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Asymmetric Organocatalysis

Asymmetric Assembly of All-Carbon Tertiary/Quaternary Nonadjacent Stereocenters through Organocatalytic Conjugate Addition of α-Cyanoacetates to a Methacrylate Equivalent

Igor Iriarte,[a] Silvia Vera,[a] Eider Badiola,[a] Antonia Mielgo,[a] Mikel Oiarbide,*[a] Jesús M. García,[b] José M. Odriozola,[b] and Claudio Palomo*[a]

Abstract: An efficient, highly diastereo- and enantioselective assembly of acyclic carbonyl fragments possessing nonadjacent all-carbon tertiary/quaternary stereoarrays is reported based on a Brønsted base catalyzed Michael addition/α-protonation sequence involving α-cyanoacetates and 2,4-dimethyl-4-hydroxypenten-3-one as novel methacrylate equivalent.

Introduction

Acyclic carbonyl compounds possessing multiple stereocenters are important building blocks for the construction of complex natural products and bioactive molecules. Huge advances have been made in the stereoselective synthesis of these stereoarrays, particularly carbonyl compounds with contiguous stereocenters at α,β- or β,γ-positions (**A** and **B**, Figure 1). In contrast, direct asymmetric entries to the α,γ-branched analogues **C**, bearing two nonadjacent stereocenters, are less common,[1] and rarely involve construction of a quaternary stereocenter as in **D**.[2,3] Among the few precedents, Deng reported a Brønsted base catalyzed Michael/α-protonation reaction cascade, which implies α-chloroacrylonitrile as the Michael acceptor,[4] and later on the group of Chen and Xiao described[5] a similar tandem reaction involving ethyl 2-phthalimidoacrylate or ethyl α-phosphonoacrylates as the doubly activated Michael acceptor (Figure 2). However, the extension of this methodology to inherently less reactive α-alkyl-substituted Michael acceptors, that is, methacrylates, remains challenging, despite the fact that the resulting α-alkyl- and more specifically α-methylcarbonyl units are present in a number of natural products and bioactive targets. In that respect, Kobayashi has reported[6] a $Ca(BOX)_2$-catalyzed (BOX = bis(oxazolidine)) conjugate addition of glycine Schiff bases to α-substituted acrylate derivatives, albeit no example involving generation of a quaternary center was gathered. More recently Pihko has described[7] enantioselective Mukaiyama–Michael addition reactions of methacrolein through iminium activation; however, this reaction led to an approximately 1:1 mixture of the two possible diastereomers. To the best of our knowledge, highly enantiose-

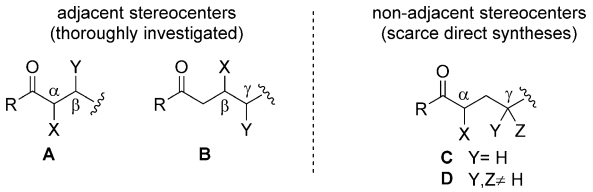


Figure 1. Acyclic carbonyl compounds with different stereoarrays.

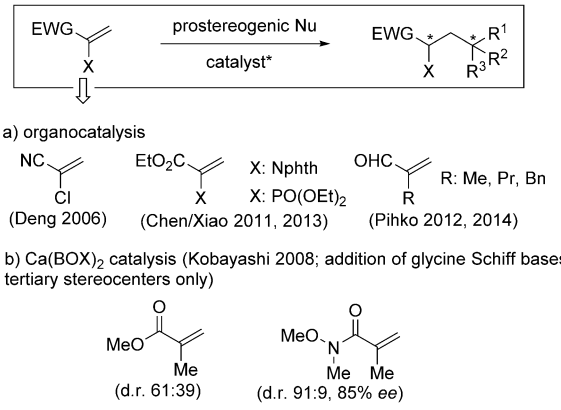


Figure 2. Advances in tandem addition/protonation approaches for the asymmetric assembly of α,γ-nonadjacent stereocenters.

