Probing α-Amino Aldehydes as Weakly Acidic Pronucleophiles: Direct Access to Quaternary α-Amino Aldehydes by an Enantioselective Michael Addition Catalyzed by Brønsted Bases

Ane García-Urricelqui,[a] Abel de Cózar,[a,b] Antonia Mielgo*[a] and Claudio Palomo*[a]

[a] A. García-Urricelqui, Dr. A. de Cózar, Dr. A. Mielgo and Prof. C. Palomo
Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU
Manuel Lardizábal 3, 20018 San Sebastián (Spain)
E-mail: antonia.mielgo@.ehu.es; claudio.palomo@ehu.es

[b] Dr. A. de Cózar
IKERBASQUE, Basque Foundation for Science
48009 Bilbao (Spain)

Abstract The high tendency of α-amino aldehydes to undergo 1,2-additions and their relatively low stability under basic conditions have largely prevented their use as pronucleophiles in the realm of asymmetric catalysis, particularly for the production of quaternary α-amino aldehydes. We now demonstrate that the chemistry of α-amino aldehydes may be expanded beyond these limits by documenting the first direct α-alkylation of α-branched α-amino aldehydes with nitroolefins. The reaction produces densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity. DFT modelling led us to propose that an intramolecular H-bonding between the NH group and the carbonyl oxygen atom in the starting α-amino aldehyde is key for reaction stereocontrol.

Introduction

Chiral α-amino aldehydes are exceptionally valuable building blocks in chemical synthesis and have application in medicinal chemistry and pharmaceutical industry.[1] The aldehyde function can be transformed into a wide variety of other functional groups leading to a diversity of substituted chiral amines, which are also of significance in the field of natural products and bioactive substances.[2] Despite this interest, little progress has been made in the development of methods for the stereoselective synthesis of α-amino aldehydes. While recent advances have been made through the asymmetric hydrogenation of α-formyl enamides which leads to tertiary α-amino aldehydes with very good enantioselectivities,[3] direct catalytic asymmetric synthesis of quaternary α-amino aldehydes,[4] other than the α-amination of α-substituted aldehydes, specifically α-substituted aryl acetaldehydes, have been very poorly investigated.[5] In general, α-functionalization of α-amino aldehydes is subjected to side reactions like self-additions and Cannizzaro or Tishchenko disproportionations, particularly under basic conditions,[6] a problem that may be attributed to the sum of the attenuated reactivity of the tertiary carbon nucleophile, plus the high reactivity of the aldehyde function against 1,2-additions. Besides these challenges, the stereochemical control elements for an effective catalytic direct α-amino aldehyde enolate alkylation are still unknown. Even in the realm of chiral auxiliary based asymmetric methodologies these problems are not well resolved.[7] Not surprisingly, whereas there are a large number of studies realized in connection with the use of α-amino aldehydes as electrophiles[1] in which useful levels of *anti*-Felkin-Anh selectivity, Figure 1a, have generally been observed,[8] their chemistry as nucleophiles, Figure 1b, remains essentially undeveloped.

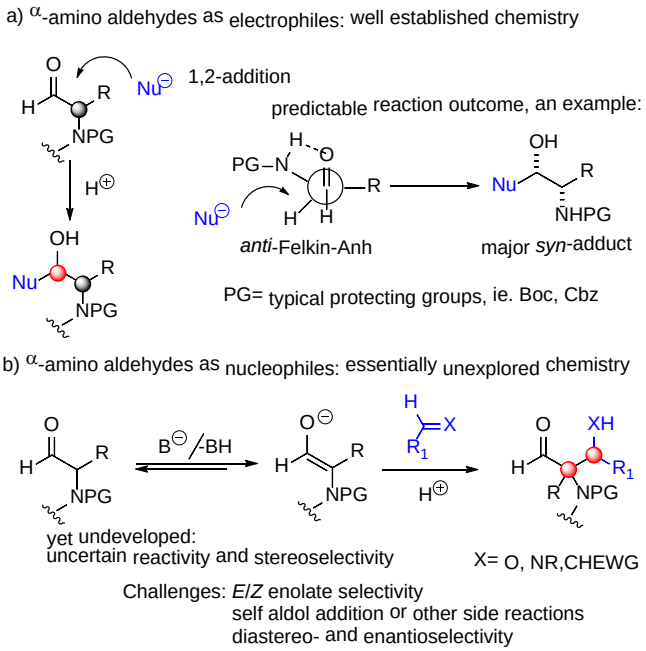


Figure 1. Chemistry of α-amino aldehydes.

Herein we report the first Brønsted base catalysis strategy towards solving the problem of the asymmetric catalytic enolate α-alkylation of α-amino aldehydes by documenting their reaction with nitroolefins leading to densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity. An internal H-bonding is postulated as key preorganizational element.

Results and Discussion

Background and working hypothesis

The most currently employed method for the production of quaternary α-amino aldehydes likely is the selective reduction of the corresponding quaternary α-amino acid and/or derivative.[1] This situation is due, at least in part, to the great number of existing methods for the stereoselective synthesis of the latter[9] wherein control of enolate configuration, a critical issue for stereoselectivity,[10] is easily achieved through the use of cyclic scaffolds like azlactones,[11] Figure 2a, or chelated metal enolate systems,[9,12] whereas for α-amino aldehydes this type of approaches to generate configurationally defined enolates are not easy to accomplish. Pioneering studies from the laboratory of Maruoka,[13a] have revealed enamine catalysis,[14] Figure 2b, to afford a solution to this problem, but the use of highly reactive

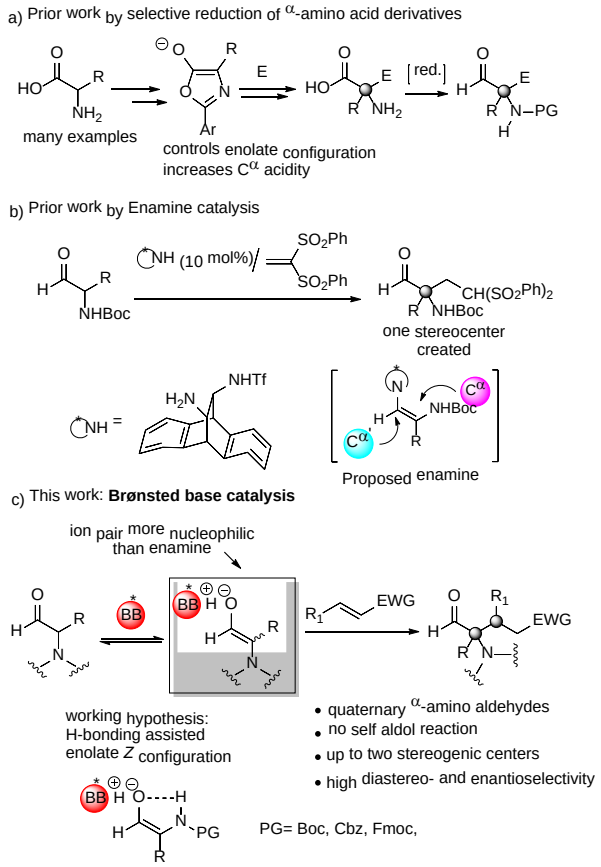
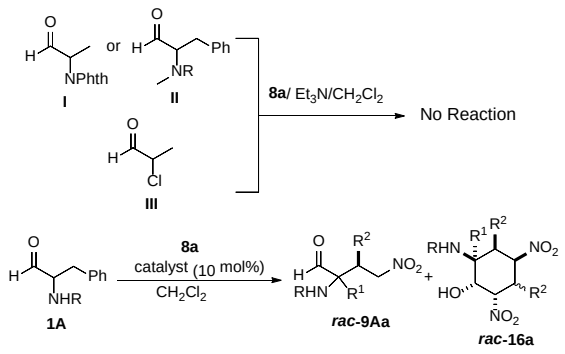


Figure 2. Precedent work on direct catalytic asymmetric synthesis of quaternary α-amino aldehydes and the new proposal. BB*= chiral Brønsted base.

