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FULL PAPER

syn-Selective Michael Reaction of α-Branched Aryl Acetaldehydes with Nitroolefins Promoted by Squaric Amino Acid Derived Bifunctional Brønsted Bases

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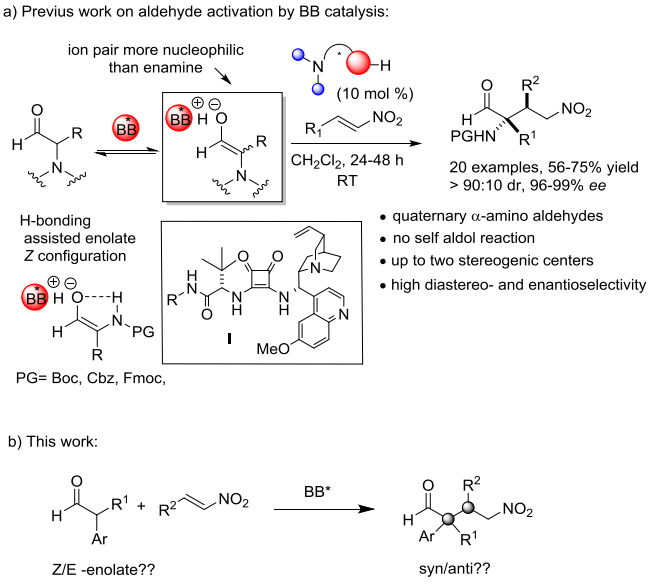
Abstract: Here we describe the direct access to 2,2,3-trisubstituted *syn* γ-nitroaldehydes from the addition reaction of α-branched aryl acetaldehydes to nitroolefins promoted by a cinchona based squaric acid-derived amino acid peptide. The reaction is quite general for different α-methyl arylacetaldehydes and β–aromatic and β-alkyl nitroolefins affording the Michael adducts in high enantioselectivity and *syn*-selectivity. NMR experiments and DFT calulations predict the reaction to occur through the *E*-enolate. The interactions between the substrates and the catalyst follow Pápai's model, wherein an intramolecular H-bonding interaction in the catalyst between the NH group of one of the *tert*-leucines and the squaramide oxygen seems to be key for discrimination of the corresponding reaction transition states.

Introduction

Organocatalysis has experienced a significant growth over the last years and today a broad range of efficient asymmetric transformations for different substrates is available.[1] In this context an extensive number of chiral bifunctional Brønsted base (BB) mediated reactions has been reported, most of them triggered by bifunctional tertiary amines.[2] Despite this progress, the use of these tertiary amine catalysts has been mainly limited to relatively acidic substrates (pka < 17)[3] and their application with aldehydes as pronucleophiles has been hardly investigated.[4] The inherent high reactivity of the carbon atom in that oxidation state which difficults effective control of side reactions,[5] may account for this lack of studies, a complication that has to be added to the usual problems associated with aldehyde activation and reaction enantiocontrol. Aminocatalysis[6] has shown to be an excellent option to solve these problems and, at present, a broad range of efficient reactions to access α-functionalized aldehydes in high stereoselectivity is available. In particular, the addition reaction of aldehydes to nitroolefins provides an expedient route to γ-nitro aldehydes, important intermediates in synthesis.[7] However, the application of this reaction to α-branched aldehydes has shown problematic, mainly because of the difficulty for the condensation of the amine catalyst with the α-branched aldehyde due to steric hindrance, the relatively lower reactivity of the resulting α,α-disubstituted enamine and the difficulty in controlling the E/Z enamine selectivity.[8] The first use of α-branched aldehydes for this reaction was reported by Barbas III in 2004.[9] Following this work, several amine catalysts have also been investigated[10] and, albeit with few exceptions,[10a,e] most provide the adducts in modest selectivity (poor *dr* and/or poor *ee*). In this context, the question of whether BB catalysis can work as a complementary alternative for the stereoselective α-functionalization of aldehydes is still open.

Recently we reported the first use of α-substituted α-amino aldehydes as pronucleohiles in a BB catalyzed Michael addition to nitroolefins[11-13] (Scheme 1, a). The reaction is promoted by the *tert*-leucine derived catalysts of type **I** and produces densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity.[11] Notably, no side reactions nor homoaldol products are observed under these conditions and an intramolecular H-bonding between the NH group and the carbonyl



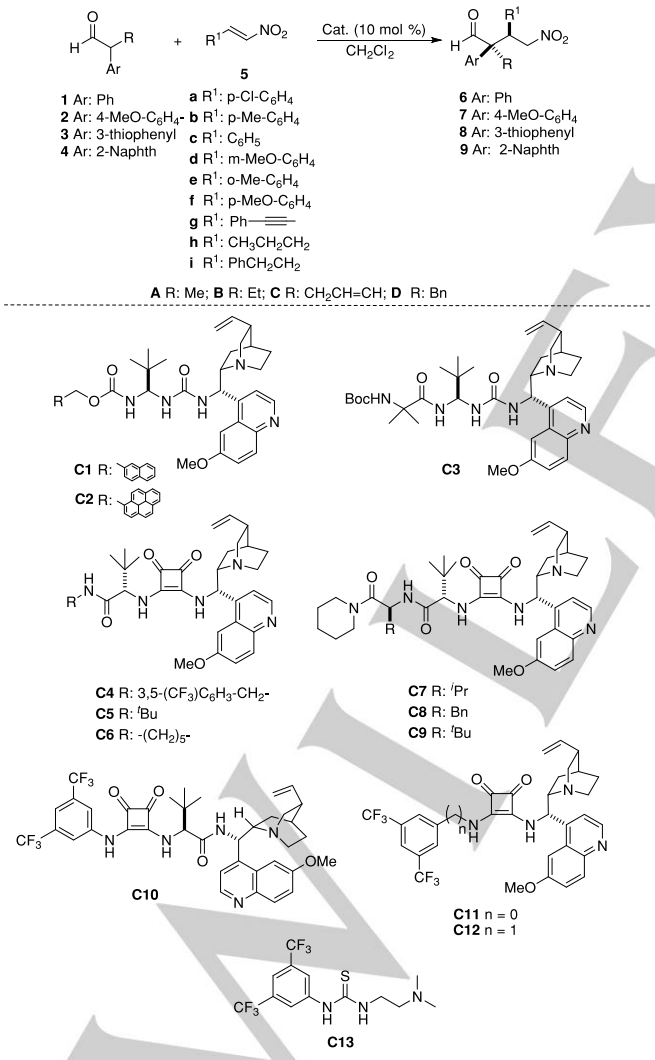
Scheme 1. Activation of α-branched aldehydes by BB catalysis. a) Previous work on α-branched α-amino aldehydes. b) This work by using α-branched aryl acetaldehydes.

oxygen atom in the starting α-amino aldehyde appears to be key for both reactivity and stereocontrol. We wondered whether this BB activation strategy might be extended to α-branched aldehydes lacking the above noted intramolecular H-bonding, such as α-branched aryl acetaldehydes (Scheme 1, b), particularly α-methyl aryl acetaldehydes, which might produce compounds of biological interest having quaternary carbon stereocenters.[14] In this instance, we expected that the BB catalyst might control both enolate configuration and face discrimination during reaction, thus enhancing the utility of the approach.

Results and discussion

Preliminary experimental observations and catalyst screening

Our initial studies were carried out on the reaction between (±)-2-phenylpropionaldehyde **1A** and nitroolefin **5a** (Scheme 2). First attempts using ureidopeptide derived bifunctional Brønsted bases previously developed by us[15] (**C1**, **C2** and **C3**) showed that the reaction indeed proceeded to afford γ-nitroaldehyde **6Aa** with



Scheme 2. Catalyst screened in the Michael addition of **(±)1A** to **5a**.