[a] I. Iriarte, Dr. S. Vera, E. Badiola, Dr. A. Mielgo, Prof. M. Oiarbide, Prof. C. Palomo
Departamento de Química Orgánica I
Universidad del País Vasco UPV/EHU
Manuel Lardizabal 3, 20018 San Sebastián (Spain)
Fax: (+34) 943015270
E-mail: claudio.palomo@ehu.es

[b] Prof. J. M. García, Dr. J. M. Odriozola
Departamento de Química Aplicada
Universidad Pública de Navarra
31006 Pamplona (Spain)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/chem.201603082.

lective Michael reactions with methacrylates or equivalents to provide carbonyl compounds with all-carbon tertiary/quaternary nonadjacent stereocenters have not been realized yet. Here we present an effective asymmetric direct entry to such stereoarrays that is founded upon the development of a newly designed methacrylate equivalent in combination with Brønsted base catalysis.

Results and Discussion

Hypothesis and working plan

The challenge posed by α-alkyl-substituted Michael acceptors is not only associated to their attenuated reactivity against neutral C-pronucleophiles, but also concerns stereocontrol during the key C–C bond formation (step 1, Figure 3a) and the subsequent α-protonation (step 2).[8]

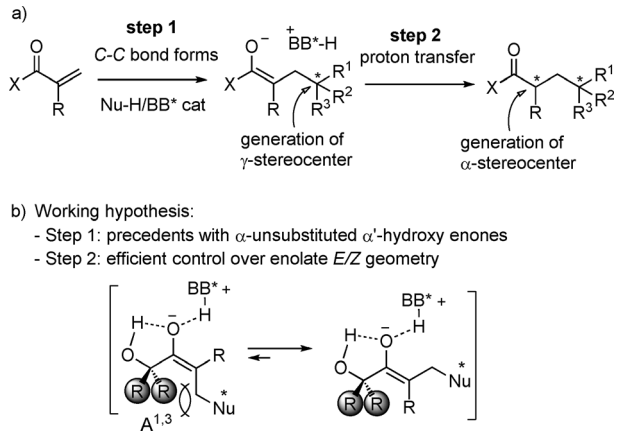
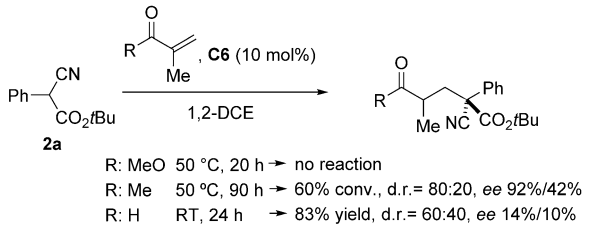


Figure 3. Construction of nonadjacent tertiary/quaternary stereocenters and working hypothesis for designed methacrylate equivalent.

Preliminary studies involving the reaction of 2-phenyl α-cyanoacetate **2a**[9] and some elementary α-substituted Michael acceptors revealed these difficulties. For instance attempts to react **2a** with methyl methacrylate in the presence of several mono- and bifunctional Brønsted base catalysts all led to recovery of unreacted material (Scheme 1). Under similar conditions, 3-methylbutenone resulted essentially unreactive at ambient temperature; 60% conversion was hardly achieved only after 90 h at 50 °C. Finally, methacrolein was more reactive, but led to unselective reaction.[7]



