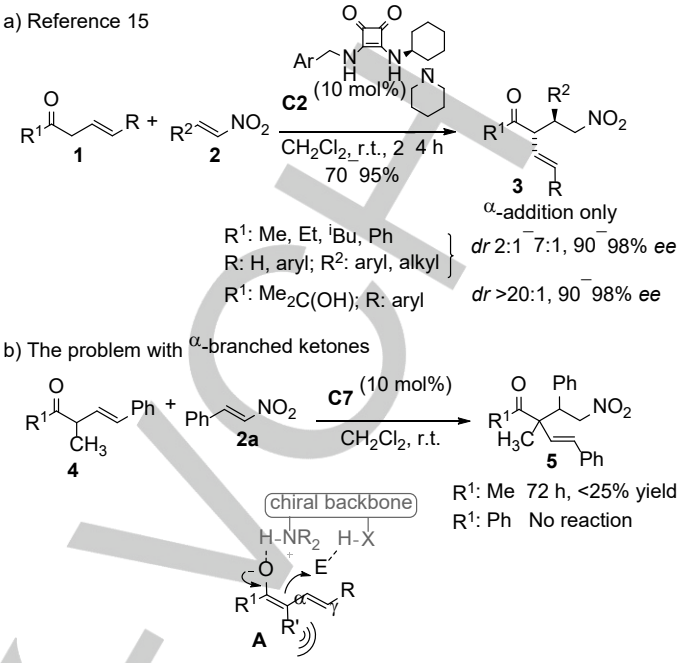
of α-substituted β,γ-unsaturated ketones assisted by Brønsted base/H-bonding catalysis. This mode of activation tolerates several carbon electrophiles, including conjugated olefins and formaldehyde and the reactions proceed with very high Cα-site selectivity giving access to all-carbon α-quaternary ketone products in high enantioselectivity (Figure 1b, ii).

Results and Discussion

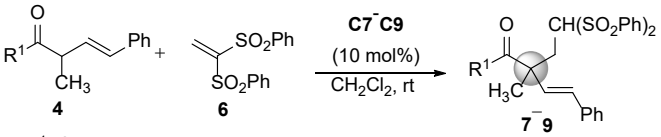
Quite recently, we have investigated the catalytic reactions of several in situ generated dienolate systems.[15] The finding was that chiral Brønsted base/H-bonding catalysts[16] are able to promote the smooth, enantioselective addition of β,γ-unsaturated ketones **1** to nitroolefins **2**, yielding the α-addition adducts **3** as exclusive products (Scheme 1a). It was noticed that increasing the size of R^1 in **1** the diastereoselectivity improved and the highest selectivity was attained when using bulky hydroxyenones (R^1: $Me_2C(OH)$) in the presence of Rawal's[17] catalyst **C2**. The observed reaction outcome is compatible with a model **A** (R'= H) in which the catalyst acts in a bifunctional manner, orienting both reactants correctly. While extrapolation of model **A** to α-branched ketone dienolates is conceivable (i.e. **A**, R'≠ H), two apparent problems to overcome in this model are the steric shielding at Cα and the enolate *E*/*Z* configurational uncertainty. With regard to the former aspect, complications may be foreseen during both the enolate generation and the subsequent approaching of the electrophilic reagent. In fact, with only two specific exceptions from this and another laboratory,[18] nearly all of the organocatalytic approaches for the asymmetric α-functionalization, including Michael additions, of α-branched ketones assisted by Brønsted bases are restricted to the use of *active* ketones bearing an adjacent electron withdrawing group (EWG= carbonyl, nitrile, sulfonyl or nitro).[13,19] Initial attempts to perform the reaction between nitrostyrene **2a** and α-branched ketones **4** using bifunctional catalyst **C7** confirmed the anticipated pitfalls, resulting in the recovery of unreacted enone (R^1: Ph) or very low conversions to product **5** (R^1: Me) as a mixture of α/γ isomers (Scheme 1b).

We reasoned that highly reactive and sterically less demanding Michael acceptors such as 1,1-bis(phenylsulfonyl)ethylene **6** might counterbalance the low reactivity of these ketones. Incidentally, the sulfonyl group in adducts would be susceptible to several ulterior transformations, including reductive removal.[20] To our delight, as the results in Scheme 2 show, α-branched ketones **4** reacted with **6** in the presence of **C7**[21], **C8**[22] or **C9**[23] (formulas in Table 1) to afford adducts **7–9** from reaction at the α-site exclusively, although in variable yields and enantioselectivity. For example, the reaction between methyl ketone **4a** and **6** in the presence of **C9** reached 81% conversion after 16 h at room temperature, and product **7** was obtained with 79% *ee*. Catalysts **C7** and **C8** were less efficient leading to **7** in yields of 39% and 38% and 63/61% *ee*, respectively. The reaction with the ethylketone **4b** also proceeded but at much more paucity giving product **8** with poor enantioselectivity, while the reaction of phenylketone **4c** to give **9** was sluggish.



Scheme 1. Impact of α-substitution on the reactivity of transiently formed acyclic ketone dienolates.

These results, whilst promising, highlighted the two main problems of catalytically generated trisubstituted carbon nucleophiles: their attenuated reactivity and the difficulties in controlling enantioface selectivity. Moreover, the significant variations on the reaction outcome when shifting from methyl to ethyl or phenyl ketone side-chain seem to indicate that slight structural changes on the substrate ketone might have huge impact on reactivity and selectivity. The above observations also corroborate the multivariable origin of the Cα/Cγ selectivity in reactions involving dienolate systems.[24]



a R^1: CH_3
b R^1: CH_3CH_2
c R^1: Ph

R^1:	CH_3 **7**	CH_3CH_2 **8**	**9**
with **C7**:	39% y (63% *ee*)		
with **C8**:	38% y (61% *ee*)	-- (--)	-- (--)
with **C9**:	72% y (79% *ee*)	29% y (58% *ee*)	14% conv.

Scheme 2. Impact of ketone side-chain R^1 on the reactivity of derived dienolates.