β-unsubstituted Michael acceptors seems to be necessary. One inherent drawback associated to enamines of *N*-protected α-aminoacetaldehyde[15] is that both Cα and Cα´ positions of the double bond may be effective sites for reaction.[15a-c] Apparently, this scenario becomes more complicated when enamines of α-substituted α-amino aldehydes are involved in which the Cα site is sterically congested thus difficulting reaction at this position with bulky acceptors. As a matter of fact, Guo and co-workers[16] have shown that using 3-indolylarylmethanols as electrophiles the reaction of α-amino aldehydes through the enamine pathway is essentially limited to *N*-ethoxycarbonyl alaninal and essentially inefficient with α-amino aldehydes with longer chain lengths (Et, ^{n}Pr, and Bn). Quite promising seems to be the combined use of transition metal / enamine catalysis introduced by Meggers[17] for the Michael reaction of *N*-Boc-alaninal with α,β-unsaturated 2-acylimidazoles. However, no examples involving longer chain α-amino aldehydes using this dual catalyst system are reported. Although, these pioneering works set the basis for further studies to address the problem of α-amino aldehyde α-alkylation via enamine pathway in much broader sense, as an alternative to this activation strategy, Brønsted base (BB) catalysis relies on the deprotonation of a C-H pronucleophile as primary activation element and in theory presents no apparent inherent limitation.[18] However, besides the problems associated with the α–functionalization of aldehydes noted above there is 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.[19] Therefore the limit of this type of catalysis for aldehyde activation is still an open question. Inspired by the well known tendency of α-amino aldehydes to undergo racemization as well by the fact that this tendency increases when a weak base is present,[1,20] we reasoned that upon exposure to a weak chiral Brønsted base, *N*-protected α-amino aldehydes could easily generate a transient enolate ion pair, Figure 2c, which should be more reactive than the corresponding enamine, thus eventually driving the catalytic addition process forward. We presumed that in a similar way H-bonding plays an important role in reactions of *N*-alkoxycarbonyl α-amino aldehydes acting as electrophiles, *vide supra*, it could also participate in the present approach by stabilizing the corresponding *Z*-enolate, thereby enabling an effective substrate/catalyst preorganization and transition state stabilization. If this were the case, a practical new platform for direct catalytic α-functionalization of α-amino aldehydes could be made feasible in which β-substituted Michael acceptors might be well tolerated leading to products with quaternary and tertiary vicinal stereocenters in a single synthetic operation. To prove this hypothesis we elected to use nitroolefins[21] as the electrophilic reaction partners because the resulting γ-nitroaldehyde adducts could be transformed into other products of relatively increased complexity.[22]

Preliminary experimental observations

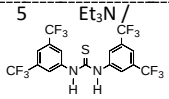
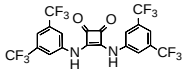
Given the problems associated with enolizable aldehydes besides the fact that α-functionalization of α-amino aldehydes assisted by Brønsted base catalysts remains unassessed, we began our study by examining the reactivity of three representative



Scheme 1. Preliminary experiments of the reaction of representative α-aminoaldehydes **I** (Phth= phthaloyl) **II** and **1A** (R=Boc), and the α-chloro aldehyde **III**, with nitrostyrene **8a** (R^2= 4-ClC$_6$H$_4$).

enolizable α-amino aldehydes, (±)-*N*-phthaloyl alaninal **I**, (±)-*N*-methyl-*N*-Boc phenylalaninal **II** and (±)-*N*-Boc phenylalaninal **1A**, against nitroolefin **8a,** Scheme 1, using several Brønsted bases of variable basic strength. We found that while no reaction takes place starting from **I** and **II** in the presence of Et_3N, the reaction of **1A** with **8a** led, after 48h at room temperature, to product **9Aa** as an almost equimolar mixture of diastereomers (Table 1, entry 1). The reaction proceeded in a modest conversion and accompanied by a little amount of the cyclized product **16a** coming from three consecutive, Michael-Michael-Henry reactions.[23] Hünig base (entry 2) was less effective than Et_3N and stronger bases such as the amidine base DBU as well as guanidines like MTBD and TBD (entries 3 and 4), led to polymerization of the nitroolefin in great extent[24] and no adducts derived from **1A** were observed. The reaction conversion into **9Aa** could be increased (entries 5 and 6) in the presence of either thiourea or squaramide hydrogen bond donors but no increase in diastereoselectivity nor in the production of cyclized product **16a**

Table 1. Base screening for the reaction of **1A** with nitroolefin **8a**.[a]

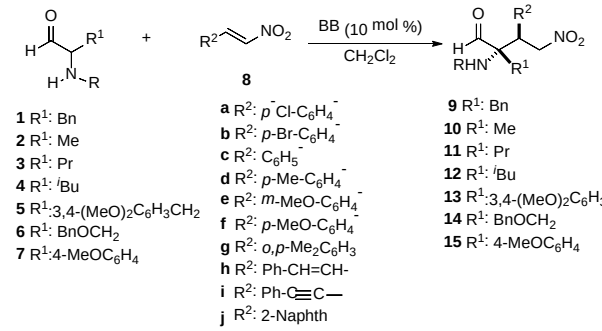
Entry	Cat.	Base (mol%)	T (ºC)	T(h)	Conv.[b] (%)	9Aa (dr)[c]	16a
1	Et_3N	20	rt	17	31	>95 (58:42)	<5
				41	62	84 (56:44)	16
2	$^iPr_2EtN$	20	rt	41	21	>99 (44:56)	<5
3	 DBU	10	0	1.5	<5 [d]	0	0
4	 R:Me, MTBD R:H, TBD	MTBD(10)	rt	20	<5 [d]	0	0
		TBD(10)	0	22	<5 [d]	0	0
5	Et_3N / 	20	rt	15	48	>99 (51:49)	<5
6	Et_3N / 	20	rt	15	69	>95 (45:55)	<5