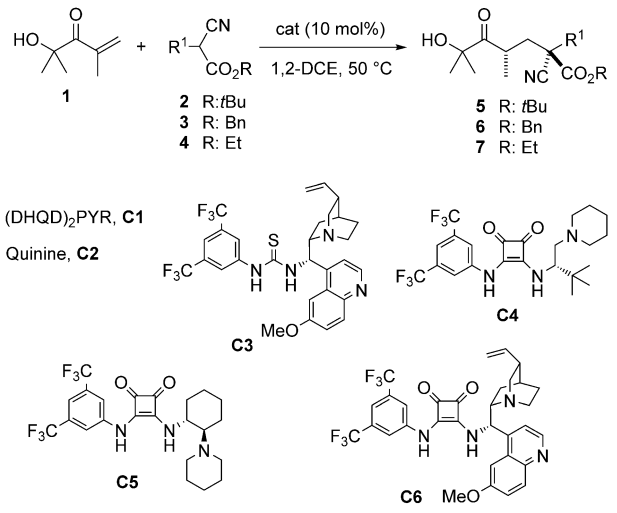
Scheme 1. Difficulties in the addition of α-cyanoester **2a** to α-methyl α,β-unsaturated ester, ketone or aldehyde under best reaction conditions.

Recently we have introduced α-unsubstituted α′-hydroxy enones as efficient acrylate equivalents in Brønsted base catalyzed enantioselective conjugate additions.[10] Both the remarkable reaction acceleration and the high level of asymmetric induction observed in these reactions were rationalized by assuming hydrogen-bond-mediated effective substrate–catalyst complexation, with the ketol moiety of substrate forming tight 1,4-proton chelates. Now we hypothesize that by using the parent α-substituted α′-hydroxy enones, the unique capacity of these type of bidentate substrates[11] to act as both hydrogen-bond donor and acceptor, in cooperation with a proper Brønsted base catalyst, may also be translated to the α-stereocenter-determining step 2. If so, a shortcut to the challenging construction of acyclic carbonyl adducts with nonadjacent stereocenters would be provided. Specifically, it is predicted that the evolved enolate from step 1 would preferentially adopt a *Z* configuration because of unfavorable $A^{1,3}$ strain in the chelated *E* form (Figure 3b), thus overcoming the problem of ill-defined enolate geometry in asymmetric α-protonations.[12,13] Eventually, the prevalence of such dynamic hydrogen-bond networks may also help during proton transfer (shuttle). To achieve high overall selectivity, however, both chiral units, namely the catalyst and the newly generated stereocenter at γ, have to work in concert in step 2, an inherent difficult of the process that at the outset remained unclear. In this respect, as far as we know, α-substituted α′-hydroxy enones have never been employed in catalytic asymmetric conjugate additions.[14]

Catalysts screening and reaction optimization

The investigation was started by studying the reaction of the newly prepared α′-hydroxy enone **1**[15] with α-substituted cyanoacetate **2a** in the presence of several bifunctional Brønsted bases (Scheme 2).[16] Among the catalysts examined, that is, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2PYR$; **C1**), quinine (**C2**), the thiourea-aminoquinine **C3**[17] and the squaramides **C4**,[18] **C5**,[19] and **C6**,[20] the last proved to be superior as shown in Table 1. Using this catalyst, the reaction between 2-phenyl α-cyanoacetate **2a** and **1** at ambient temperature afforded adduct **5a** with essentially perfect enantio- and diastereocontrol (d.r. > 99:1, 99% *ee*; entry 6). This result indicates that not only the initial addition that renders the γ-stereocenter, but also the subsequent α-protonation, both proceeded with remarkable face selectivity. Interestingly, this almost perfect chirality transfer was reproduced (entry 7) when the reaction was run at 50 °C, which allowed attaining full reaction conversion at shorter time (24 h).

Under these conditions (10 mol% **C6** in 1,2-DCE at 50 °C) the reaction of **1** worked equally well with an array of 2-aryl α-cyanoacetates **2** to afford the corresponding adducts **5** as essentially single diastereomer in yields within the range from 62% to 95% and *ee* values greater than 95% in most cases. As Table 2 shows, these results seem to be independent upon the meta/para substitution pattern of the aromatic ring or their electron donating/withdrawing character. Entry 6 was an ex-



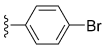
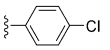
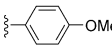
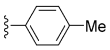
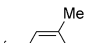
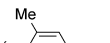
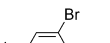
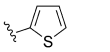
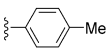
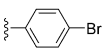
Scheme 2. Reaction of **1** with α-cyanoacetates catalyzed by chiral Brønsted bases.