Hypothesis and working plan. To surmount the intrinsic difficulties mentioned above cyclic ketones were adopted in which the double bond is tethered at the Cα-position of the carbonyl function. The corresponding dienolates might fit better based on: (i) the higher nucleophilicity of cyclic systems as compared with the more flexible, open-chain counterparts;[25] (ii) a more rigidified transition state and, thus, more efficient chirality transfer; (iii) the problem of enolate geometry (*E*/*Z* uncertainty) gets cancelled. For an initial assessment of the reactivity associated with these nucleophilic systems, we determined the charge distribution and Fukui nucleophilicity index (f^-)[26] at the α carbon of linear (**I**) and cyclic (**II**) dienolates (Figure 2). Computed data[27] showed that the differences in negative charge at that specific carbon is negligible in the two enolates considered. Similarly, the Fukui indexes of these enolates showed to be essentially identical (–0.34 and –0.35, respectively). Accordingly, it appears that purely intrinsic electronic properties might not be informative in dictating these reactivity trends, and the role of the bifunctional catalyst as well as structural factors (steric hindrance, enolate rigidity) or α-CH acidity should also be considered. For a more comprehensive analysis, energies for the reaction of each enolate system with bis-sulfone **6** were computed in the presence of a model achiral squaramide-tertiary amine catalyst ($TS_{(I–II)}$). As data in Figure 2 show, the computed activation energy for the reaction of cyclic dienolate **II** (20.8 kcal/mol) is affordable at room temperature. In contrast, the activation barrier for the reaction involving acyclic species **I** is ca. 24.6 kcal/mol, which correlate with a much more sluggish reactivity, in good agreement with our preliminary experimental studies. Calculated data for this model reaction involving **II** also support the preference of the α-addition pathway vs. the γ-addition pathway, the latter showing a barrier about 6 kcal/mol higher. The preference of the α- vs. the γ-addition pathway was also found for the catalysed reaction involving acyclic enolate **I** (24.6 vs. 27.4 kcal/mol). These data were revealing given the scarcity of mechanistic information dealing with latent dienolate systems.[28]

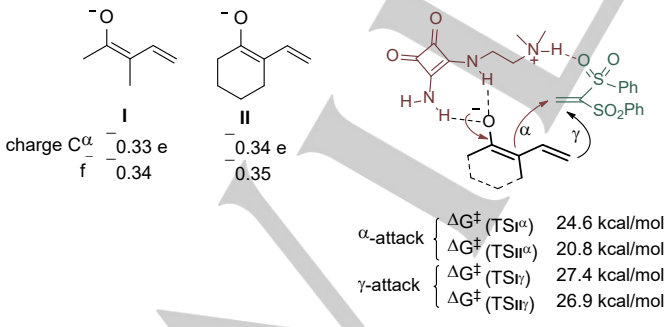
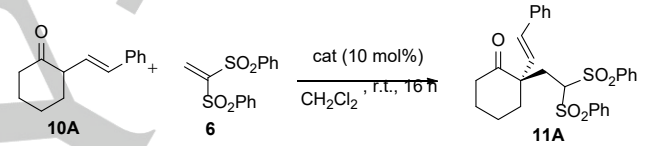


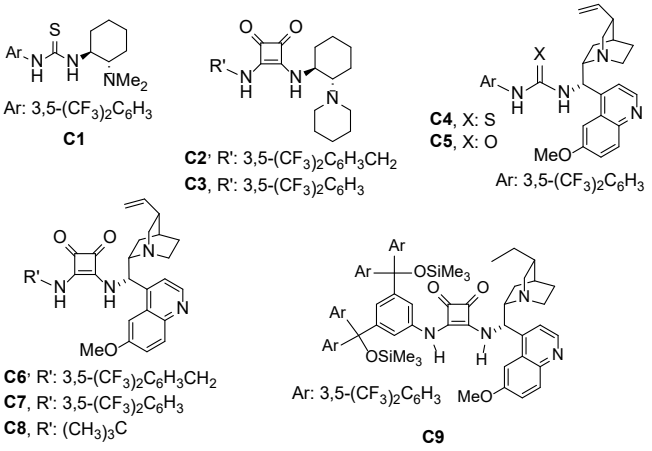
Figure 2. Reactivity parameters of two representative ketone dienolates.

Cyclic ketone dienolates: catalyst screening and substrate scope. Encouraged by these theoretical predictions, the reaction between α-styryl cyclohexanone **10A** and bis(phenylsulfonyl)ethylene **6** was studied in the presence of an assortment of chiral bifunctional catalysts. By using Takemoto's catalyst **C1**[29] in CH_2Cl_2 as solvent at room temperature, product **11A** was formed in a poor 26% isolated yield (Table 1, entry 1). Further screening showed that both the nature of the H-bond donor site and the structure of the tertiary amine in the catalyst were critical in terms of reactivity as well as stereoselectivity. Thus, the reaction did not proceed at all with Rawal's[17] squaramides **C2** and **C3** (entries 2 and 3), whilst the quinine-derived thiourea **C4**[30] and urea **C5**[30] were more active, though enantioselectivity was poor (entries 4 and 5). Using squaramide **C6**, which was effective for the reaction of α-unsubstituted dienolates with nitroolefins,[15] reactions proceeded, but with a modest 60% *ee* (entry 6). With catalyst **C7**[21] same level of reactivity and a promising stereoselectivity

Table 1. Catalyst screening for the reaction of cyclohexanone **10A** with vinyl sulfone **6** to give **11A**.