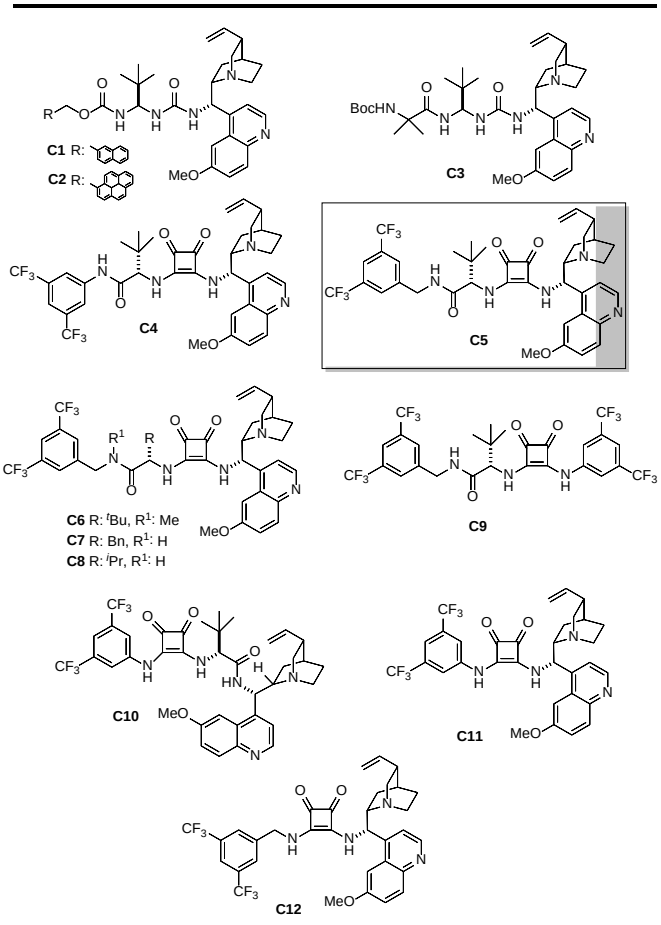
[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/ 3:1). [b] Conversion determined by the disappearance of the starting aldehyde. [c] Determined by ^{1}H-NMR analysis. [d] Nitrostyrene polymerized.

was noticed. Again, no reaction took place from **I** and **II** using Et_3N / thiourea or Et_3N / squaramide combinations. These results revealed that, i) under these smooth basic reaction conditions nitroolefin polymerization may be avoided and ii) product distribution from the reaction of these α-amino aldehydes with these acceptors could be perfectly controllable by simply using a Brønsted base/ H-bonding bifunctional catalyst to afford only the corresponding addition product and, most remarkable, iii) the free N-H bond in the starting aldehyde seems to be necessary for transient α-amino aldehyde enolate generation by means of weak Brønsted bases. Presumably, an intramolecular H-bonding interaction between the NH group and the carbonyl oxygen atom increases the Cα acidity of the α-amino aldehyde, albeit no enolate E/Z selectivity is produced. As it was suggested before, the α-chloro aldehyde **III**, Scheme 1, did not react either with nitrostyrene under similar reaction conditions.

Catalyst screening and reaction optimization

In view of the observations noted above, the next question we addressed was to establish which Brønsted base/ H-bonding bifunctional catalyst could control both reaction diastereo- and enantioselectivity. The study was initiated by examining the reaction of (±)-*N*-Boc phenylalaninal **1A** with nitroolefin **8a**, Scheme 2, using ureidopeptide derived Brønsted bases **C1**, **C2** and **C3**, previously reported by us, which proved to be effective in





Scheme2. Direct asymmetric Michael additions of α-amino aldehydes to nitroolefins promoted by Brønsted base catalysts **C1-C12**. BB= Brønsted base.

conjugate additions to nitroolefins.[25] However, in each case the product **9Aa** was produced with very poor diastereoselectivity, and negligible enantioselectivity (Table 2, entries 1-3). With the aim of improving stereocontrol we modified the catalyst by replacing the urea unit by a squaric acid moiety to increase H-bonding capability.[26,27] *L-tert*-Leucine derived catalysts **C4**, **C5**, and **C6**, were prepared[28] and, to our delight, better, not only diastereoselectivities, but also enantioselectivities were provided from these bifunctional Brønsted bases (entries 4-6). The best result was attained with catalyst **C5** that afforded product **9Aa** in a diastereomeric ratio of 90:10 and in 98% *ee* for the major isomer.[29] While similar result was achieved from catalyst **C4** longer time was required for reaction completion (entry 4).

Table 2. Catalyst screening for the 1,4-addition of (+)-*N*-Boc-phenylalaninal **1A** to nitroolefin **8a** to afford **9Aa**.[a]

Entry	Cat.	t(h)	T(ºC)	Conv. (%)[b]	Yield (%)[c]	dr[d]	ee[e]
1	**C1**	63	rt	88 (61)	nd	39:61	nd
2	**C2**	39	rt	29 (2)	nd	64:36	nd
3	**C3**	39	rt	71(40)	31	50:50	37
4	**C4**	45	rt	>99(8)	77	89:11	98
5	**C5**	24	rt	96(9)	91	90:10	98
6	**C6**	23	rt	97(2)	81	85:15	97
7	**C7**	15	rt	90(3)	70	82:18	91
8	**C8**	24	rt	88(12)	69	86:14	94
9	**C9**	15	rt	0 [f]	0	--	--
10	**C10**[g]	120	rt	58(no)	33	70:30	25
11	**C11**[g]	21	rt	92(28)	55	68:32	81
12	**C12**	16	rt	68(no)	64	66:34	73

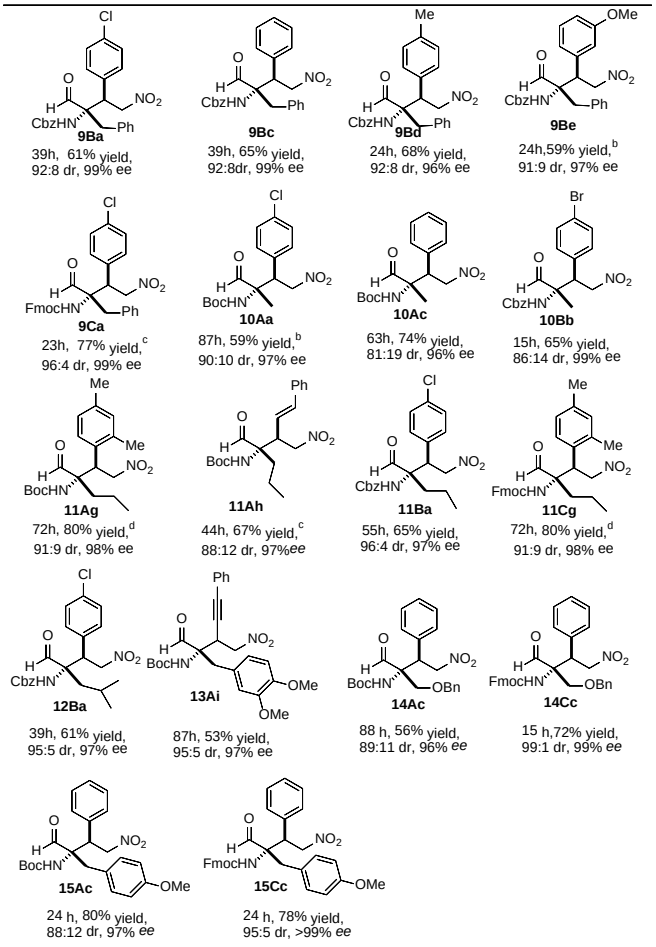
[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets the percentage of the product coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC. Data in parenthesis refer to the minor diastereomer. nd: not determined. no: not observed. [f] In the presence of Et_3N (10 mol%) after 39 h 26% conversion and 57:43 dr were observed. In the presence of $^iPr_2EtN$ (10 mol %) after 15 h 23% conversion and 52:48 dr were detected. [g] 20 mol% catalyst was used.