Table 1. Catalyst screening for the reaction of **1** with **2a** ($R^1 = Ph$).[a]

	Catalyst	*t* [h]	Conv [%]	Yield [%][b]	d.r.	*ee* [%][c]
1	**C1**	72	100	72	70:30	30
2	**C2**	72	65	49	75:25	16
3	**C3**	72	70	46	80:20	68
4	**C4**	72	23	n.d.[e]	n.d.	n.d.
5	**C5**	40	100	75	75:25	−12
6[d]	**C6**	96	n.d.	40	>99:1	99
7	**C6**	24	100	81	>99:1	98

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C (molar ratio of **1**/**2a**/catalyst 1:1.5:0.1). [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at room temperature. [e] n.d.: not determined.

Table 2. Scope of the conjugate addition of α-cyanoacetates to **1**.[a]

	R^1	Product	*t* [h]	Yield [%][b]	d.r.	*ee* [%][c]
1		**5b**	24	69	98:2	98
2		**5c**	24	95	98:2	96
3		**5d**	40	70	>98:2	>98
4		**5e**	40	67	98:2	>98
5		**5f**	40	83	>98:2	97
6		**5g**	40	NR[d]	–	–
7		**5h**	16	62	97:3	96
8		**5i**	20	72	96:4	97
9		**6e**	24	76	90:10	92
10		**7b**	24	88	88:12	91

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C (molar ratio of **1**/cyanoester/**C6** 1:1.5:0.1). [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] NR: no reaction.

ception probably because of steric constraints imposed by the *ortho* substituent. Using the less sterically demanding benzyl and ethyl cyano esters **3** and **4**, a slight loss of stereoselection was produced (entries 9 and 10), albeit it was still acceptable. The configuration of adduct **5e** was established by a single-crystal X-ray analysis[21] and that of the remaining adducts by assuming a uniform reaction mechanism.

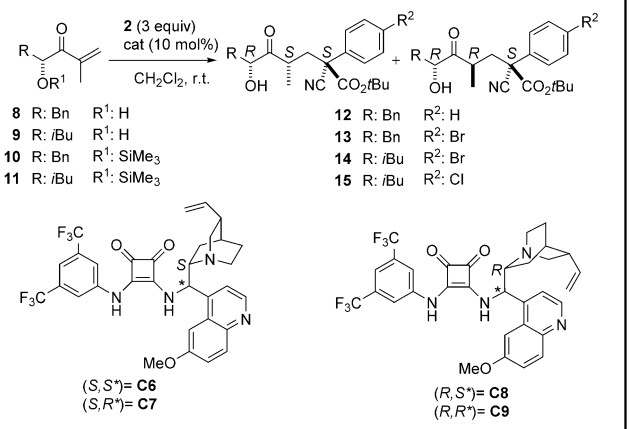
Double asymmetric induction

Given the paucity of methods for the construction of tertiary/quaternary nonadjacent stereocenters, this organocatalytic Michael/protonation cascade was next extended to chiral α′-oxy enones **8/9** and **10/11**,[22] a type of substrate that, as far as we know, have neither been previously investigated within the realm of organocatalysis.[23,24] As the results in Table 3 show, the stereochemical outcome of the reactions varies notably depending on the catalysts used. With Et_3N as the only promoter (entries 1 and 8), adducts **12** and **14** were produced with moderate diastereoselectivity (ratio of *RSS*/other isomers 60:40 and 71:29, respectively). Again, the best catalyst was **C6**, which afforded only two out of the four possible diastereomers in all the cases studied (entries 2, 3, 6, 9 and 10), with remarkable diastereoselectivity (*RSS*/*RRS*/others up to 91:9:0). Catalyst **C7** led to no reaction (entry 4), and **C8** and **C9** led to poor selectivity (entries 5 and 7). It is worth noting that in the above reactions *O*-silylated enones **10**/**11** behaved in a more superior fashion than hydroxy enones **8**/**9** as the results in entries 2/3 (d.r. of 67:32 and 89:11, respectively) and 8/9 (d.r. of 71:29 and 91:9, respectively) show.[25]