Table 1. Catalyst screening for the 1,4-addition of (±)-2-propionaldehyde **1A** to nitroolefin **5a** to afford **6Aa**.[a]

Entry	Cat.	t(h)	T(ºC)	Conv. (%)[b]	Yield (%)[c]	dr[d]	ee[e]
1	**C1**	29	rt	92	69	83:17	47
2	**C2**	13	rt	74	68	85:15	-2
3	**C3**	72	rt	88	90	81:19	24
4	**C4**	72	rt	>99	91	86:14	84
5	**C5**	35	rt	98	85	88:12	89
6	**C6**	30	rt	98	89	90:10	94
7	**C7**	15	rt	>99	87	86:14	85
8	**C8**	20	rt	>99	92	88:12	93
9	**C9**	10	rt	98	82	91:9	88
10		15	0	85	84	95:5	94
11	**C10**	15	rt	88	78	92:8	74
12	**C11**	23	rt	93	74	84:16	96
13	**C12**	40	0	98	71	86:14	96

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). [b] Determined by the disappearance of the starting aldehyde. [c] Yield of the isolated two isomers. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

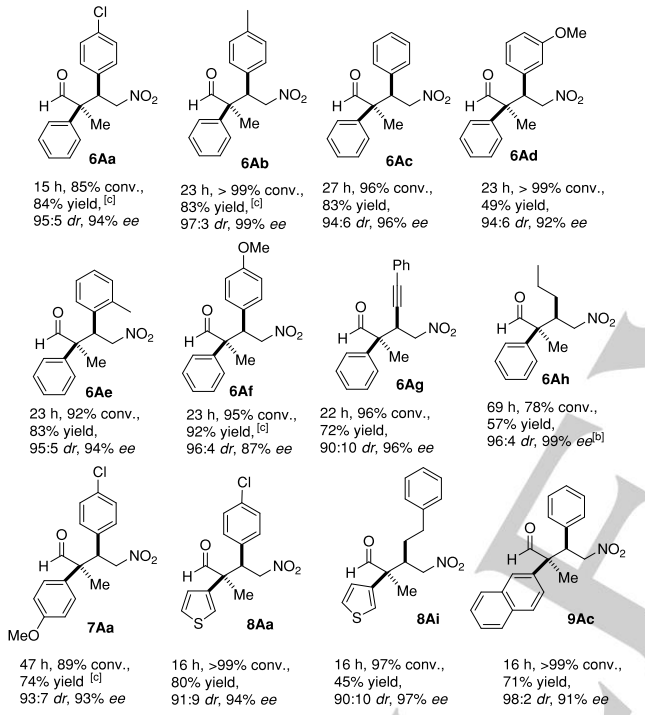
moderate *syn* diastereoselectivity,[16] but the enantioselectivity was essentially negligible (Table 1, entries 1-3). The reaction catalyzed by the *tert*-leucine derived squaric acid **C4**, which provided the best results for α-branched α-amino aldehydes,[11] afforded the Michael adduct in better enantioselectivity and quite good *syn* selectivity (84% *ee*, 86:14 *dr*, entry 4), but improvement was still needed. Variations at the amide terminus in catalyst **C4** led to **C5** and **C6** and the reaction in the presence of these catalysts (entries 5 and 6) showed significant stereoselectivity improvement. Whilst the *tert*-butylamine derived catalyst **C5** provided **6Aa** in better enantio- and diastereoselectivity, catalyst **C6** led to excellent enantioselectivity and quite good diastereoselectivity. At this point and, with the aim to further improve reaction diastereoselectivity, we considered the incorporation of a second amino acid unit in catalyst **C6**. Accordingly, catalysts **C7**, **C8** and **C9**,[17,18] were synthesized and tested. Whereas **C7** provided adduct **6Aa** in lower diastereo- and enantioselectivity than **C6**, catalyst **C8** produced **6Aa** in similar diastereo- and enantioselectivity. In the presence of **C9**, which incorporates two *tert*-leucine units, product **6Aa** was obtained in higher *syn* selectivity, although slightly lower enantioselectivity. Lowering the temperature to 0 ºC, the reaction using this catalyst led to product **6Aa** with better diastereo- and enantioselectivity in reasonable time (entry 10). The position of the amino acid unit in these catalysts seems also to be significant as the reaction in the presence of **C10**, which incorporates the *tert*-leucine unit at other position, provided adduct **6Aa** in lower enantioselectivity.[19] Further proof of the robustness of this subclass of catalysts was provided from the reaction of **1A** with **5a** using the commercially

available standard squaramides **C11** and **C12** which led to **6Aa** in good enantioselectivity but in both cases with lower levels of diastereoselectivity.[20] Therefore, the scope of the reaction was studied with the dipeptide derived catalyst **C9**.

Reaction scope

As the results in Table 2 show, the above conditions were equally efficient for the Michael addition of (±)-2-phenylpropionaldehyde **1A** to different nitroolefins (**5b-i**). The reaction tolerates well nitrostyrenes carrying both electron-withdrawing and electron-donating substituents at the aromatic ring of the nitroolefin independently of the substituent position. In every case the corresponding adducts **6Aa**-**6Ah** were obtained in excellent enantioselectivity and very good *syn*-diastereoselectivity.

Table 2. Scope of the Michael reaction of α-methyl aryl/heteroaryl acetaldehydes **1**-**4** with nitroolefins **5a**-**i** assisted by **C9**.[a]



[a] Reactions conducted at 0 ºC on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major diastereoisomer. Diastereomeric ratio determined by ^1H NMR (300 MHz) analysis on the crude product. Enantioselectivity determined by chiral HPLC. [b] Reaction carried out at RT. [c] Yield of the isolated two isomers.

Significantly, the most recalcitrant β-aliphatic nitroolefins such as **5g** and **5h** also react under these conditions to provide the Michael adducts **6Ag** and **6Ah** with excellent enantio- and *syn*-diastereocontrol. Similarly, the reaction may be extended to other aryl and heteroaryl α-methyl acetaldehydes leading to Michael adducts such as **7Aa**, **8Aa**, **8Ai** and **9Ac** with excellent diastereo- and enantioselectivity. In general, the dipeptide derived catalyst **C9,** which bears several H-bond donors,[21] is somewhat better than **C4-C6** catalysts not only regarding reaction stereoselectivity,[22] but also with respect to the reaction conversion. For instance, the reaction between **1A** and **5a** at RT in the presence of **C6** and **C9**, Figure 1, shows that with the former catalyst the reaction progresses relatively slower than with the dipeptide derived catalyst **C9**.