Further experiments with the *L*-phenylalanine and *L*-valine derivatives **C7** and **C8** revealed that both are equally effective as the *tert*-leucine derived catalyst **C5** in terms of diastereoselectivity, but slightly worse regarding enantioselectivity. Catalyst **C9,** lacking the Brønsted base,[28a-e] was completely unfruitful in promoting the reaction even when an external base was employed as co-catalyst (entry 9). Importantly, not only the cinchona base is needed for reaction effectivity but also its position in the catalyst seems to be critical for efficient enantiocontrol as the result obtained using the known catalyst **C10**[30] illustrates (entry 10). Therefore, this catalyst conception in which the squaramide moiety is in between the α-amino acid residue and the Brønsted base seems to be quite promising. In support of this assumption is the fact that during the preparation of this manuscript two independent works concerning this subclass of squaramide catalysts have appeared.[31] Further proof of the robustness of this subclass of catalysts was provided from the reaction of **1A** with **8a** using the commercially available standard squaramides **C11** and **C12** which led to **9Aa** in lower levels of diastereo- and enantioselectivity.[32] On the other hand, while these reactions were performed in dichloromethane as solvent, 1,2-dichloroethane and acetonitrile may also be employed with equal effectiveness but toluene and tetrahydrofuran were inefficient in terms of either reaction conversion or side product formation.[28]

Reaction Scope. Variation of aldehyde and nitroolefin

As the results in Table 3 show, the reaction promoted by catalyst **C5** was equally efficient for nitroolefins (**8b**-**h**) carrying both electron-withdrawing and electron-donating substitution patterns at the aromatic ring, independently of their *o*-, *m*-, or *p*- position.

Table 3. Scope of the Michael reaction of α-amino aldehydes **1-7** with nitroolefins **8** assisted by **C5**.[a]

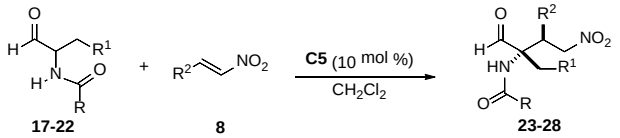


[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major isomer. Diastereomeric ratio determined by ^{1}H NMR (300 MHz) analysis on the crude product. Enantiomeric excess determined by chiral HPLC. [b] Less than 5% of the product coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization was observed. [c] Yield of the isolated two isomers. [d] Reaction was performed using 20 mol% of catalyst.

In general, the reactions were performed at 0.2 mmol scale but increasing the scale up to 1 mmol same results were attained without loss of stereochemical information. α-Amino aldehydes with usual *N*-protecting groups i.e. *N*-Boc, *N*-Cbz and *N*-Fmoc, participate in such a reaction to give the adducts **9**-**15** in very good *anti*-diastereoselectivity and excellent enantioselectivity for the major isomer. As a general trend, reactions with *N*-Fmoc α-amino aldehydes proceeded somewhat faster, typically within 20-24 h, than the related *N*-Boc and *N*-Cbz aldehydes. An initially limited applicability of this catalyst system was observed. α-Amino aldehydes with bulky side chains such as *N*-protected *tert*-leucinal and valinal were quite unreactive under the above reaction conditions independently of the protective group. The relative and absolute configuration of compound **9Bd** was established by X-ray single crystal structure analysis and that of the remaining adducts was assumed on the basis of an uniform reaction mechanism.[33]

The approach may also be extended to α-amino aldehydes bearing aromatic and aliphatic *N*-acyl groups, Table 4, to furnish

Table 4. Reaction of α-amino aldehydes **17**-**22** with nitroolefins **8**.[a]



17-22 **8** **23-28**

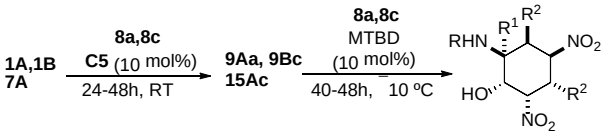
Comp.	R	R^1	R^2	t(h)	Yield (%)[b]	dr[c]	ee[d]
23	2-pyridyl	Ph	Ph	63	40[f]	68:32	86
24	Ph	Ph	4-ClC_6H_4	24	71[f]	93:7	>99[e]
25	2-MeC_6H_4	4-$MeOC_6H_4$	3$MeOC_6H_4$	48	77	85:15	99
26	4-BrC_6H_4	4-$MeOC_6H_4$	4-MeC_6H_4	82	64	93:7	99
27	$PhCH_2$=CH_2	$(Me)_2CH$	2-Naphth	64	45	96:4	>99
28	CH_3	Ph	4-ClC_6H_4	40	43	93:7	>99

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Yield of the isolated major *anti* isomer. [c] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] Enantiomeric excess determined by chiral HPLC. [e] 5% of the cyclisized product coming from a tandem Michael-Michael-Henry reaction. [f] Yield of the isolated two isomers.

the corresponding products with very good diastereo- and enantioselectivity as well. Exception was α-aminoaldehyde **17** bearing the pyridine ring, which afforded product **23** with lower diastereomeric ratio albeit in acceptable *ee* for the major isomer.

Adducts Elaboration: Fully Cα substituted amines

In general we employed in these reactions 1.3-1.5 equiv. of the corresponding nitroolefin, but using 3 equiv. in combination with an amine base, the intermediate adducts may be converted, as noted at the onset of this work, into otherwise difficult to synthesize fully substituted cyclohexylamines bearing a tetrasubstituted stereogenic Cα-carbon. For example, Scheme 3, **16a** was prepared, in non racemic form, from the reaction of α-amino aldehyde **1A** with the nitroolefin **8a** using catalyst **C5** and then triethylamine (TEA), 30 mol%, for the last two Michael-Henry reaction steps. The product was obtained, in a single pot operation as an almost equimolar mixture of diastereomers epimeric at Cγ . The ratio of diastereomers could be increased

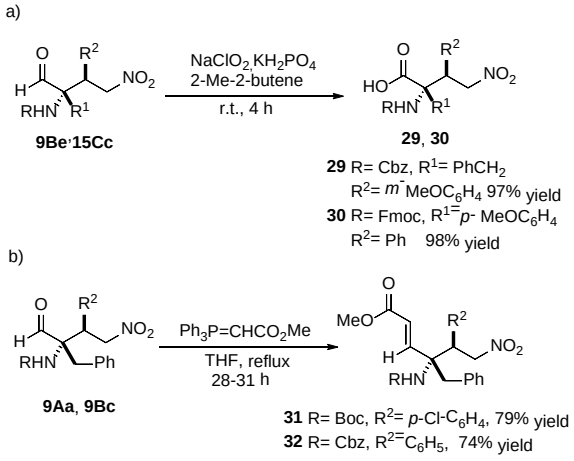


a R= Boc R^1= Bn R^2 = 4-ClC_6H_4, 85:15 dr, 81% yield
b R= Cbz R^1= Bn R^2 = Ph 80:20 dr , 83% yield
c R= Boc R^1= 4-$MeOC_6H_4CH_2$ R^2 = Ph 88:12 dr , 82% yield