At this point it remained unclear whether the above substrate/catalyst combinations correspond to a matched stereochemical relationship. To answer that question, the reaction between **2a** and the (*S*)-configured ent-**10** was carried out in the presence of catalyst **C6**. As the data in Scheme 3 show, a 69:12:12:7 mixture of diastereomers was obtained, with (*S*,*S*,*S*)-**16** as the major product. By comparison with data in entry 3 of Table 3, it seems clear that the pair **10**/**C6**, with the configurations (*R*)-substrate/(*S*,*S*)-catalyst, corresponds to the matched combination. Experiments using bifunctional Brønsted base catalysts derived from other chiral 1,2-primary/tertiary diamines also revealed (*R*)-substrate/(*S*,*S*)-catalyst as the best combination to induce formation of adducts of *RSS* configuration.[26]

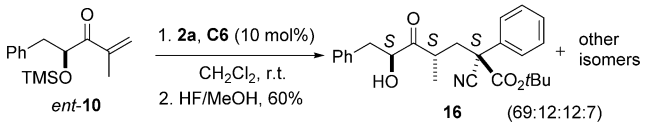
Given these observations and the absence of studies concerning double asymmetric induction in this field, we next examined briefly the reaction of chiral α′-hydroxy enones without substituents at Cα position. Under optimized conditions it was

Table 3. Michael addition/protonation cascade involving chiral enones (double asymmetric induction).[a]



	Enone	Cat	*t* [h]	Product	Yield [%]	*RSS*:*RRS*:others
1	**8**	Et_3N	24	**12**	75[b]	60:23:17:0
2	**8**	**C6**	24	**12**	70[b]	67:32:0:0
3	**10**	**C6**	60	**12**	73	89:11:0:0
4	**10**	**C7**	24	**12**	NR[e]	–
5	**10**	**C8**	64	**12**	70	49:41:10:0
6	**10**	**C6**	72	**13**	75[c]	83:17:0:0
7	**10**	**C9**	72	**13**	65[c,d]	22:21:57:0
8	**9**	Et_3N	24	**14**	83[b]	71:29:0:0
9	**11**	**C6**	72	**14**	90[c]	91:9:0:0
10	**11**	**C6**	72	**15**	80[c]	90:10:0:0

[a] Reactions conducted on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 using 3 equiv α-cyanoester **2a–c**. [b] Yield of isolated product (mixture of isomers). [c] Yield of isolated product (mixture of isomers) after desilylation with HF/MeOH. [d] Configuration of major isomer unknown. [e] NR: no reaction.



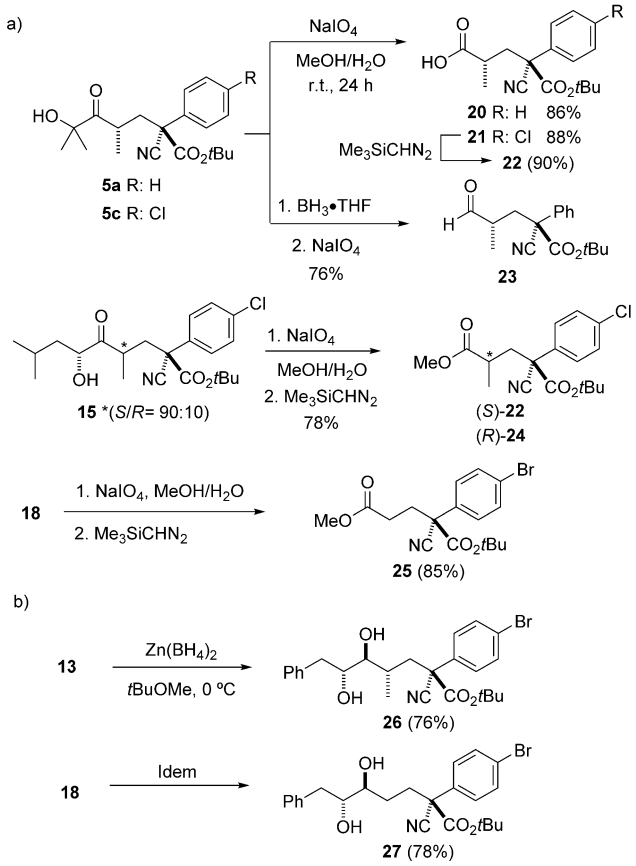
Scheme 3. Reaction involving substrate/catalyst mismatchaed combination. TMS: trimethylsilyl.