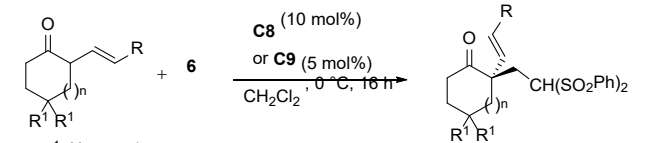
Entry	Catalyst	Yield (%)[b]	*ee* (%)[c]
1	**C1**	26	--
2	**C2**	NR	--
3	**C3**	NR	--
4	**C4**	72	10
5	**C5**	79	40
6	**C6**	83	60
7	**C7**	88	73
8	**C8**	87	98
9[d]	**C9**	89	98



[a] Reactions carried out at 0.15 mmol scale, using 2 equiv. of vinyl disulfone and 10 mol% catalyst in 0.3 mL CH_2Cl_2 at room temperature. No product from γ-addition was detected by ^{1}H NMR (Cα/Cγ >95:5). [b] Yield after chromatography. [c] *ee* determined by chiral HPLC. [d] Reaction run at 0 °C.

was observed (entry 7). To our delight with squaramide **C8**, a sterically congested catalyst developed by Connon,[22] the reaction between **10A** and **6** to afford **11A** proceeded in good isolated yield and, most significantly, in 98% *ee* (entry 8). A similar result was obtained (entry 9) with catalyst **C9**. With both **C8** and **C9** selected as the best catalysts, the scope of suitable alkenyl cycloalkanone substrates was explored . As Table 2 shows, 4-substituted cyclohexanones **12B** and **14A** provided the corresponding addition products **13B** and **15A** in good yield and high enantioselectivity. Most important, the method turned out to be equally effective with cycloalkanones of varying ring size. For instance, the **C9**-catalyzed reaction of α-branched cycloheptanones **16A** and **16D** afforded adducts **17A** and **17D** in yields of 86% and 79%, and selectivities of 96% *ee* and 93% *ee*, respectively. Likewise, reaction with branched cyclooctanone **18A** afforded product **19A** in high yield, although diminished (88% *ee*) enantioselectivity. In this latter case, shifting the solvent from CH_2Cl_2 to toluene caused the increase of enantioselectivity to 94% *ee*. Under these conditions **18B** led to **19B** in 88% yield and essentially single enantiomer. The method also tolerates alkenyl cyclopentanones like **20A** and **20E** which produced **21A** and **21E** with acceptable *ee*'s. Cyclohexanone **10F** was an exception, leading to the corresponding adduct **11F** in good yield, but limited 65% *ee*. Eventually, the enantioselectivity could be increased to 80% *ee* by carrying out the reaction at –20 °C. In general, similar results were obtained with both catalysts **C8**/**C9** albeit the latter led to better chemical yields for cycloalkanones bearing the *p*-methoxyphenylvinyl moiety(products **11B**, **13B** and **19B**).

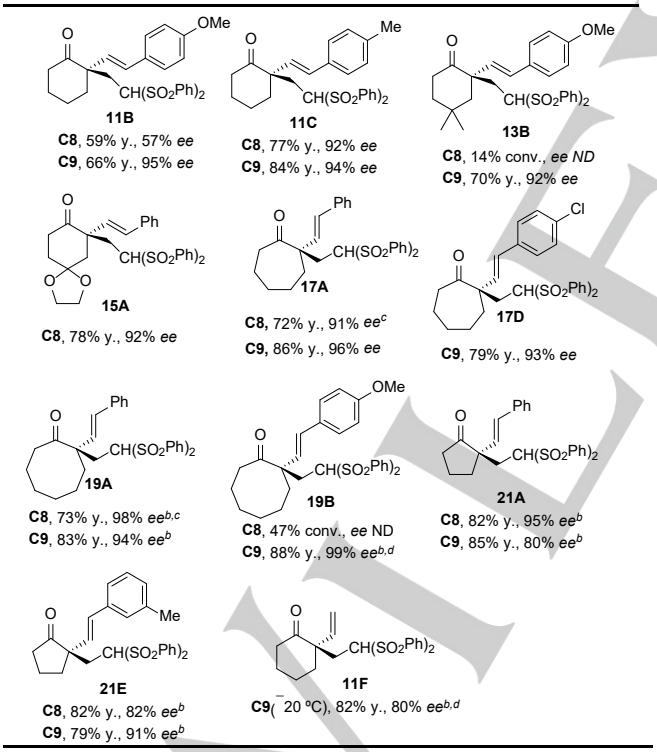
Table 2. Scope of the reaction of α-alkenyl cycloalkanones with **6** catalyzed by **C8**/**C9**.[a]



10 R^1: H n=1
12 R^1: Me n=1
14 R^1,R^1: $O(CH_2)_2O$ n=1
16 R^1: H n=2
18 R^1: H n=3
20 R^1: H n=0

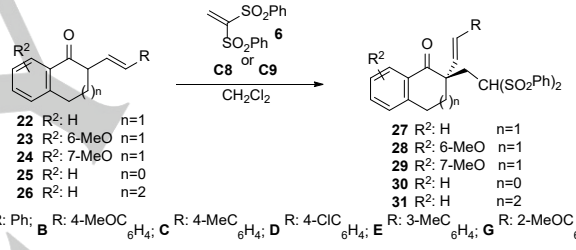
A R: Ph
B R: 4-$MeOC_6H_4$
C R: 4-MeC_6H_4
D R: 4-ClC_6H_4
E R: 3-MeC_6H_4
F R: H

11 R^1: H n=1
13 R^1: Me n=1
15 R^1,R^1: $O(CH_2)_2O$ n=1
17 R^1: H n=2
19 R^1: H n=3
21 R^1: H n=0



[a] Reactions carried out at 0.15 mmol scale, using 10 mol% catalyst **C8** or 5 mol% catalyst **C9** in 0.3 mL of CH_2Cl_2 unless otherwise stated. Yield of isolated product after chromatography. *Ee* determined by chiral HPLC. No product from γ-addition was detected by ^{1}H NMR (Cα/Cγ >95:5). [b] Reaction carried out in toluene at RT. [c] With 3 equivalents of **6** and 48 h reaction. [d] 10 mol% of catalyst loading. ND= not determined