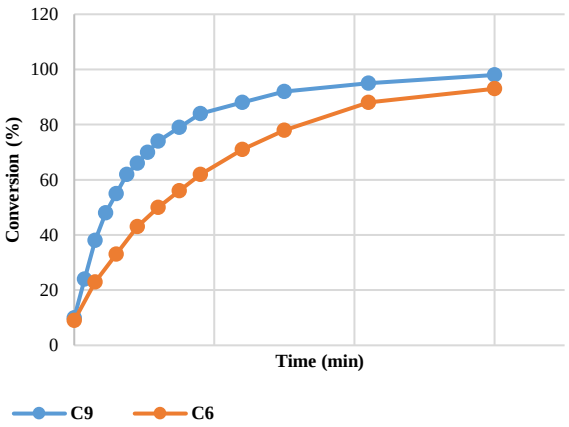
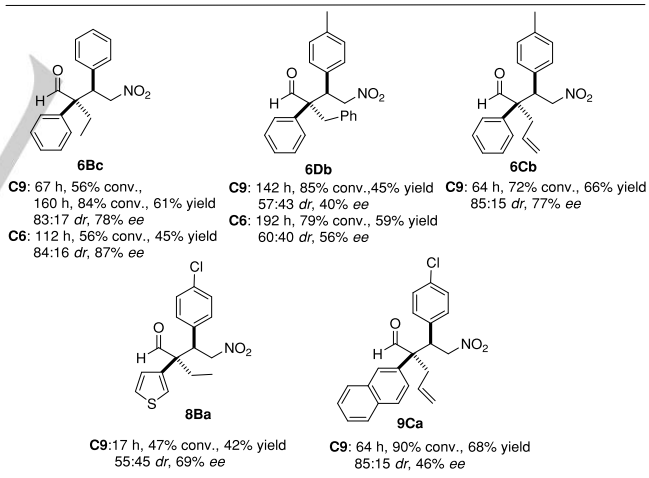


Figure 1. Conversion evolution of the reaction between **(+) 1A** and nitroolefin **5a** in the presence of **C6** and **C9** catalysts at RT.

The above difference between both catalysts was also observed in the reaction of the ethyl and benzyl derivatives **1B** and **1D** with nitroolefins **5c** and **5b** respectively (Table 3). In the presence of **C9**, the Michael adduct **6Bc** was produced after 67 h at 0ºC in 56% conversion, while catalyst **C6** necessitates 112 h to reach the same conversion. Likewise, adduct **6Db** was formed in 85% conversion after 142 h of reaction when **C9** was used, but in the presence of **C6** the reaction progresses more slowly.

Table 3. Scope of the Michael reaction of α-branched aryl/heteroaryl acetaldehydes **1**-**4** with nitroolefins **5a**-**c** assisted by **C9**/**C6**.[a]



On the other hand, as shown in Table 3, under the usual conditions and in the presence of **C9** catalyst a decrease in both reactivity and stereoselectivity was observed when changing from α-metyl aryl acetaldehydes to other α-susbtituted derivatives. With α-ethyl and α-allyl phenyl acetaldehydes **1B** and **1C** adducts **6Bc** and **6Cb** were obtained in quite good diastereo- and enantioselectivity (83:17 *dr* and 78% *ee* for **6Bc** and 85:15 *dr* and 77% *ee* for **6Cb**). However, In the case of the α-benzyl acetaldehyde **1D** poor diastereomeric ratio and enantiomeric excess were measured in the synthesis of **6Db** (57:43 *dr* and 40% *ee*). The α-ethyl 3-thiophenyl acetaldehyde **3B** also reacted with *p*-chloro nitrostyrene **5a**, although the Michael adduct **8Ba** was produced in moderate stereoselectivity. Finally, the more acidic

α-allyl 2-naphthylacetaldehyde **4C** proved to be more active as 90% conversion was detected after 64h reaction and adduct **9Ca** was obtained in quite good diastereoselectivity, (85:15 *dr*) albeit in relatively poor enantiomeric excess (46% *ee*). Accordingly, while this BB approach may be extended to other α,α-disubstituted aryl acetaldehydes,[23] better conditions are still needed to improve both reaction time and stereocontrol. In this respect, during the preparation of racemic adducts we observed that reaction of **1A** with nitroolefin **5c** carried out in the presence of triethylamine (30 mol%) at RT for 16 h led to ***rac*-6Ac** in 71:29 *dr*, (90:10 *dr* with **C9**). Similarly, reaction of **3A** with **5i** promoted by catalyst **C13** (10 mol%) at RT provided after 16h ***rac*-8Ai** in 76:24 *dr* while using the chiral catalyst **C9** the adduct was formed in 90:10 *dr*. Thus, a combination of both, substrate and catalyst control may be operating for the observed *syn* selectivity. A single crystal X-ray analysis of **6Ab** (Figure 2)[24] confirmed both its relative and absolute configuration and that of the remaining adducts was assumed on the basis of a uniform reaction mechanism.

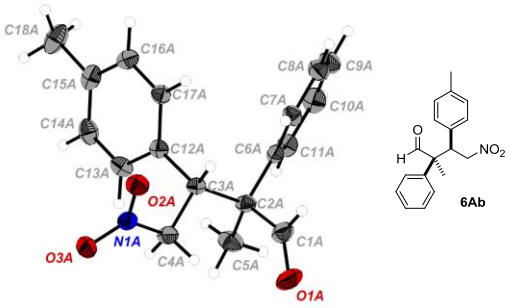


Figure 2. ORTEP diagram of compound **6Ab**. View of the molecular structure of **6Ab** with 50% probability displacement ellipsoids.

Other interesting point of this protocol is that these transformations can be scaled up without lost of yield nor stereoselectivity as shown by the reaction of (±)-2-phenylpropionaldehyde **1A** with nitroolefin **5c** on a 4 mmol scale, which provided adduct **6Ac** in 82% yield and with 94:6 *dr* and 95% *ee* for the major *syn*-isomer. Notably, the catalyst was recovered after flash column chromatography in 87% yield.[25]

Theoretical probes and mechanistic observations

In order to get insights into the mechanism of the reaction and the origin of the *syn*-selectivity in these transformations, we next performed some DFT calculations[26] on the reaction of (±)-2-phenyl propanal **1A** with nitrostyrene **5c** promoted by **C9**.

Up to (at least) three different non covalent coordination patterns (model A or Takemoto's proposal, model B or Pápai's proposal and model C or Wang's proposal, Figure 3) have been documented for reactions promoted by bifunctional thiourea (or squaramide)-tertiary amine catalysts.[27] In our reaction we identified two of the previous H-bonding net activation modes, Takemoto's proposal (electrophile dual-activation by the squaramide core, model A) and Papai's proposal (nucleophile dual-activation by the squaramide core, model B). All attempts to find transition structures following Wang's model (squaramide-activation of both reagents) evolved to Takemoto's model and therefore were discarded. For this study, we considered that the system behaves under Curtin–Hammett kinetic scenario, where the product ratio depends on the free Gibbs activation energy difference of the corresponding transition structure, and both *E*– and *Z*–enolate configurations were evaluated.

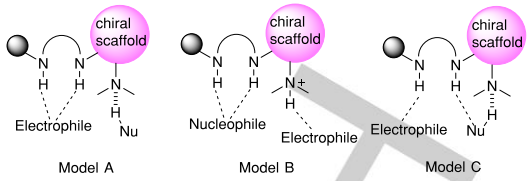


Figure 3. Three alternative substrate-catalyst combinations proposed for bifunctional Brønsted base activation mode.