found that reaction of **17** with either **2b** or **2c** produced the corresponding adducts **18** and **19**, respectively, essentially as single diastereomers (Scheme 4). This result thus confirms that generation of the quaternary stereocenter proceeds with almost perfect asymmetric induction with catalyst **C6** for both α-substituted and unsubstituted enones.

Scheme 4. Generation of a quaternary γ-stereocenter in chiral α-unsubstituted α′-hydroxy ketones. TES: triethylsilyl.

Adduct elaboration and proposed reaction models

The results obtained are of special interest in that treatment of adducts **5a** and **5c** with $NaIO_4$ in $MeOH/H_2O$ provides the carboxylic acids **20** and **21** in 86% and 88% yield, respectively, along with acetone as the only organic side product formed (Scheme 5).



Scheme 5. Elaboration of adducts: a) conversion of ketol into carboxy and aldehyde functions; b) stereoselective 1,2-diol formation.

Acid **21** was transformed into its methyl ester **22** for comparative purposes, vide infra. Alternatively, reduction of the carbonyl group of **5a** followed by diol cleavage as above furnished the aldehyde **23** in 76% yield over the two steps. Thus, the lack of reactivity and selectivity associated with methacrylate esters and methacrolein (vide supra) may now be remediated with this new methacrylate equivalent. Finally, to confirm the stereochemical assignment of reactions involving double asymmetric induction (Table 3), adduct **15** (90:10 diastereomeric mixture) was subjected to the oxidative cleavage conditions to afford the same product **22** to that obtained from **5c**, along with the minor isomer **24**. Similarly, **18** upon oxidative cleavage of the ketol moiety as above and subsequent esterification of the resulting carboxylic acid provided the methyl

ester **25**. The absolute configuration of both **24** and **25** was established by chemical correlation.[26] In addition to the above transformations, stereoarrays bearing up to four stereogenic centers may also be produced from this approach. Thus, diols **26** and **27** were obtained as essentially single *anti*-diol isomer through reduction of the respective α′-hydroxy ketone **13** and **18** with $Zn(BH_4)_2$.[27]

The high fidelity with which chirality is transferred from the catalyst to the reaction products could be explained by the stereomodels depicted in Figure 4. By analogy to previously calculated TS geometries for the related conjugate addition of cyanoesters to α-unsubstituted enone analog to **1**,[10] ternary complex **A** would account for the conjugate addition step, which would proceed with the catalyst interacting with both reaction components through several hydrogen bonds. Once the addition adduct is formed, the local negative charge would no longer be located in the cyano esther moiety, but in the enolate site. This will weaken the hydrogen bond between the protonated quinuclidine and the cyano esther carbonyl. Finally, proton transfer, either directly from the protonated catalyst to the enolate or alternatively mediated by some proton–shuttle mechanism, would preferentially occur through the enolate *Re* face, as depicted in proposed model **B**.