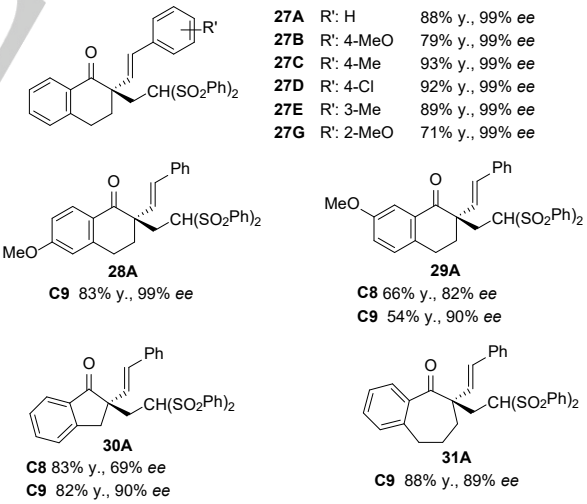
Table 3. Extension to benzofused cycloalkanones.[a]



22 R^2: H n=1
23 R^2: 6-MeO n=1
24 R^2: 7-MeO n=1
25 R^2: H n=0
26 R^2: H n=2

27 R^2: H n=1
28 R^2: 6-MeO n=1
29 R^2: 7-MeO n=1
30 R^2: H n=0
31 R^2: H n=2

A R: Ph; **B** R: 4-$MeOC_6H_4$; **C** R: 4-MeC_6H_4; **D** R: 4-ClC_6H_4; **E** R: 3-MeC_6H_4; **G** R: 2-$MeOC_6H_4$

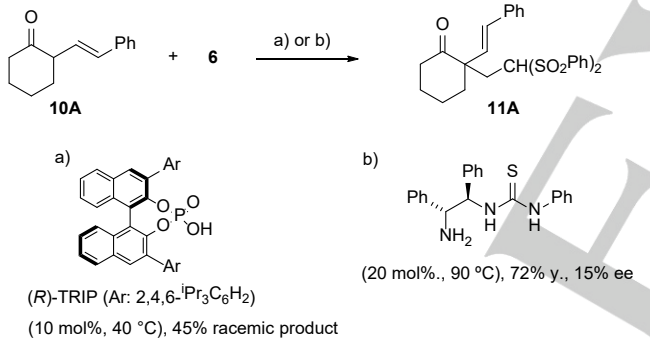


[a] Reactions carried out at 0.15 mmol scale, using 10 mol% catalyst **C8** or 5 mol% catalyst **C9** in 0.3 mL of CH_2Cl_2 unless otherwise stated. Yield of isolated product after chromatography. *Ee* determined by chiral HPLC. No product from γ-addition was detected by ^{1}H NMR (Cα/Cγ >95:5).

Benzo-fused cycloalkanones **22**–**26** were also excellent substrates for this catalytic reaction, affording the α-quaternary cycloalkanones **27**–**31**. As the results in Table 3 show, using catalyst **C9** adducts were obtained in good yields and

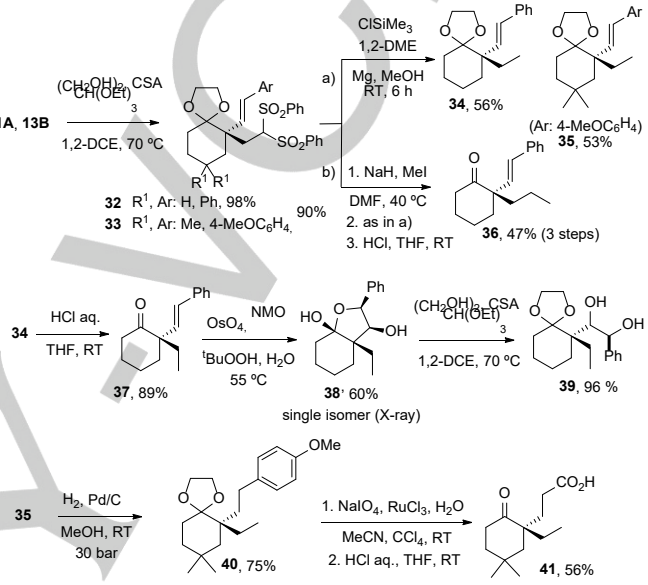
remarkably high enantioselectivity regardless the nature of the substituents at both the aromatic ring (R^2) and the olefin (R). Once again, the method demonstrated general with regard to the ketone ring size and equally tolerated 5, 6 or 7-membered cycloalkanones.

Control experiments showed that for the above reactions the alternative Brønsted acid[14,31] and enamine activation[32] approaches were clearly inferior. For example (Scheme 3), in the presence of 10 mol% (*R*)-TRIP in toluene at room temperature no reaction occurred between **10A** and **6**, while the same reaction at 40 °C proceeded to give product **11A** in 45% yield, but essentially racemic. Likewise, while the addition of unsubstituted ketones to vinyl bis(sulfone) **6** has been reported to proceed selectively via enamine intermediacy,[33] attempts to react **10A** with **6** in the presence of chiral primary amines at room temperature were unfruitful. At 90 °C product **11A** was formed (72% yield) albeit in very low (15% *ee*) selectivity, indicating that the amine catalyst is probably acting as a base rather than via enamine formation. This latter observation suggests that the enamine pathway is marginal with sterically congested ketones such as **10A** in line with previous observations by Carter[32a,b] and Kotsuki[32c] who have shown that amine catalysis is still unpractical for branched ketones with α-substituents larger than methyl or ethyl



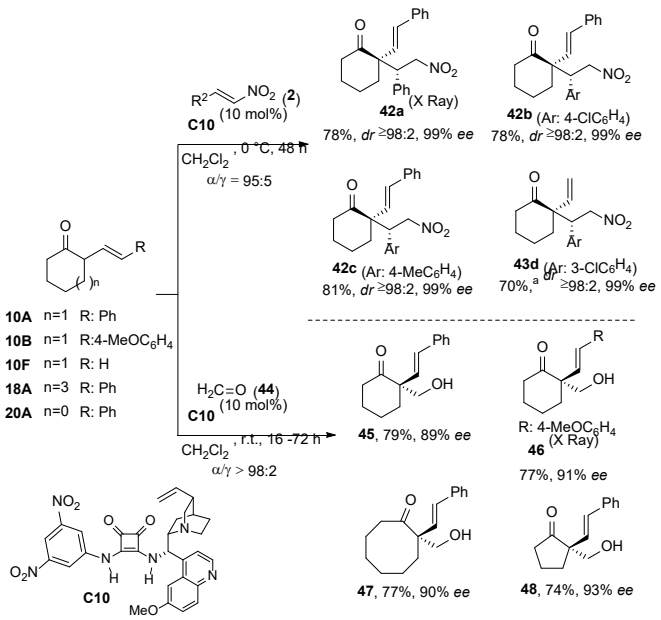
Scheme 3. Control experiments involving Brønsted acid and enamine based activation approaches for this reaction.