Scheme 3. One-pot procedure for the preparation *of* fully substituted cyclohexylamines tetrasubstituted at C_1.

to 85:15 using MTBD (10 mol%) as base and carrying out the reaction at -10º C.[34] Cyclohexylamines **16b** and **16c** were also produced with similar results in one pot operation from **1B** and **7A** and nitroolefin **8c**. Under these latter conditions polymerization of the corresponding nitroolefin also occurred although to small extent. In each case, the configuration of the isolated adducts was established by NOE experiments.[28]

On the other hand, simple exposure of adducts **9Be** and **15Cc** to oxidative standard conditions, Scheme 4a, provided the *N*-acyl quaternary α-amino acids **29** and **30** with two adjacent, quaternary and tertiary, stereocenters in essentially quantitative yields. In addition to these transformations, Wittig reaction, Scheme 4b, provides *N*-protected allyl amines, fully substituted at Cα, ready for subsequent functional group elaborations. [35]



Scheme 4. a) Access to quaternary α-amino acids. b) Access to fully α-substituted allylamines amines.

Theoretical proves and mechanistic observations

A rationale to the above experimental observations is provided (Figure 3) within the DFT framework[36] by the calculated energies of the TS for the carbon-carbon bond forming step in its four possible combinations. In a first instance, we examined the non catalyzed reaction between *N*-Boc phenylalaninal **1A** and nitrostyrene **8c** and the calculations showed the existence of an intramolecular H-bonding interaction in transition states **TS1** and **TS2** coming from the aldehyde *Z*-enolate, which renders them energetically favored over **TS3** and **TS4** (*E*-enolates). In addition,

the energy barrier for the approach of the *Z*-enolate to the prochiral *Si* face of **8c** (**TS1**) was found to be the less energetic one, although the energetic difference with **TS2** (reaction with the *Re* prochiral face of **8c**) is only of 0.7 kcal mol^{-1} and it will be associated to a lower theoretical diasteromeric ratio (dr_{theor}~ 76:24). To get further insight into the catalyst behavior we next studied the transition states for the same reaction in the presence of catalyst **C5**. The first question to elucidate was the preferred H-bond pattern formed between the catalyst and both substrates in

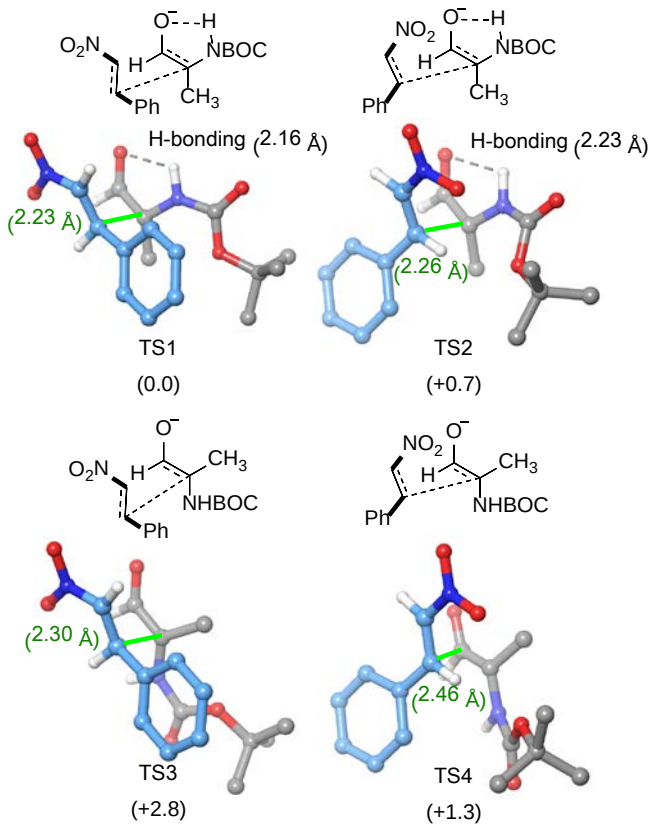


Figure 3. Computed possible transition states for the non catalyzed reaction of *N*-Boc-alaninal **1A** and nitrostyrene **8c**. Relative Gibbs free energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K).

the TS corresponding to the C−C bond forming step. In this respect, up to (at least) three different ternary complexes (A,[37] B[38] and C,[39] Figure 4) have been proposed for reactions involving noncovalent cooperative activation of the intervening

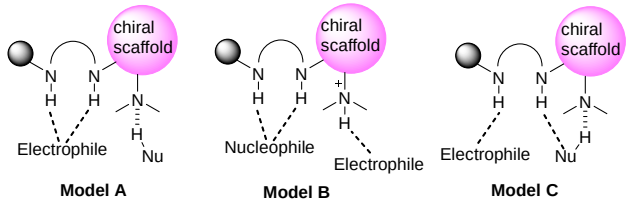


Figure 4. Three alternative substrate-catalyst combinations proposed for bifunctional Brønsted base activation mode.

nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)-tertiary amine catalyst. In most cases, moreover, different activation modes have been invoked for reactions involving quite similar nucleophile and/or electrophile partners.[40]