Our calculations show that the less energetic transition structures,[25] correspond to a Pápai's activation mode wherein the enolate interacts with the squaramide core of the catalyst and the nitroolefin is activated through H-bonding interaction with the cinchona moiety of **C9**, as previously described for the Michael addition of α-amino aldehydes to β-nitro styrenes catalyzed by analogous BB catalysts.[11] Remarkably, transition structures involving *E*-enolates are more stabilized than analogues from *Z*-enolates, as shown by the energy difference of +4.2 kcal mol^{-1}

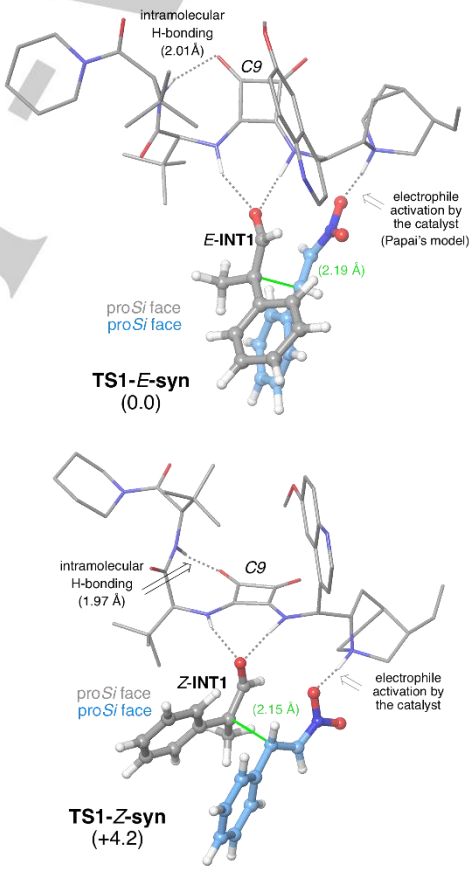


Figure 4. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **1A** and **5c** catalyzed by **C9** that lead to the formation of *syn*-*S*,*R*-**6Ac** considering *E*– and *Z*–enolates. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.

between **TS1-*E*-syn** and **TS1-*Z*-syn** (Figure 4), despite reactive complexes involving *Z*-enolates being close in energy to their *E*-counterparts. This is a consequence of the higher deformation required to adopt the geometry of the transition structure in *Z*-

enolates, where oxygen–phenyl repulsion during the C–C bond formation leads to an additional torsion in the phenyl group.

Noteworthy, the observed facial selection is consequence of the existence of an intramolecular H-bonding interaction between the NH of one of the *tert*-leucines and the carbonyl of squaramide moiety that fix the catalyst conformation independently of the activation mode considered. Within this conformational restricted catalytic system, **TS1-*E*-syn** was found to be the least energetic transition structure due to a lower steric hindrance between the *t*-butyl group of *tert*-leucine and the phenyl group of the enolate, thus yielding compound *syn-S,R*-**6Ac**. Note that in **TS1$_{ENT}$-*E*-syn** and **TS1-*E*-anti** (Figure 5) the enolate has to rotate due to steric hyndrance, leading to less optimal catalyst-substrate H-bonding interactions. These calculations predict a theoretical *ee* of 99% and *dr* >99:1, in good agreement with the experimental results.

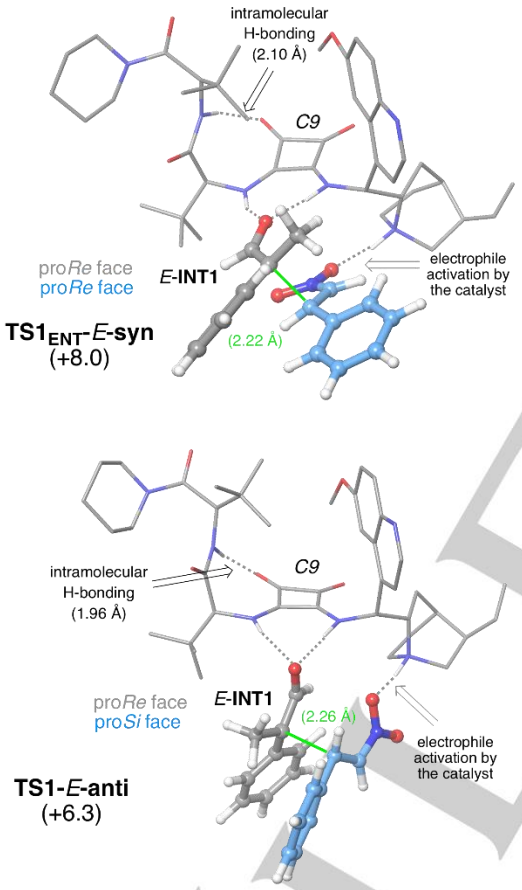
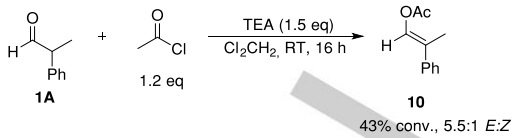


Figure 5. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **1A** and **5c** catalyzed by **C9** that lead to the formation of *syn-S,R*-**6Ac** considering *E*– and *Z*–enolates. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.

Concordant with the above DFT observations, treatment of (±)-2-phenyl propanal **1A** with triethylamine (TEA) (1.5 equiv.) and acetyl chloride (1.2 equiv.) in Cl_2CH_2 at RT for 16h provided a 5.5:1 (85:15) mixture of the corresponding **10** *E* and Z enol acetates[28,29] (Scheme 3).



Scheme 3. Formation of the *E*/*Z* enol acetates from (±)-2-phenylpropanal **1A** in the presence of triethylamine (TEA) and acetyl chloride.

Conclusion

In summary, we have demonstrated that the α-functionalization of α-methyl aryl acetaldehydes may be accomplished by Brønsted base activation catalysis, thus providing a complementary alternative platform to the known enamine strategy. The protocol seems to work through the formation of the corresponding *E* ammonium enolate by the action of a cinchona based squaric acid-derived amino acid peptide. Further reaction of the transient ammonium enolate with different nitroolefins provides 2,2,3-trisubstituted *syn* γ-nitroaldehydes in high enantio- and diastereoselectivity and in the absence of homoaldol reaction.

Experimental Section

Catalytic conjugate additions of α-branched aryl/heteroaryl acetaldehydes to nitroolefins.

General Procedure: The corresponding aldehyde (0.2 mmol, 1 equiv), nitroolefin (0.6 mmol, 3 equiv) and catalyst **C6** or **C9** (0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting mixture was stirred at 0 ºC. Reaction completion was followed by ^{1}H NMR and after the indicated time the mixture was directly submitted to flash column chromatography on silica gel. Reaction conversions and diastereomeric ratios were determined by ^{1}H NMR. Enantiomeric ratios were determined by chiral HPLC.

The corresponding racemic reactions were ran following the above procedure but using achiral catalyst **C13** (30 mol%).

(*2S*,*3R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-phenylbutanal (6Aa). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5a** and catalyst **C9** to afford a 95:5 diastereomer mixture. The product was isolated as a colorless oil in a 88:12 diastereomeric ratio (53.9 mg, 0.169 mmol, 84% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 21.6 min (minor) and 23.1 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.49-7.11 (m, 5H), 7.07 (dd, *J* = 7.7, 2.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.05-4.83 (m, 2H), 4.21 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 138.6, 135.7, 132.3, 130.9, 130.1, 130.0, 129.0, 78.0, 58.2, 50.7, 18.1. UPLC-DAD-QTOF: $C_{17}H_{16}ClNO_3Na$ $[M+Na]^+$ calcd.: 340.0716, found: 340.0731.

(*2S*,*3R*)-2-Methyl-4-nitro-2-phenyl-3-(p-tolyl)butanal (6Ab). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5b** and catalyst **C9** to afford a 97:3 diastereomer mixture. The product was isolated as a colorless solid in a 91:9 diastereomeric ratio (49.2 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate=1 mL/min). Retention times: 12.5 min (minor) and 18.1 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.42-7.24 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.97 (d,

J = 7.9 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15-4.75 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 138.7, 133.5, 130.9, 130.5, 130.4, 130.3, 129.4, 128.7, 77.7, 58.0, 50.8, 22.3, 18.4. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1266.