Elaboration of adducts. Transformations in Scheme 4 illustrate the versatility of the adducts as both groups, the alkene and the sulfone, are amenable for chemical elaboration. For instance, protection of the carbonyl as ketal and posterior reductive cleavage of the bis(sulfonyl) group proved feasible. Thus, ketalization of **11A** and subsequent treatment of the resulting **32** with TMSCl/1,2-dimethoxyethane and Mg metal[34] afforded the α-ethyl product **34** in good overall yield. A similar reaction sequence applied to adduct **13B** gave rise to product **35** satisfactorily. This sequence, if complemented with an intermediate bis(sulfone) α–alkylation step, (e.g., methylation of **32**) allows access to superior α–alkyl systems (e.g., α–propyl ketone **36**). On the other hand, product **34** could be converted into diol **39** in a completely stereoselective manner. The transformation required some carbonyl deprotection/reprotection tactics, and eventually allowed to get a crystal structure of intermediate **38** which served to determine the configuration of adducts.[35] Hydrogenation of **35** to give the α,α-dialkyl product **40** shows another possibility. In this case, further Sharpless oxidative scission of the *p*-methoxyphenyl moiety[36] afforded the quaternary ω-keto acid **41** in good overall yield. These are a few illustrative examples that demonstrate the potential of this approach to access functionalized cycloalkanones with an all-carbon quaternary Cα-stereocenter.

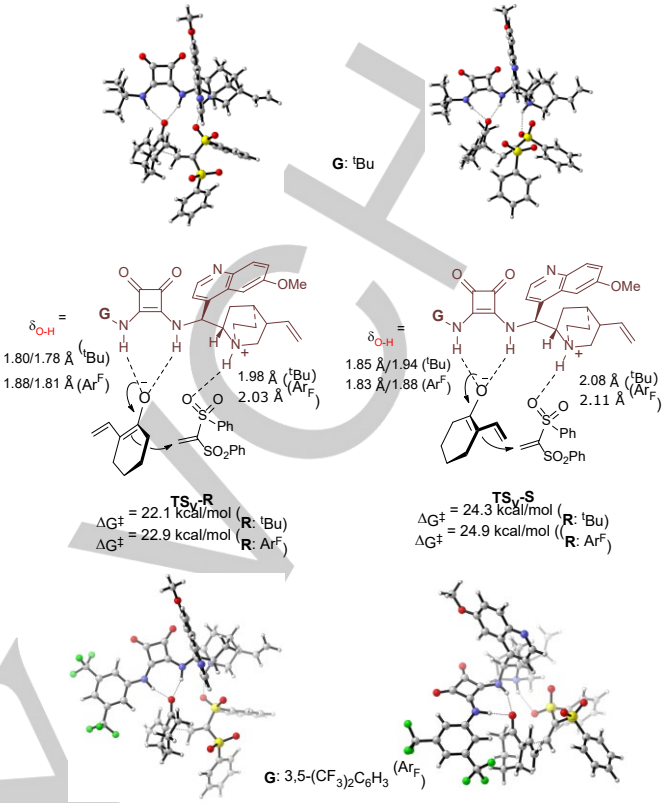


Scheme 4. Chemical elaboration of the bis(sulfonyl) adducts.

Extension to other carbon electrophiles. Given the observations noted above, the suitability of carbon electrophiles other than the vinyl bis(sulfone) **6** was next explored. Initial attempts with some β-substituted Michael acceptors like *β*-phenyl vinylsulfones and chalcones proved unsuccessful. However, it was delighting to observe that β-substituted nitroolefins were competent reaction partners.[37] For instance, the reaction of 2-styryl cyclohexanone with nitroolefin **2a** in CH_2Cl_2 at room temperature catalyzed by **C6** afforded a mixture of the α- and γ-addition adducts in 75:25 ratio, essentially perfect diastereoselectivity and high enantioselectivity for each isomer. Further screening of catalysts revealed **C10**[38] superior, giving rise a 85:15 α/γ selectivity ratio and high dr and *ee*.[39] Finally, as Scheme 5 illustrates, further improvement was achieved by carrying out the reaction at 0 °C and product **42a**[35] was obtained in 78% isolated yield and with essentially perfect diastereo- and enantiocontrol (dr>98:2, 99% *ee*). These results contrast with the poor behaviour of the parent open chain α–branched allyl ketones, vide supra, which under same conditions resulted to be unreactive. Brief exploration of the reaction scope with nitroolefins (Scheme 5 top) demonstrated similar efficiency for related systems. Thus, good yields, α/γ ratio of about 95:5 and excellent enantioselectivity for the major isomer were achieved regardless the electron-donor (4-MeC_6H_4)



Scheme 5. Catalytic additions to nitroolefins and formaldehyde. [a]Reaction run for 72 h.



Scheme 6. TS structures and selected parameters for the model reaction between α-branched dienolate **II** and bis(phenylsulfonyl)ethene.

or electron-acceptor (4-ClC_6H_4, 3-ClC_6H_4) character of the aryl groups. Once again, control experiments with **10A** and **2a** under Brønsted acid catalysis and amine catalysis, respectively, to obtain adduct **42a** failed or led to no selectivity,[39] reinforcing the unique capacity of the Brønsted base/H-bonding activation strategy. The utility of this catalytic activation could be extended to the α-hydroxymethylation reaction[40] as well. In these instances the reactions of various cycloalkanones with paraformaldehyde **44** using catalyst **C10** were perfectly site-selective and adducts **45**–**48** were formed in *ee*'s in the range 89–93% irrespective of the cycloalkanone ring size (Scheme 5 bottom).[41] In prospect, these results suggest that application of this Brønsted base/H-bonding strategy might be suitable to additional carbon electrophiles considerably broadening the pool of α,α-disubstituted cycloalkanones available until now.