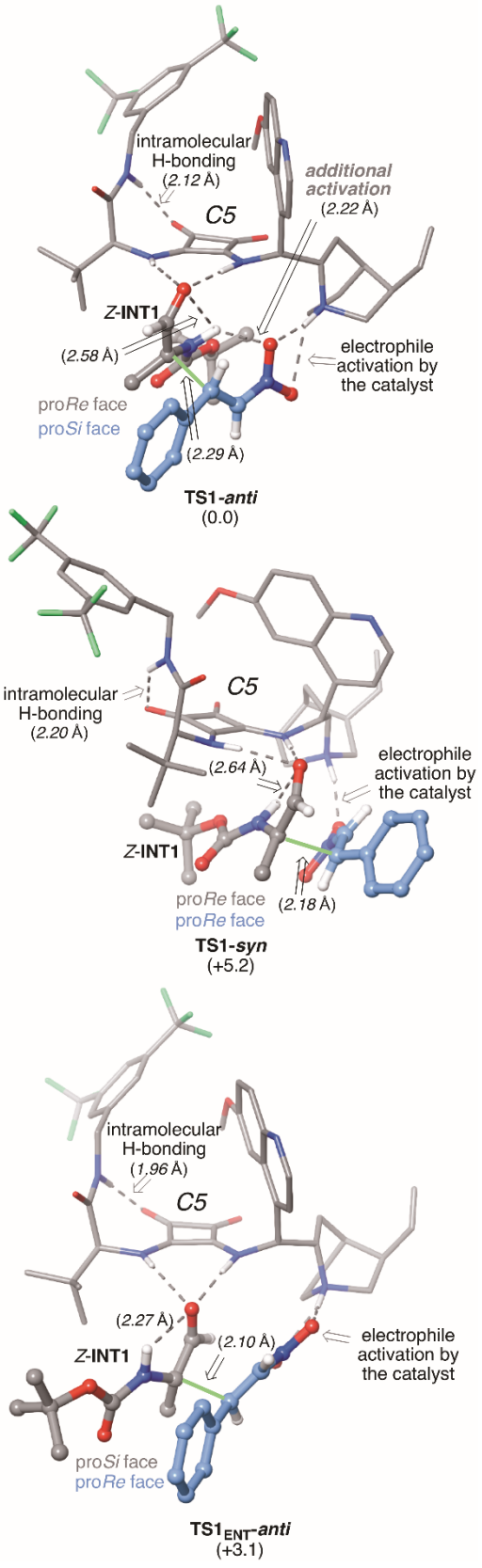


Figure 5. Main geometrical features and relative Gibbs free energies of least energetic transition structures **TS1** and **TS2** associated with the reaction of **1A** and **8c** catalyzed by **C5** according to Pápai's model. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in blue and grey respectively.

different reactions within this catalysis category seems to be still open and more data are desirable. For the study we assumed Curtin-Hammet kinetics in which the product ratio should depend on the free Gibbs activation energy difference of the corresponding transition structures. Interestingly, with catalyst **C5** a strong H-bonding interaction between the NH coming from the *tert*-leucine residue and the carbonyl of the squaramide (1.9-2.1 Å) was observed with negligible variations in the distance in each model.

A direct consequence of this intramolecular binding is that whilst increasing H-bonding capability,[41] the catalyst adopts a fix conformation wherein the position of the *tert*-butyl group seems to be important for facial selectivity. In fact, commercially available standard squaramides **C12** and **C13** (entries 12-13, Table 1) lacking this intramolecular H-bonding interaction provided adduct **9Aa** in lower levels of diastereo- and enantioselectivity. The study shows that, in the least energetic transition structures, (Figure 5), the catalyst-reagents coordination pattern follows Papai´s model B (**TS1**) where the nucleophile (enolate *Z*-**INT1**) interacts with the squaramide core of **C5**, and the electrophile (**8c**) is activated by H-bonding interaction with the cinchona moiety of **C5**. As previously observed on the non catalyzed reaction, here again the transition states involving the *Z*-enolate are less energetic than those involving the *E*-enolate and in all of them the intramolecular aldehyde H-bond interaction between the carbonyl oxygen atom and the NH is maintained. In addition, considerable energetic discrimination over the possible approach over the pro*Si* and pro*Re* faces of **8c** was obtained as consequence of an additional H-bonding interaction between the NH group of **Z-INT1** and the nitro group of **8c** found in **TS1-*anti*** (2.22 Å) that is not present in **TS1-*syn***, thus favoring formation of *anti*-Michael adducts. This result clearly supports the putative α-amino aldehyde intramolecular H-bonding as key preorganizational element. In addition, in all transition structures a pseudo-eclipsed conformation between the new C–C bond was found, a structural feature that may justify the absence of reaction of sterically hindered aldehydes, *vide supra*. Finally, in **TS1ENT-*anti***, the least energetic TS leading to the 2*R*,3*R* *anti*-Michael adduct, the strong intramolecular H-bonding interaction that fixes **INT1** in a *Z* conformation, places the N–H bond of **Z-INT1** far away of the squaramide core and more importantly, of the electrophile. In that conformation the long distance between that N–H bond and the nitro group of **8c** avoids any interaction between them. As a consequence, **TS1ENT-*anti*** is 3.1 kcal mol^{-1} less stable than **TS1-*anti*** that provides the experimentally observed 2*S*,3*S* *anti*-Michael adduct.

Conclusion

In summary, we have demonstrated that asymmetric α-functionalization of α-branched *N*-acyl amino aldehydes may be accomplished using Brønsted base non-covalent catalysis. The method is operationally very simple and employs a readily available bifunctional Brønsted base catalyst enabling direct generation of a transient aldehyde enolate ion pair which reacts with nitroolefins in high diastereo- and enantioselectivity. Therefore, this realization complements the covalent enamine activation approach and represents a practical direct entry for the stereoselective construction of α-amino aldehydes and derivatives therefrom featuring two vicinal quaternary and tertiary carbon stereocenters. The present work underscores for the first time, from both theoretical and experimental standpoints, the role of an internal H-bonding as key preorganizational element during aldehyde enolate alkylation as well as a basis for expanding the chemistry of α-amino aldehydes beyond the limits of their general and quite exclusive use as electrophiles.[42]

Acknowledgements

Support has been provided by the University of the Basque Country UPV/EHU (UFI QOSYC 11/22), Basque Government (GV grant IT1236-19), and Ministerio de Ciencia e Innovación (MINECO, Grant PID2019-109633GB-C21), Spain. We appreciate the experimental support of J. Izquierdo from this laboratory. A. G. thanks Basque Government. We also thank SGIker (UPV/EHU) for providing NMR, HRMS, X-Ray, and computational resources.

Keywords: Brønsted bases • squaric acid peptides • quaternary stereocenters • H-bonding • *anti* γ-nitroaldehydes

[1] For reviews on α-amino aldehydes, see: a) R. Hili, S. Baktharaman, A. K. Yudin, *Eur. J. Org. Chem.* **2008**, 5201–5213; b) D. Gryko, J. Chalko, J. Jurczak, *Chirality*, **2003**, *15*, 514–541; c) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561– 2576; d) M. T. Reetz, *Chem. Rev*. **1999**, *99*, 1121–1162; e) L. E . Fisher, J. M . Muchowski; *Org. Pre. Proc.* **1990**, *22*, 399–484; f) J. Jurzak, A. Golebiowski, *Chem. Rev*. **1989**, *89*, 149–164.

[2] T. C. Nugent, Chiral Amine Synthesis: Methods, Developments and Applications; Wiley-VCH: Weinheim, Germany, **2010**.

[3] J. Zhang, J. Jia, X. Zeng, Y. Wang, Z. Zhang, I. D. Gridnev, W. Zhang, *Angew. Chem.* **2019**, *131*, 11629–11636, *Angew. Chem. Int. Ed.* **2019**, *58*, 11505–11512.

[4] Direct α-functionalization of aldehydes: a) J. Vesely, R. Rios, *ChemCatChem* **2012**, *4*, 942–953; b) A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron* **2014**, *70*, 2491–2513; c) D. M. Hodgson, A. Charlton, *Tetrahedron* **2014**, *70*, 2207–2236.

[5] Representative examples: a) T. Baumann, M. Baechle, C. Hartmann, S. Braese, *Eur. J. Org. Chem.* **2008**, *13*, 2207─2212; b) S.-G. Kim, T.-H. Park, *Tetrahedron Lett.* **2006**, *47*, 9067–9071; c) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429─431; d) J. T. Suri, D. D. Steiner, C. F. Barbas III. *Org. Lett.* **2005**, *7*, 3885─3888. Recent reviews: e) T. Vilaivan, W. Bhanthumnavin, *Molecules* **2010**, *15*, 917; f) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637─1656; g) F. Zhou, F.-M. Lia, J.-S. Yu, J. Zhou, *Synthesis* **2014**, *46*, 2983; h) B. Maji, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 753; i) P Kumar, B. M. Sharmaa, *Synlett* **2018**, *29*, 1944─1956; j) ref.4a.