(*2S*,*3R*)-2-Methyl-4-nitro-2,3-diphenylbutanal (6Ac). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5c** and catalyst **C9** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a colorless oil (46.8 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 21.8 min (minor) and 39.2 min (major). $[\alpha]_D^{23}$ = 113.99º (c=1, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.40-7.26 (m, 4H), 7.21-6.92 (m, 6H), 5.17-4.81 (m, 2H), 4.22 (dd, *J* = 11.5, 3.8 Hz, 1H), 1.55 (s, 3H). All the spectroscopic data were consistent with those previously reported.[31]

(*2S*,*3R*)-3-(3-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (6Ad). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5d** and catalyst **C9** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a white foam (30.9 mg, 0.099 mmol, 49% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate=1 mL/min). Retention times: 18.8 min (minor) and 25.9 min (major). $[\alpha]_D^{23}$ = 83.10º (c=1, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.38-7.21 (m, 3H), 7.15-7.00 (m, 3H), 6.68 (dd, J = 8.3, 2.5 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.45-6.32 (m, 1H), 5.00 (dd, J = 13.2, 11.4 Hz, 1H), 4.84 (dd, J = 13.2, 3.9 Hz, 1H), 4.17 (dd, J = 11.4, 3.8 Hz, 1H), 3.61 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.08, 159.30, 137.43, 137.03, 129.21, 129.14, 128.19, 127.47, 121.36, 115.43, 113.36, 76.22, 75.15, 56.72, 55.17, 49.72, 16.79. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1209.

(*2S*,*3R*)-2-Methyl-4-nitro-2-phenyl-3-(o-tolyl)butanal (6Ae). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5e** and catalyst **C9** to afford a 95:5 diastereomer mixture. The product was isolated as a colorless oil (49.3 mg, 0.166 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 17.3 min (major) and 19.3 min (minor). $[\alpha]_D^{23}$ = 88.18º (c=1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.31 (dt, J = 6.5, 3.8 Hz, 4H), 7.22-7.14 (m, 1H), 7.12 (dd, J = 7.4, 1.4 Hz, 1H), 7.10-7.04 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 5.05 (dd, J = 13.1, 11.5 Hz, 1H), 4.89 (dd, J = 13.2, 3.7 Hz, 1H), 4.59 (dd, J = 11.4, 3.7 Hz, 1H), 2.07 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.99, 138.43, 137.94, 134.64, 131.01, 129.01, 128.15, 127.64, 127.31, 127.23, 126.10, 77.23, 56.92, 43.67, 19.84, 17.73. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1256.

(*2S*,*3R*)-3-(4-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (6Af). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5f** and catalyst **C9** to afford a 96:4 diastereomer mixture. The product was isolated as a yellow oil in a 92:8 diastereomeric ratio (57.5 mg, 0.184 mmol, 92% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 25.7 min (minor) and 47.9 min (major). $[\alpha]_D^{23}$ = 95.45º (c=1, 92:8 dr, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37-7.29 (m, 3H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.07-4.78 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 160.2, 138.7, 131.6, 130.3, 129.7, 129.3, 128.6, 127.3, 114.9, 77.7, 58.0, 56.4, 50.3, 18.2. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1213.

(*2S*,*3R*)-2-Methyl-3-(nitromethyl)-2,5-diphenylpent-4-ynal (6Ag). Prepared according to the General Procedure, starting from aldehyde **1A**, nitroolefin **5g** and catalyst **C9** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (44.1 mg, 0.143 mmol, 72% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 24.7 min (minor) and 39.1 min (major). $[\alpha]_D^{23}$ = 74.32º (c=0.5, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.49-7.37 (m, 3H), 7.37-7.31 (m, 2H), 7.30-7.19 (m, 5H), 4.654.51 (m, 2H), 4.19 (dd, J = 9.6, 4.9 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.42, 136.76, 131.78, 129.36, 128.66, 128.60, 128.32, 127.52, 122.32, 86.40, 84.47, 76.37, 55.84, 38.19, 16.95. UPLC-DAD-QTOF: $C_{19}H_{17}NO_3Na$ $[M+Na]^+$ calcd.: 330.1106, found: 330.1098.

(*2S*,*3R*)-2-Methyl-3-(nitromethyl)-2-phenylhexanal (6Ah). Prepared according to the General Procedure, but at room temperature, starting from aldehyde **1A**, nitroolefin **5h** and catalyst **C9** to afford a 96:4 diastereomer mixture. The product was isolated as a yellow oil (28.4 mg, 0.114 mmol, 57% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 13.7 min (minor) and 18.3 min (major). $[\alpha]_D^{20}$ = 30.45º (c=1, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.46-7.39 (m, 2H), 7.38-7.32 (m, 1H), 7.32-7.29 (m, 1H), 7.29-7.27 (m, 1H), 4.48 (dd, J = 13.4, 4.3 Hz, 1H), 4.28 (dd, J = 13.4, 7.3 Hz, 1H), 3.14 (ddt, J = 8.6, 4.3, 2.7 Hz, 1H), 1.48 (s, 3H), 1.28-0.99 (m, 4H), 0.74 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.91, 137.67, 129.34, 128.17, 127.54, 77.75, 57.01, 41.80, 31.84, 21.01, 15.29, 14.10. UPLC-DAD-QTOF: $C_{14}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 272.1263, found: 272.1263.

(*2S*,*3R*)-3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-methyl-4-nitrobutanal (7Aa). Prepared according to the General Procedure starting from aldehyde **2A**, nitroolefin **5a** and catalyst **C9** to afford a 93:7 diastereomer mixture. The final product was isolated as a colorless oil in a 93:7 diastereomeric ratio (51.5 mg, 0.148 mmol, 74% yield) after flash column chromatography on silica gel (90:10 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 33.4 min (minor) and 37.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.15-7.07 (m, 2H), 6.98-6.90 (m, 2H), 6.89-6.77 (m, 4H), 4.94 (dd, J = 13.1, 11.2 Hz, 1H), 4.85 (dd, J = 13.1, 4.3 Hz, 1H), 4.16 (dd, J = 11.2, 4.3 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.51, 159.47, 134.23, 133.66, 131.14, 130.68, 129.46, 128.67, 128.46, 128.33, 76.12, 55.98, 55.41, 49.03, 16.43. UPLC-DAD-QTOF: $C_{18}H_{18}ClNO_4Na$ $[M+Na]^+$ calcd.: 370.0822, found: 370.0822.

(*2S*,*3R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-(thiophen-3-yl)butanal (8Aa). Prepared according to the General Procedure starting from aldehyde **3A**, nitroolefin **5a** and catalyst **C9** to afford a 91:9 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (51.9 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (90:10 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=0.5 mL/min). Retention times: 82.6 min (minor) and 98.1 min (major). $[\alpha]_D^{24}$ = 128.59º (c=1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.37 (dd, J = 5.1, 3.0 Hz, 1H), 7.20-7.13 (m, 2H), 6.94-6.84 (m, 4H), 4.95 (dd, J = 13.2, 11.5 Hz, 1H), 4.78 (dd, J = 13.2, 4.0 Hz, 1H), 4.16 (dd, J = 11.4, 3.9 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.32, 138.30, 134.05, 133.99, 130.53, 128.66, 127.50, 126.10, 123.45, 76.09, 54.74, 49.02, 17.80. UPLC-DAD-QTOF: $C_{15}H_{14}NO_3SClNa$ $[M+Na]^+$ calcd.: 346.0281, found: 346.0282.