Origin of stereoselectivity and plausible H-bond network. In order to shed light on the most favorable arrangement of the substrates and the catalyst during the transition state, we undertook DFT calculations for the model reaction between the vinyl cyclohexanone enolate **II**, vinyl bis-sulfone **6** and either catalyst **C7** (R=Ar^F: 3,5-$(CF_3)_2C_6H_3$) or **C8** (R: ^{t}Bu).[27] As could be anticipated for this type of bifunctional Brønsted base/H-bonding catalysis, the located TS structures each showed well defined H-bond networks that strongly bias the spatial arrangement of reactants, determining the stereochemical outcome of the reaction. Calculations at the M06/def2tzvpp (IEFPCM, solvent = dichloromethane)//B3LYP/6-31g(d,p) level of theory for the reaction above identified two Papai-type[42] TS exclusively, namely **TS-R**, leading to the *R*-configured product, and **TS-S**, leading to the *S* enantiomer, for each catalyst (Scheme 6). In spite of serious efforts, the alternative Takemoto-type activation mode,[29] with the sulfone oxygens hydrogen-bonded to the squaramide NH groups, could not be found, probably due to the low H-bond acceptor character and high steric hindrance of the sulfone group. In agreement with the experimental observations, transition state **TS-R** presents the lowest activation energy (22.1 kcal/mol for catalyst **C7**) in comparison to 24.3 kcal/mol predicted for **TS-S** (slightly higher values of 22.9 and 24.9 kcal/mol, respectively, for catalyst **C8**). The strongest H-bonds (shortest XH···Y bond) were measured for the interaction between oxyanion **II** and the two squaramide NH moieties (1.80 and 1.78 Å for catalyst **C7**) in **TS-R**, in comparison to the values found for **TS-S** (1.85 and 1.83 Å). Similarly, the weak interaction between one oxygen of the bis-sulfone group and the protonated amine group in **C7** is less notorious in **TS-S** *vs* **TS-R** (2.08 and 1.98 Å bond distances, respectively). This same trend in H-bonds strength was calculated for TS involving catalyst **C8**, although the slightly longer δ(O…H) values between dienolate oxygen and squaramide NH groups (1.88/1.81 Å vs. 1.80/1.76 Å) in this latter case appear to indicate a worse accommodation of the large ^{t}Bu group. Summarizing, it seems that an optimally congested microenvironment is formed around protonated catalyst **C7** for best fitting of both reactants through an efficient H-bond network.

Conclusions

In summary, we have reported that bifunctional Brønsted base/H-bonding catalysis activation is able to generate dienolates from α-branched allylic ketones and induce their reaction with various carbon electrophiles to occur at Cα mainly or exclusively. Under these catalytic conditions the reaction of α-branched cyclic ketone dienolates with vinyl bis(sulfone) afforded the corresponding all-carbon quaternary α-addition adducts with very high enantioselectivities. The parent acyclic dienolate systems are comparatively less reactive, but still the reactions may proceed with paucity for α'-methyl ketones (not so for the α'-ethyl and α'-phenyl ketones). Quantum calculations with model α-substituted ketone dienolates predict correctly the observed preference of α vs. γ-reactivity as well as the sense of enantioinduction based on a Pápai-type activation geometry. Importantly, the approach may be extended to additional carbon electrophiles, such as nitroolefins and formaldehyde, thus offering a robust platform for further development.

Experimental Section

Reaction of cyclic ketones 10–20 and 22–26 with 1,1-bis(phenylsulfonyl)ethylene 6. General Procedure: Catalyst **C8** (10 mol%) or **C9** (5 mol%) was added to a solution of the corresponding cyclic α-alkenyl ketone (0.15 mmol) and 1,1-bis(phenylsulfonyl)ethylene (69 mg, 0.23 mmol) in CH_2Cl_2 at 0 °C (ketones **10**–**20**) or room temperature (ketones **22**–**26**). The resulting solution was stirred until the reaction was completed (typically 16 h) as monitored by TLC (hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography, affording the corresponding adducts as essentially pure compounds.

Compound 11A: Obtained from ketone **10A** (30 mg, 0.15 mmol) using catalyst **C9**. Yield: 68 mg, 89%. White solid. m.p. 92 °C. $[\alpha]_D^{25}$= –95.8° (*c*= 1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–7.85 (m, 2H), 7.71–7.61 (m, 3H), 7.57–7.45 (m, 3H), 7.45–7.25 (m, 7H), 6.42 (d, *J* = 16.6 Hz, 1H), 6.12 (d, *J*= 16.6 Hz, 1H), 4.56 (t, *J*= 4.3 Hz, 1H), 3.18 (dd, *J*= 16.6, 4.0 Hz, 1H), 2.64–2.51 (m, 1H), 2.49–2.37 (m, 2H), 2.26 (dd, *J*= 16.6, 4.6 Hz, 1H), 2.06–1.69 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 138.3, 137.3, 136.1, 134.5, 134.1, 132.6, 130.3, 130.2, 129.5, 128.9, 128.8, 128.3, 126.6, 80.8, 54.4, 39.7, 36.1, 31.1, 27.0, 21.3. MS (ESI, m/z): $C_{28}H_{32}N_2O_5S_2$ [M+NH_4^+] calcd.: 526.6855, found: 526.1727.