[6] For more details on these problems, see: a) ref.4c; b) C. Mazet, *Chimia* **2013**, *67*, 658–662.

[7] S. Wenglowsky, L. S. Hegedus, *J. Am. Chem. Soc.* **1998**, *120*, 12468–12473.

[8] Representative examples: a) A. Dondoni, D. Perrone, P, Merino, *J. Org. Chem.* **1995**, *60*, 8074–8080; b) C.- K. Jung, M. J. Krishe, *J. Am. Chem. Soc.* **2006**, *128*, 17051–17056; c) A. Nakano, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2006**, *8*, 5357–5360; d) P. Haghshenas, M. Gravel, *Org. Lett.* **2016**, *18*, 4518–4521; e) A. Duan, J. S. Fell, P. Yu, C. Y.-H. Lam, M. Gravel, K. N. Houk, *J. Org. Chem*. **2019**, *84*, 13565−13571.

[9] Reviews on stereoselective synthesis of α-amino acids: a) C. Cativiela, M. Ordoñez, J. L. Viveros-Ceballos *Tetrahedron* https://doi.org/10.1016/j.tet.2019.130875g; b) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem*. **2005**, 5127–5143; c) H. Vogt, S. Brase, *Org. Biomol. Chem.* **2007**, *5*, 406–430; d) R. A. Monsey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762; e) K. Bera, I. N. N. Namboothiri, *Asian J. Org. Chem*. **2014**, *3*, 1234–1260. Reviews on catalytic approaches: f) C. Najera, J. M. Sansano, *Chem. Rev.* **2007**, *107*,

4584–4671; g) A. E. Metz, M. C. Kozlowski, *J. Org. Chem*. **2015**, *80*, 1–7.

[10] Quaternary stereocenters in acyclic systems, see: a) J. Feng, M. Holmes, M. J. Krische, *Chem. Rev*. **2017**, *117*, 12564–12580; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593–4623. Also, see: c) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res*. **2015**, *48*, 740–751; d) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181–191. Organocatalytic Formation of Quarternary Stereocenters: e) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614.

[11] Reviews: a) P. P. de Castro, A. G. Carpanez, G. W. Amarante, *Chem. Eur. J*. **2016**, *22,* 10294–10318; b) A. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720–734; c) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008,** *19*, 2755–2762.

[12] a) Y. Wang, X. Song, J. Wang, H. Moriwaki, V. A. Soloshonok, H. Liu, *Amino Acids* **2017**, *49*, 1487–1520; b) Y. Yamashita, S. Kobayashi, *Chem. Eur. J.* **2013**, *19*, 9420–9427; c) M. J. O'Donnell, *Tetrahedron* **2019**, *75*, 3667–3696.

[13] a) S. A. Moteki, S. Xu, S. Arimitsu, K. Maruoka, *J. Am. Chem. Soc.* **2010**, *132*, 17074–17076. Also, see: b) K. Nakashima, M. Murahashi, H. Yuasa, M. Ina, N. Tada, A. Itoh, S. Hirashima, Y. Koseki, T. Miura, *Molecules* **2013**, *18*, 14529–14542; c) Y. Kanada, H. Yuasa, K. Nakashima, M. Murahashi, N. Tada, A. Itoh, Y. Koseki, T. Miura, *Tetrahedron Lett*. **2013**, *54*, 4896–4899.

[14] For selected reviews on enamines, see: a) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) L. Albrecht, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2014**, *20*, 358–368. c) P. Melchiore, *Angew. Chem.* **2012**, *124*, 9886–9909, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770. For enamine catalysis in Michael additions, see: d) N. Mase in *Asymmetric Organocatalysis 1: Brønsted Base and Acid Catalysts, and Additional Topics* (Ed.: B. List), Thieme, Stuttgart, **2012**, pp. 135–216.

[15] For enamine reactions of α-aminoacetaldehyde, see: a) R. Thayumanavan, F. Tanaka, C. F. Barbas, III, *Org. Lett.* **2004**, *6*, 3541–3544; b) T. Urushima, Y. Yasui, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 2966–2969; c) T. Kano, R. Sakamoto, M. Akakura, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 7516–7520; d) K. Albertshofer, R. Thayumanavan, N. Utsumi, F. Tanaka, C. F. Barbas, III, *Tetrahedron Lett.* **2007**, *48*, 693–696; e) S. Belot, S. Sulzer-Mosse, S. Kehrli , A. Alexakis, *Chem*. *Commun*. **2008**, 4694–4696; f) T. Kano, R. Sakamoto, K. Maruoka, *Org. Lett.* **2014**, *16*, 944–947; g) T. Sandmeier, S. Krautwald, H. F. Zipfel, E. M. Carreira, *Angew. Chem.* **2015**, *127*, 14571–14575, *Angew. Chem. Int. Ed.* **2015**, *54*, 14363–14367.

[16] Z.-L. Guo, J.-H. Xue, L.-N. Fu, S.-E. Zhang, Q.-X. Guo, *Org. Lett.* **2014**, *16,* 6472–6475.

[17] L. Song, L. Gong, E. Meggers, *Chem*. *Commun*. **2016**, *52*, 7699–7702.

[18] For selected reviews on Brønsted base-promoted asymmetric reactions: a) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, 37, 621–631; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; c) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200; d)"Cinchona Alkaloid Organocatalysts": R. P. Singh, L. Deng in Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 41–118; e) "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.

[19] Q.-Z. Li, Y. Liu, H.-J. Leng, J.-L. Li, *Synlett* **2018**, *29*, 2601–2607.

[20] For selected discussions on the configurational stability of α-amino aldehydes, see: a) W. D. Lube, H. Rapoport, *J. Am. Chem. Soc.* **1987**, *109*, 236–239; b) A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman, S. Kwon, *Tetrahedron Lett.* **2000**, *41*, 1359–1362; c) A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman, S. Kwon, *Org. Lett.* **2000**, *2,* 3337–3340.

[21] 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. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601; c) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. J. Ramón, *Molecules* **2017**, *22*, 895–946.

[22] For the use of γ -nitroaldehydes in synthesis, see: a) A. Y. Sukhorukov, A. A. Sukhanova, S. G. Zlotin, *Tetrahedron*, **2016**, *72*, 6191–6281; b) G. Koutoulogenis, N. Kaplaneris, C. G. Kokotos, *Beilstein J. Org. Chem*. **2016**, *12*, 462–495; c) A. Z.Halimehjani, I. N. N. Namboothiri, S. E. Hooshmanda, *RSC Adv.* **2014**, *4*, 31261–31299; d) X. Yang, J. Wang, P. Li, *Org. Biomol. Chem.* **2014**, *12*, 2499–2513; e) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909–1930.