(*2S*,*3R*)-2-Methyl-3-(nitromethyl)-5-phenyl-2-(thiophen-3-yl)pentanal (8Ai). Prepared according to the General Procedure starting from aldehyde **3A**, nitroolefin **5i** and catalyst **C9** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (28.9 mg, 0.091 mmol, 45% yield) after flash column chromatography on silica gel

(95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane : ^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 24.9 min (major) and 26.8 min (minor). $[\alpha]_D^{21}$ = 21.39º (c=1, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.38 (dd, J = 5.1, 2.9 Hz, 1H), 7.25-7.14 (m, 3H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.02-6.95 (m, 2H), 6.92 (dd, J = 5.1, 1.4 Hz, 1H), 4.50 (dd, J = 13.2, 4.6 Hz, 1H), 4.34 (dd, J = 13.2, 7.2 Hz, 1H), 3.17-3.05 (m, 1H), 2.59 (ddd, J = 16.7, 8.4, 3.4 Hz, 1H), 2.33 (ddd, J = 13.6, 9.7, 7.2 Hz, 1H), 1.73-1.55 (m, 2H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.74, 140.82, 138.82, 128.65, 128.51, 127.44, 126.37, 126.22, 123.44, 77.48, 55.44, 41.17, 34.26, 31.78, 15.67. UPLC-DAD-QTOF: $C_{17}H_{19}NO_3SNa$ $[M+Na]^+$ calcd.: 340.0983, found: 340.0982.

(2*S*,3*R*)-2-Methyl-2-(naphthalen-2-yl)-4-nitro-3-phenylbutanal (9Ac). Prepared according to the General Procedure starting from aldehyde **4A**, nitroolefin **5c** and catalyst **C9** to afford a 98:2 diastereomer mixture. The product was isolated as a white foam (47.3 mg, 0.142 mmol, 71% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 19.1 min (major) and 21.7 min (minor). $[\alpha]_D^{21}$ = 175.05º (c=1, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.88-7.72 (m, 3H), 7.54-7.44 (m, 3H), 7.23 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 5.1, 2.0 Hz, 3H), 6.99 (dd, J = 5.2, 1.6 Hz, 2H), 5.10 (dd, J = 13.1, 11.5 Hz, 1H), 4.87 (dd, J = 13.1, 3.8 Hz, 1H), 4.31 (dd, J = 11.5, 3.8 Hz, 1H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.27, 135.48, 134.82, 133.20, 132.69, 129.46, 129.18, 128.42, 128.21, 127.89, 127.69, 127.03, 126.92, 126.83, 124.45, 76.46, 56.96, 49.87, 17.54. UPLC-DAD-QTOF: $C_{21}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 356.1263, found: 356.1259.

(2*S*,3*R*)-2-Ethyl-4-nitro-2,3-diphenylbutanal (6Bc). Prepared according to the General Procedure starting from aldehyde **1B**, nitroolefin **5c** and catalyst **C9** to afford an 83:17 diastereomer mixture. The product was isolated as a white oil in a 82:18 diastereomeric ratio (36.3 mg, 0.122 mmol, 61% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 12.5 min (major) and 15.9 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.47-7.36 (m, 3H), 7.29-7.21 (m, 3H), 7.18-7.11 (m, 2H), 7.11-7.02 (m, 2H), 4.98 (dd, J = 13.2, 11.7 Hz, 1H), 4.68 (dd, J = 13.3, 3.4 Hz, 1H), 4.16 (dd, J = 11.7, 3.4 Hz, 1H), 1.96 (dq, J = 14.4, 7.1 Hz, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.10, 137.03, 135.44, 129.80, 129.26, 128.56, 128.19, 128.07, 127.97, 77.06, 50.96, 27.77, 9.04. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.125.

(*S*)-2-((*R*)-2-Nitro-1-(p-tolyl)ethyl)-2-phenylpent-4-enal (6Cb). Prepared according to the General Procedure starting from aldehyde **1C**, nitroolefin **5b** and catalyst **C9** to afford an 85:15 diastereomer mixture. The product was isolated as a colorless oil in a 79:21 diastereomeric ratio (42.7 mg, 0.132 mmol, 66% yield) after flash column chromatography on silica gel (99:1 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 10.7 min (minor) and 12.2 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.46-7.31 (m, 3H), 7.15 (dd, J = 6.8, 1.6 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 5.58-5.37 (m, 1H), 5.10-4.96 (m, 3H), 4.69 (dd, J = 13.2, 3.4 Hz, 1H), 4.11 (dd, J = 11.7, 3.3 Hz, 1H), 2.77 (ddt, J = 14.7, 5.9, 1.4 Hz, 1H), 2.67-2.55 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.81, 138.19, 132.44, 130.06, 129.88, 129.52, 129.21, 129.19, 128.40, 128.03, 120.22, 77.78, 59.50, 50.87, 39.16, 21.37. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 346.1419, found: 346.1411.

(2*S*,3*R*)-2-Benzyl-4-nitro-2-phenyl-3-(p-tolyl)butanal (6Db). Prepared according to the General Procedure starting from aldehyde **1D**, nitroolefin **5b** and catalyst **C9** to afford a 57:43 diastereomer mixture. The product was isolated as a white solid in a 63:37 diastereomeric ratio (33.6mg, 0.09 mmol, 45% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times for the major diastereomer: 34.3 min (minor) and 60.5 min (major) and for minor diastereomer: 15.1 min (minor) and 16.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H, minor diastereomer), 9.69 (s, 1H, mayor diastereomer), 7.47-7.40 (m, 3H, mayor diastereomer), 7.36 (d, J = 7.2 Hz, 3H, minor diastereomer), 7.18-7.11 (m, 7H, both diastereomers), 7.11-6.99 (m, 9H, both diastereomers), 6.97 (dd, J = 6.5, 3.1 Hz, 2H, both diastereomers), 6.77 (d, J = 8.1 Hz, 2H, mayor diastereomer), 6.64 (dd, J = 8.0, 1.5 Hz, 2H), 4.91 (dd, J = 13.2, 11.8 Hz, 1H, minor diastereomer), 4.79 (dd, J = 12.0, 3.3 Hz, 1H, mayor diastereomer), 4.68 (dd, J = 13.2, 3.2 Hz, 1H, minor diastereomer), 4.38-4.27 (m, 2H, both diastereomers), 4.22 (dd, J = 11.9 Hz, 1H, mayor diastereomer), 3.30-3.18 (m, 2H, minor diastereomer), 3.19-3.07 (m, 2H, mayor diastereomer), 2.34 (s, 3H, minor diastereomer), 2.31 (s, 3H, mayor diastereomer). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.45, 204.33, 138.28, 138.06, 137.51, 135.58, 134.64, 134.58, 131.97, 131.50, 130.54, 130.50, 130.28, 129.87, 129.63, 129.54, 129.32, 129.17, 128.99, 128.79, 128.69, 128.48, 128.19, 128.12, 127.20, 126.91, 77.45, 77.30, 60.62, 59.55, 51.09, 47.30, 42.23, 41.66, 21.21. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 396.1576, found: 396.1573.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-ethyl-4-nitro-2-(thiophen-3-yl)butanal (8Ba). Prepared according to the General Procedure starting from aldehyde **3B**, nitroolefin **5a** and catalyst **C9** to afford a 55:45 diastereomer mixture. The product was isolated as a yellow oil in a 62:38 diastereomeric ratio (28.4 mg, 0.084 mmol, 42% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times for the major diastereomer: 12.4 min (major) and 13.4 min (minor) and for minor diastereomer: 21.5 min (major) and 31.1 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.44 (dd, J = 5.1, 2.9 Hz, 1H), 7.27-7.18 (m, 2H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.01-6.90 (m, 3H), 4.86 (dd, J = 13.3, 11.6 Hz, 1H), 4.65 (dd, J = 13.3, 3.7 Hz, 1H), 4.07 (dd, J = 11.6, 3.7 Hz, 1H), 1.95 (qd, J = 7.4, 1.1 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.11, 130.97, 130.85, 128.84, 128.65, 127.27, 126.26, 123.87, 76.96, 57.92, 50.36, 28.22, 9.09. UPLC-DAD-QTOF: $C_{17}H_{20}NO_4S$ $[M+ CH_3OH\text{-}Cl]^+$ calcd.: 334.1113, found: 334.1113.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-(naphthalen-2-yl)pent-4-enal (9Ca). Prepared according to the General Procedure starting from aldehyde **4C**, nitroolefin **5a** and catalyst **C9** to afford an 85:15 diastereomer mixture. The product was isolated as a white foam in a 80:20 diastereomeric ratio (53.6 mg, 0.136 mmol, 68% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 17.5 min (minor) and 29.5 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.88-7.77 (m, 2H), 7.60-7.52 (m, 1H), 7.51-7.45 (m, 1H), 7.31-7.13 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 5.61-5.43 (m, 1H), 5.16-5.01 (m, 3H), 4.70 (dd, J = 13.4, 3.3 Hz, 1H), 4.21 (dd, J = 11.7, 3.2 Hz, 1H), 2.92 (dd, J = 14.8, 5.5 Hz, 1H), 2.65 (dd, J = 14.7, 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.21, 134.28, 133.98, 133.77, 133.15, 132.76, 131.81, 131.34, 129.64, 128.84, 128.26, 127.76, 127.65, 127.19, 127.12, 124.43, 120.47, 76.67, 59.28, 50.37, 38.66. UPLC-DAD-QTOF: $C_{23}H_{20}ClNO_3Na$ $[M+Na]^+$ calcd.: 416.1029, found: 416.1033.