Compound 13B: Obtained from ketone **12B** (39 mg, 0.15 mmol) using catalyst **C9** (12 mg, 0.0075 mmol). White solid. m.p. 107 °C. Yield: 70% (59 mg, 0.105 mmol). $[\alpha]_D^{25}$= +10.8° (*c*= 1.00, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.72 (m, 4H), 7.66–7.51 (m, 2H), 7.49–7.22 (m, 6H), 6.89 (d, *J*= 8.8 Hz, 2H), 6.13 (d, *J*= 16.7 Hz, 1H), 5.98 (d, *J*= 16.7 Hz, 1H), 4.89–4.80 (m, 1H), 3.83 (s, 3H), 2.98 (d, *J*= 20.0 Hz, 1H), 2.74–2.54 (m, 1H), 2.42–2.32 (m, 1H), 2.32–2.21 (m, 1H), 2.13 (d, *J*= 14.2 Hz, 1H), 1.75 (d, *J*= 14.2 Hz, 1H), 1.68 (dd, *J*= 9.1, 4.6 Hz, 2H), 1.16 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 159.6, 138.3, 134.1, 134.1, 130.8, 130.3, 129.7, 129.7, 129.1, 128.8, 128.8, 127.7, 114.2, 80.9, 55.3, 52.5, 51.0, 38.3, 36.3, 33.0, 32.1, 30.9, 27.3. MS (ESI, m/z): $C_{31}H_{35}O_6S_2$ [M+H^+]: calcd. 567.1875, found: 567.1882.

Compound 32. Ketone **11A** (125 mg, 0.25 mmol), ethylene glycol (60 µL, 1.0 mmol) and triethyl orthoformate (80 µL, 0.50 mmol) were dissolved in 1,2-DCE (0.6 mL) and camphorsulphonic acid (16 mg, 0.07 mmol) was added. The resulting solution was stirred at 70 °C overnight. Then the mixture was directly submitted to silica gel flash column chromatography (hexane/EtOAc 80:20) to give the title compound as a white solid. m.p. 67–69 °C. Yield: 135 mg, 98%. $[\alpha]_D^{25}$= –69.0° (*c*= 1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H), 7.72–7.65 (m, 1H), 7.60–7.52 (m, 4H), 7.50–7.44 (m, 3H), 7.42–7.34 (m, 2H), 7.29 (d, *J*= 7.2 Hz, 1H), 7.20–7.12 (m, 2H), 6.37 (d, *J*= 4.4 Hz, 3H), 4.43 (t, *J*= 4.0 Hz, 2H), 4.04–3.80 (m, 4H), 2.79 (dd, *J*= 16.2, 4.0 Hz, 1H), 2.34 (dd, *J*= 16.2, 4.0 Hz, 2H), 2.05 (d, *J*= 14.1 Hz, 2H), 1.82–1.43 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 137.6, 137.3, 134.7, 134.1, 132.3, 131.2, 130.8, 129.6, 129.0, 128.9, 128.9, 127.9, 126.8, 111.7, 81.4, 65.2, 65.1, 49.5, 32.5, 30.4, 27.9, 23.5, 21.0. MS (ESI, m/z): $C_{30}H_{36}N_2O_5S_2$ [M+NH_4^+]: calcd.: 570.7385, found: 570.1994.

Compound 34. Ketal **32** (138 mg, 0.25 mmol) was dissolved in MeOH (2 mL) and magnesium powder (61 mg, 2.5 mmol) was added. The resulting suspension was cooled to 0 °C and a drop of trimethylsilyl chloride and a drop of 1,2-dibromoethane were added. The resulting mixture was warmed to room temperature observing the formation of hydrogen, and the reaction was followed by TLC (hexane/EtOAc 80:20). After completion of the reaction (2 h) the mixture was filtered through a pad of Celite and washed with MeOH. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (10 mL). The organic solution was washed with water (2 × 10 mL), dried over $MgSO_4$, volatiles were removed under reduced pressure and the resulting crude compound was purified by silica gel flash column chromatography (hexane/EtOAc 95:5) to give the title compound as a colourless oil. Yield: 38 mg, 56%. $[\alpha]_D^{25}$= –16.2° (*c*= 0.80, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J*= 7.1 Hz, 2H), 7.30 (t, *J*= 7.4 Hz, 2H), 7.19 (t, *J*= 7.2 Hz, 1H), 6.34 (d, *J*= 16.7 Hz, 1H), 6.23 (d, *J*= 16.7 Hz, 1H), 4.03–3.82 (m, 4H), 1.94–1.82 (m, 1H), 1.74–1.51 (m, 8H), 1.51–1.38 (m, 1H), 0.74 (t, *J*= 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 134.4, 130.3, 129.1, 128.8, 127.4, 126.7, 126.1, 113.3, 65.9, 65.6, 49.0, 32.7, 29.8, 25.7, 24.2, 21.3, 8.4. MS (ESI, m/z) $C_{18}H_{25}O_2$ [M+H^+]: calcd.: 273.3955, found: 273.1722.

Compound 37. Ketal **34** (16 mg, 0.6 mmol) was dissolved in a mixture of THF (0.5 mL) and aqueous 6M HCl (0.5 mL) and the resulting mixture was stirred at room temperature overnight. THF was eliminated under reduced pressure and the remaining aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to give the title compound essentially pure (liquid). Yield: 12.2 mg, 89%. $[\alpha]_D^{25}$= –30.3° (*c*= 0.50, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (m, 4H), 7.26–7.22 (m, 1H), 6.30 (d, *J*= 3.9 Hz, 2H), 2.62–2.47 (m, 1H), 2.42–2.29 (m, 1H), 2.14–2.04 (m, 1H), 1.99–1.59 (m, 7H), 0.84 (t, *J*= 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 137.1, 133.2, 130.6, 128.6, 127.5, 126.1, 54.8, 39.6, 36.0, 30.3, 27.3, 21.6, 8.2.