[23] For selected reviews on organocatalytic cascade or domino reactions involving aldehydes and nitroalkenes, see: a) X. Li, L. Guo, C. Peng, B. Han, *Chem.Chem. Rec*. **2019**, *19*, 394–423; b) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832–1844; c) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; e) H. Pellissier, *Asymmetric Domino Reactions*, RSC Publishing, Cambridge, **2013**. Pioneer work: f) D. Enders, M. R. M. Hgttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863. For direct Michael-Michael-Henry reactions, see: g) Z. Mao, Y. Jia, Z. Xu, R.Wang, *Adv. Synth. Catal.* **2012**, *354*, 1401–1406; h) S. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soos, *Org. Lett.* **2011**, *13*, 5416–5419; i) Y. Chen, X. Liu, W. Luo, L. Lin, X. Feng, *Synlett* **2017**, *28*, 966–969; j) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem.* **2017**, *129*, 2091–2095; *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.

[24] The reaction of either **I** or **II** with **8a** using these guanidine bases also proceeded but accompanied of nitroolefin polymerization. For details on nitroolefin polymerization, see: T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami, Y. Hatanaka, *Org. Lett.* **2016**, 18, 646–649.

[25] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, I. Olaizola, A. Mielgo, R. López, C. Palomo, *Angew. Chem.* **2013**, *125*, 12062–12067; *Angew. Chem. Int. Ed.,* **2013**, 52, 11846–11851.

[26] Pioneering works on squaramides: 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 as bifunctional Brønsted bases, 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) A. Rouf, C. Tanyeli, *Curr. Org. Chem.* **2016,** *20,* 2996-3013; f) P. Chauhan, S. Mahahan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281; g) L. A. Marchetti, L. K. Kumawat, N. Mao, J. C. Stephens, R. B. P. Elmes, *Chem.* **2019**, *5*, 1398–1485.

[27] Squaramides containing amino acids and/or peptides acting as H-bond donors 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. Kumar, S. Mukherjee, *Chem. Commun.* **2013**, *49*, 11203–11205. For other applications,see: f) M. B. Onaran, A. B. Comeau, Ch. T. Seto, *J. Org. Chem.* **2005**, *70*, 10792–10802; g) P. Sejwal, Y. Han, A. Shah, Y.-Y. Luk, *Org. Lett.* **2007**, *9,* 4897–4900; h) T. Shinada, T. Ishida, K. Hayashi, Y. Yoshida, Y. Shigeri, Y. Ohfune, *Tetrahedron Lett.* **2007**, *48*, 7614–7617; i) P. M. C. Glória , J. Gut , L. M. Gonçalves , P. J. Rosenthal , R. Moreira, M. M. M. Santos *Biorg. & Med. Chem.* **2011**, *19*, 7635–7642; j) 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; k) L. Martinez-Crespo, E. C. Escudero-Adán, A. Costa, C. Rotger, *Chem. Eur. J.* **2018**, *24*, 17802–17813.

[28] See the Supporting Information.

[29] When the reaction of **1A** and **8** was carried out with the analogous catalyst of **C5** incorporating *D-tert*-leucine instead of *L-tert*-leucine lower levels of diastero- and enantioselectivity were observed, revealing **C5** as the matched combination.

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

[31] a) U. Farid, M. L. Aiello, S. J. Connon, *Chem. Eur. J.* **2019**, *25*, 10074–10079 ; b) D. Majee, S. Jakkampudi, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2019**, *21*, 9166−9170.

[32] Standard thiourea- and urea- based bifunctional Brønsted bases also provided poorer results. See the Supporting Information for details.

[33] The relative *anti* configuration was designated according to Masamune´s convention, see: S. Masamune, T. Kaiho, D. S. Garvey, *J. Am. Chem. Soc.* **1982**, *104*, 5521–5523. The absolute configuration was established by a single- crystal X-Ray structure analysis of compound **9Bd**. CCDC 1982135 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre. See the Supporting Information for details.

[34] Experiments carried out with cycloadduct **16a** as a 73:27 mixture of diastereomers in the presence of 10 % MTBD at –10 ºC for 1.5 h revealed the absence of epimerization, as the adduct was recovered in 71:29 diastereomeric ratio. However, after allowing the mixture to reach room temperature and further stirring for 1 h, adduct **16a** was recovered in a 62:38 diastereomeric ratio together with a 19% of the adduct coming from the first Michael addition. Worth of mention is the fact that adducts on Table 3 obtained from the first Michael addition are stable after stirring in CH_2Cl_2 in the presence of 10 mol% of catalyst **C5** at rt for 116 h.

[35] For the chemistry of allylamines, see: S. Nag, S. Batra, *Tetrahedron* **2011**, *67*, 8959–9061.

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

[37] 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.

[38] a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160; b) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631–5639.

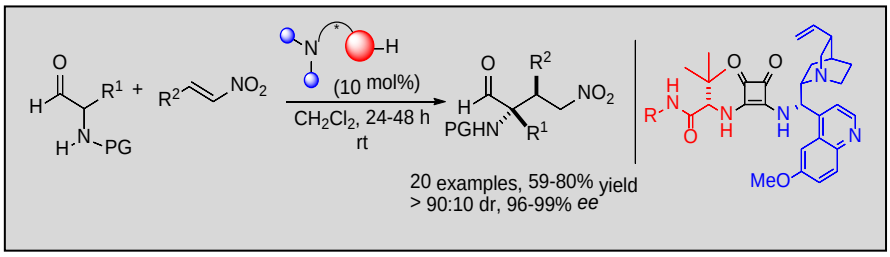
[39] J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. E. Wang, *J. Org. Chem.* **2012**, *77*, 9813–9825.

[40] Vinylogous Michael addition to nitroolefins: Model A, a) C. Curti, L. Battistini, A. Sartori, G. Rassu, G. Pelosi, M. Lombardo, F. Zanardi, *Adv. Synth. Catal*. **2018**, *360*, 71–721. Vinylogous Michael addition to enones: Model C, b) ref. 39. Michael addition to nitroolefins: Model B, c) ref. 38

[41] Strategies for Enhanced Hydrogen-Bond Donor Catalysts: a) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, *13*, 2633–2646; b) T. James, M. Van Gemmeren, *B. List, Chem. Rev*. **2015**, *115*, 9388–9409.

[42] The tolerance of α-amino aldehydes to catalysts with different basicity strength also makes the use of less reactive acceptors, according to Mayr electrophilicity values, to be suitable. For example, while TEA was not effective, TBD promoted the reaction of phenyl vinyl ketone with **1A** leading to the corresponding adduct in 80% yield albeit in racemic form. See Supporting Information. For the Mayr electrophilicity scale, see: D. S. Allgäuer, H. Jangra, H. Asahara, Z. Li, Q. Chen, H. Zipse, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2017**, *139*, 13318−13329.

Entry for the Table of Contents



Harnessing limitations: The ease with which α-amino aldehydes racemize is the starting point for their utilization beyond the limits of their essentially exclusive use as electrophiles as it is exemplified in the reaction of *N*-alkoxycarbonyl α-amino aldehydes with nitroolefins assisted by a weak bifunctional Brønsted base to give quaternary α-amino aldehydes with an adjacent ternary stereogenic center.