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Keywords: α-branched arylacetaldehydes • Brønsted bases • Michael reaction • nitroolefins • organocatalysis

[1] a) *Comprehensive Asymmetric Catalysis*, *Vol I-III*, *Suppl. I-II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin **1999**; b) *Asymmetric Organocatalysis I: Brønsted Base and Acid Catalysts and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**; c) *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts and Additional Topics* (Ed.: B. List), Thieme, Stuttgart, **2012**. d) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, Vol. 1-3, **2013**.

[2] For a review on catalytic asymmetric transformations under proton transfer conditions, see: a) N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**,*123*, 4856–4868; *Angew. Chem. Int. Ed*. **2011**, *50*, 4760–4772. For selected general reviews on Brønsted bases, see: b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, 37, 621–631; c) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; d) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200; e) ref. 1b, pp. 41–118; f) *Bifunctional Cinchona Alkaloid Organocatalysts*, H. B. Jang, J. S. Oh, C. E. Song in *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 119–168.

[3] For the pka values of some BB catalysts and the α-carbon of some carbonyl compounds, see: a) X. Ni, X. Li, Z. Wang, J. P. Cheng, *Org. Lett.* **2014**, *16*, 1786–1789; b) X. Li, H. Deng, B. Zhang, J. Li, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 450–455; c) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724–1727; d) J. Ho, V. E. Zwicker, K. K. Y. Yuen, K. A. Jolliffe, *J. Org. Chem.* **2017**, *82*, 10732–10736. For a webpage of pK_a values (acidities in DMSO) of different compounds, see Bordwell pka table: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

[4] For a rather specific example that documents the reaction of α-chloroaldehydes with β-alkylidene α-keto amides wherein the final cyclization of the resultant addition adduct appears to be the driving force of the process, see: Q.-Z. Li, Y. Liu, H.-J. Leng, J.-L. Li, *Synlett* **2018**, *29*, 2601–2607.

[5] For more details on these problems, see: a) D. M. Hodgson, A. Charlton, *Tetrahedron* **2014**, *70*, 2207–2236; b) C. Mazet, *Chimia* **2013**, *67*, 658–662.

[6] For selected reviews on aminocatalysis, see: a) L. Albrecht, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2014**, *20*, 358–368; b) N. Mase in ref 1c pp. 135–216; c) D. W. C. MacMillan in ref 1c pp. 271–307; d) P. Melchiore, *Angew. Chem.* **2012**, *124*, 9886–9909, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770; e) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[7] For the synthetic use of γ-nitroaldehydes in synthesis, see: a) A. Z. Halimehjani, I. N. N. Namboothiri, S. E. Hooshmanda, *RSC Adv.* **2014**, *4*, 31261–31299; b) G. Koutoulogenis, N. Kaplaneris, C. G. Kokotos, *Beilstein J. Org. Chem*. **2016**, *12*, 462–495; c) X. Yang, J. Wang, P. Li, *Org. Biomol. Chem.* **2014**, *12*, 2499–2513; d) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909–1930 ; e) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601. For selected reviews on organocatalytic cascade or domino reactions involving aldehydes and nitroolefins, see: f) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832–1844; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431; h) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; i) H. Pellissier, *Asymmetric Domino Reactions*, RSC Publishing, Cambridge, **2013**.

[8] For a review on the α-functionalization of α,α-disubstituted aldehydes via enamine activation, see: A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron* **2014**, *70*, 2491–2513.

[9] N. Mase, R, Thayumanavan, F, Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530.

[10] a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514–6518; *Angew. Chem. Int. Ed.* **2006**, 45, 6366–6370; b) Y.-F. Ting, Ch. Chang, R. J. Reddy, D. R. Magar, K. Chen, *Chem. Eur. J*. **2010**, *16*, 7030–7038; c) J.-R. Chen, Y.-Q. Zou, L. Fu, F, Ren, F. Tan, W.-J. Xiao, *Tetrahedron* **2010**, *66*, 5367–5372; d) T. C. Nugent, M. Shoaib, A. Shoaib, *Org. Biomol. Chem.* **2011**, *9*, 52–56; e) P. Szczśniak, O. Staszewska-Krajewska, B. Furman, J. Młynarsky, *Chemistry Select* **2017**, *2*, 2670–2676. For other contributions on the addition of aldehydes to nitroolefins which include some specific examples on α,α-disubstitued aldehydes, see: d) S. H. Mc Cooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; e) M. Yoshida, A. Sato, S. Hara, *Org. Biomol. Chem.* **2010**, *8*, 3031–3036. For a protocol on solid phase under continuos flow conditions: f) R. Porta, M. Benaglia, F. Coccia, F. Cozzi, A. Puglisi, *Adv. Synth. Catal.* **2015**, *357*, 377–383.

[11] a*)* A. García-Urricelqui, A. de Cózar, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2021**, *27*, 2483–2492. Also, see*:* b) U. Farid, M. L. Aiello, S. J. Connon, *Chem. Eur. J.* **2019**, *25*, 10074 –10079; c) D. Majee, S. Jakkampudi, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2019**, *21*, 9166–9170.

[12] For reviews on catalytic enantioselective Michael reactions, see: a) J. M. Hayashi, R. Matsubera, *Tetrahedron Lett.* **2017**, *58*, 1793–1805; b) O. V. Matsev, I. P. Beletskaya, S. G. Zloti, *Russ. Chem. Rev.* **2011**, *80*, 1067–113; c) Y. Zhang, W. Eang, *Cat. Sci. Technol.* **2012**, *2*, 42–53; d) L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, **2010**, RSC; e) B. N. Nguyen, K. K. Hii, W. Szymanski, D. B. Janssen in *Stereoselective Synthesis 1, Stereoselective Reactions of Carbon-Carbon Double Bonds*, (Ed.: J. G. de Vries), Science of Synthesis, Thieme: Stuttgart, **2011**, pp.571–688.