Compound 38. Alkene **37** (62 mg, 0.25 mmol) and citric acid (72 mg, 0.75 mmol) were dissolved in a mixture of *tert*-butanol (36 mL) and water (1 mL). To the resulting solution *N*-methylmorpholine *N*-oxide (136 mg, 0.75 mmol) and osmium tetraoxide (2.5 wt % in tBuOH) (1.2 mL, 0.1 mmol) were added and the reaction mixture was stirred at 55 °C for 24 h. Part of the solvent was eliminated under reduced pressure and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and volatiles were removed under reduced pressure and the residue was purified by silica gel flash column chromatography (hexane/EtOAc 85:15) to give the title compound as an oil. Yield: 38 mg, 60%. $[\alpha]_D^{25}$= –18.1° (*c*= 1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.34 (m, 4H), 7.34–7.24 (m, 1H), 5.49 (d, *J*= 4.2 Hz, 1H), 3.99 (d, *J*= 2.5 Hz, 2H), 2.12–1.78 (m, 3H), 1.70 (d, *J*= 4.0 Hz, 1H), 1.66–1.17 (m, 8H), 0.96 (t, *J*= 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 128.6, 127.7, 126.7, 107.7, 83.3, 79.1, 51.9, 31.9, 27.2, 22.5, 20.6, 18.8, 8.9. MS (ESI, m/z) $C_{16}H_{21}O_2$ [M–OH^-]: calcd.: 245.1536, found: 245.1551.

Compound 39. Product **39** was obtained as a white spume following the same acetalization procedure described above starting from hemiketal **38** (25 mg, 0.10 mmol). Yield: 29 mg, 96%. $[\alpha]_D^{25}$= +20.1° (*c*= 0.50, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.19 (m, 5H), 5.54 (d, *J*= 4.7 Hz, 1H), 4.04–3.87 (m, 2H), 3.73–3.61 (m, 3H), 2.80 (d, *J*= 10.7 Hz, 1H), 2.35–2.21 (m, 1H), 2.08–1.95 (m, 1H), 1.89 (d, *J*= 13.3 Hz, 2H), 1.74–1.67 (m, 1H), 1.62–1.50 (m, 2H), 1.49–1.36 (m, 3H), 1.32–1.20 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 128.0, 126.9, 126.4, 83.6, 79.0, 62.1, 61.7, 52.7, 28.7, 27.9, 22.7, 20.6, 18.8, 8.7. MS (ESI, m/z) $C_{18}H_{27}O_5$ [M+H$^+$]: calcd.: 307.1904, found: 307.1917.

Reaction of 10A with nitrostyrene 2a to give 42a: Catalyst **C10** (9 mg, 0.015 mmol) was added to a solution of ketone **10A** (30 mg, 0.15 mmol) and nitroolefin **3a** (45 mg, 0.30 mmol) in CH_2Cl_2 at 0 °C. The resulting solution was stirred until the reaction was completed as monitored by TLC (48 h). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 95:5) to afford the title compound. Colourless oil. Yield: 41 mg, 78%. $[\alpha]_D^{25}$= –123.4° (*c*= 1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.25 (m, 8H), 7.18 (dd, *J*= 7.4, 2.0 Hz, 2H), 6.18 (d, *J*= 4.0 Hz, 2H), 5.23 (dd, *J*= 13.0, 3.8 Hz, 1H), 4.64 (dd, *J*= 12.9, 11.4 Hz, 1H), 4.03 (dd, *J*= 11.3, 3.8 Hz, 1H), 2.88–2.73 (m, 1H), 2.45–2.21 (m, 2H), 2.08–1.91 (m, 1H), 1.76–1.57 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 136.4, 135.8, 134.7, 129.5, 129.2, 128.9, 128.6, 128.4, 127.8, 126.3, 77.8, 56.5, 49.1, 39.7, 38.9, 28.1, 21.6. MS (ESI, m/z) $C_{22}H_{24}NO_3$ [M+H$^+$]: calcd.: 350.1756, found: 350.1761.

Reaction of 10A with formaldehyde to give 45: Catalyst **C10** (9 mg, 0.015 mmol) was added to a solution of ketone **10A** (20 mg, 0.10 mmol) and paraformaldehyde (30 mg, 1 mmol) in CH_2Cl_2 at room temperature. The resulting solution was stirred until the reaction was completed as monitored by TLC (16 h). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 90:10), affording the titled compound essentially pure. White foam. Yield: 18 mg, 79%. $[\alpha]_D^{25}$= +20.7° (*c*= 0.50, 89% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 6.36 (d, *J*= 16.6 Hz, 1H), 6.14 (d, *J*= 16.6 Hz, 1H), 3.83 (d, *J*= 11.4 Hz, 1H), 3.44 (d, *J*= 11.5 Hz, 1H), 2.64 (td, *J*= 13.8, 6.0 Hz, 1H), 2.49 (bs, 1H), 2.38–2.28 (m, 1H), 2.04 (m, 3H), 1.84 (m, 2H), 1.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 136.4, 133.2, 129.8, 128.6, 128.0, 126.3, 67.9, 57.3, 40.0, 34.6, 27.5, 21.5. MS (ESI, m/z) $C_{15}H_{19}O_2$ [M+H$^+$]: calcd.: 231.1385, found: 231.1389.

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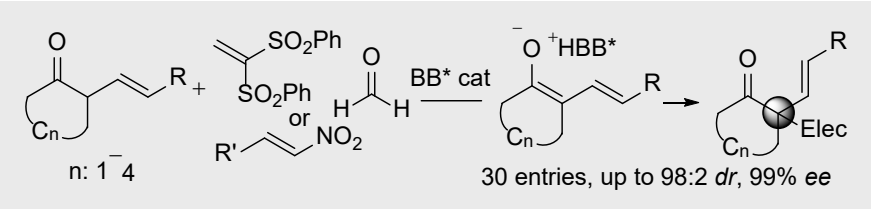

Getting quaternary: It is found that under bifunctional Brønsted base/H-bond catalysis α-substituted ketone dienolates, especially the cyclic ones, may be generated and smoothly reacted with representative carbon acceptors (vinyl sulfones, nitroolefins, formaldehyde) through the Cα (>95:5 ratio of regioisomers), leading to all-carbon quaternary stereogenic centers in good yields and very high enantioselectivity.

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