[13] For reviews on conjugate additions to nitroolefins, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1884; b) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. J. Ramón*, Molecules* **2017**, *22*, 895–946. For representative examples using linear aldehydes, see: c) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am.Chem. Soc*. **2004**, *126*, 9558–9559; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287, *Angew. Chem. Int. Ed*. **2005**, *44*, 4212–4215; e) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed*. **2005**, *44*, 1369–1371; f) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. III. Barbas, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; h) C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130–6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984–5987; g) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562; h) D. Lu, Y. Gong, W. Wang, *Adv. Synth. Catal.* **2010**, *352*, 644–650.

[14] Recent reviews on quaternary stereocenters, see: a) J. F. M. Holmes, M. J. Krishe, *Chem. Rev.* **2017**, 117, 12564–12580; b) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740–751; c) T. Ling, F. Rivas, *Tetrahedron* **2016**, 72, 6729–6777; d) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745–2759; e) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593–4623; f) M. Bella, T. Caspery, *Synthesis* **2009**, 1583–1614; g) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem.* **2007**, 5969–5614; h) B. M. Trost,C. Jiang, *Synthesis* **2006**, 369–396; i) *Quaternary Stereocenters* (Eds: J. Christoffers, A. Baro) Wiley-VCH, Weinheim, **2005**; j) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367.

[15] a) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem.* **2013**, *125*, 12062–12067; *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851; b) S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014,** *20*, 6526–6531; c) H. Echave, R. López, C. Palomo, *Angew. Chem.* **2014**, *128*, 3425–3429; *Angew. Chem. Int. Ed.,* **2016**, *55*, 3364-3368; d) I. Bastida, M. San Segundo, R. López, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 13332–13336. For a concept review, see: e) R. López, C. Palomo *Chem. Eur. J*. **2021**, *27*, 20–29.

[16] The relative configuration was designated according to Masamune´s convention, see: S. Masamune, T. Kaiho, D. S. Garvey, *J. Am. Chem. Soc.* **1982**, *104*, 5521–5523.

[17] Squaric amino acids and/or peptides in medicinal chemistry and drug discovery: For a review, see: a) R. W. Frederik, H.-A. Klok, *Chem. Soc. Rev.* **2013**, *42*, 8220–8236. For selected examples, see: b) M. B. Onaran, A. B. Comeau, Ch. T. Seto, *J. Org. Chem.* **2005**, *70*, 10792–10802; c) P. Sejwal, Y. Han, A. Shah, Y.-Y. Luk, *Org. Lett.* **2007**, *23,* 4897–4900; d) T. Shinada, T. Ishida, K. Hayashi, Y. Yoshida, Y. Shigeri, Y. Ohfune, *Tetrahedron Lett.* **2007**, *48*, 7614–7617; e) P. M. C. Glória , J. Gut , L. M. Gonçalves , P. J. Rosenthal , R. Moreira, M. M. M. Santos *Biorg. & Med. Chem. Lett.* **2011**, *19*, 7635–7642; f) B. Palitzsch, S. Hartmann, N. Stergiou, M. Glaffig, E. Schmidt, H. Kunz, *Angew. Chem.* **2014**, *126*, 14469–14473; *Angew. Chem. Int. Ed.* **2014**, *53*, 14245–14249; g) M. Lu, Q.-B. Lu, J. F. Honek, *Bioorg. & Med. Chem. Lett.* **2017**, *27*, 282–287.

[18] Squaric amino acids or derivatives in organocatalysis, see: a) E. Matador, M. de Gracia Retamosa, D. Monge, J. Iglesias-Sigüenza, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2018**, *24*, 6854–6860; b) A. R. Ray, S. Mukherjee, *Chem. Sci.* **2016**, *7*, 6940–6945; c) R. Y. Liu, M. Wasa, E. N. Jacobsen, *Tetrahedron Lett.* **2015**, *56*, 3428–3430; d) H. Zhang, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, *136*, 16485–1648; e) V. Kumarand, S. Mukherjee, *Chem. Commun.* **2013**, *49*, 11203–11205; g) H.-X. He, D-M. Du, *Eur. J. Org. Chem.* **2014**, 6190–6199; h) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756.

[19] H.-X. He, D-M. Du, *Eur. J. Org. Chem.* **2014**, 6190–6199.

[20] For pioneering work, see: a) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; b) Y. Zhu, J. P. Malerich, V. R. Rawal, *Angew. Chem.* **2010**, *122*, 157–160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156. For reviews on squaramides, see: c) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346; d) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; e) P. Chauhan, S. Mahahan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281.

[21] Review on small-molecule H-bond donors in asymmetric catalysis: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. **2007**, *107*, 5713–5743. For catalysts with multiple H-bond donors, see: b) X. Fanga, C.-J. Wang, *Chem. Commun*. **2015**, *51*, 1185–1197**.**

[22] To ensure that no resolution of the aldehyde via deprotonation / protonation by the the catalyst occurs, racemic aldehyde **2A** was subjected to treatment with catalyst **C9** (20 mol %) at 0º C for 16 h. After usual work-up the starting aldehyde was recovered in complete racemic form.

[23] An additional experiment involving the reaction of diphenylacetaldehyde with nitrostyrene at 0ºC in the presence of **C9** revealed the formation of the corresponding adduct in 76% conversion after 68 h, but in racemic form. Using squaramide **C12** the product was formed in 30% *ee*.

[24] CCDC 2070327 contains the supplementary crystallographic data for compound **6Ab**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[25] For more details, see the Supporting Information

[26] R. G. Parr, W. Yang, *Density-Functional Theory of Atoms and Molecules*; Oxford, New York, **1989**.

[27] For Takemoto's model, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125. For Pápai's model, see: c) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160; d) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631–5639. For Wang's model see: e) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. E. Wang, *J. Org. Chem.* **2012**, *77*, 9813–9825.

[28] For the NMR data of **10** *E*-enol acetate, see: a) Ch. Liu, J. Yuan, Z. Wang, Z. Zhang, W. Zhang, *Org. Lett.* **2018**, *20*, 108–111; b) J. Ruan, X. Li, O. Saidi, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425. For NMR data of the mixture of **10** *E*- and *Z*-enol acetates, see: c) J. S. Sharley, A. M. Collado, E. Espinos Ferri, A. Fernández Miranda, I. R. Baxendale,*Tetrahedron* **2016**, *72*, 2947–2954.

[29] Further trials by treating aldehyde **1A** with acetyl chloride in the presence of catalyst **C9** in a 1:1 ratio aldehyde: catalyst at 0ºC for 16 h revealed the absence of enol acetates and the complete disappearance of the catalyst, possibly due to its acetylation.

[30] F. Felluga, P. Nitti, G. Pitacco, E. Valentin, E. *J. Chem. Soc. Perkin Trans. 1,* **1992**, 2331–2335.

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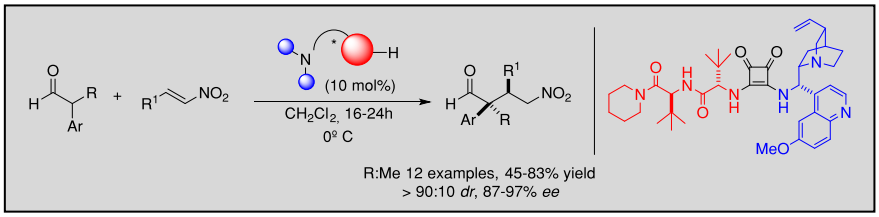

Expanding the substrate scope for BB catalysis: α-Branched aryl acetaldehydes are efficiently activated by a cinchona based squaric acid-derived peptide to provide, upon reaction with nitroolefins, 2,2,3-trisubstituted *syn* γ-nitroaldehydes with high diastereo- and enantioselectivity.