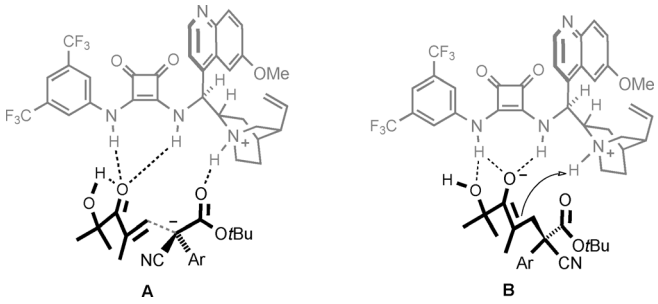


Figure 4. Proposed approaching models for the addition and protonation steps, respectively.

Conclusion

Direct approaches to the construction of acyclic carbonyl compounds with nonadjacent all carbon tertiary/quaternary stereocenters that proceed with high diastereo- and enantioselectivity are lacking. Here an effective solution to this longstanding problem is reported based on a bifunctional Brønsted base catalyzed Michael/α-protonation cascade that involves 2,4-dimethyl-4-hydroxypenten-3-one as design methacrylate equivalent. A key feature of this template is the ability to act as either hydrogen-bond donor or/and acceptor, a distinguishing feature among known bidentate enoate equivalents employed in organocatalysis.[11] Control experiments with other elementary Michael acceptors lacking such ambivalent character led to inferior reactivity and/or selectivity. This design element also demonstrated successful in Michael/protonation cascades involving chiral α′-oxyenones. In this latter case, double asymmetric induction occurs with substrate/catalyst matched combination providing adducts in up to >98:2 d.r. The obtained adducts are easily transformed into the corresponding acyclic carboxylic acids, aldehydes, and 1,2-diols with up to four configurationally-defined stereocenters. We believe this new family of enoate equivalents will rapidly find further applications in organocatalysis.

Experimental Section

Selected experimental procedures

All experimental details can be found in the Supporting Information. The material includes compound characterization, stereochemical determinations and copies of spectra of new compounds.

4-Hydroxy-2,4-dimethylpent-1-en-3-one (1): To a solution of commercial methyl 2-hydroxy-2-methylpropanoate (15 mmol, 1.77 g) and *N*,*O*-dimethylhydroxylamine hydrochloride (22.5 mmol, 2.14 g, 1.5 equiv) in THF (50 mL), a 2 M solution of *i*PrMgCl in THF (60 mmol, 4 equiv) was added at −20 °C. Once the reaction mixture was stirred for 1.5 h at room temperature, it was quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to obtain the desired Weinreb amide product. Yield: 1.99 g (90%), colorless oil. To a solution of this material (10 mmol, 1.85 g) in Et_2O (20 mL) at −20 °C, a solution of isopropenyl magnesium bromide (0.5 M in THF, 60 mL, 3 equiv) was added, and the resulting mixture was stirred at 0 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2×50 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O 95:5) to obtain compound **1**. Yield: 833 mg (65%), colorless oil; ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[28]

Preparation of chiral α′-hydroxy enones 8/9: To a solution of methyl 2-hydroxy-3-phenylpropanoate or methyl 2-hydroxy-4-methylpentanoate (10 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv) in THF (35 mL), at −20 °C a 2 M solution of *i*PrMgCl in THF (40 mmol, 20 mL, 4 equiv) was added. The reaction mixture was stirred for 1.5 h at 0 °C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to obtain the corresponding Weinreb amide. To a solution of 2-bromopropene (9 mmol, 0.79 mL, 3 equiv) in Et_2O (5 mL) at −78 °C, a solution of *tert*-butyllithium (1.6 M in pentane, 6.75 mL, 3.6 equiv) was added, and the resulting mixture was stirred at the same temperature for 1 h. Subsequently, a solution of the corresponding Weinreb amide (3 mmol) in Et_2O (10 mL) was added and the reaction mixture was stirred at −60 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95:5).

Preparation of chiral α′-silyloxy enones 10/11: To a solution of the corresponding α′-hydroxy enone **8/9** (2 mmol) in CH_2Cl_2 (20 mL) at −20 °C, were added successively 2,6-lutidine (0.55 mL,

4.8 mmol, 2.4 equiv) and TMSOTf (0.72 mL, 4 mmol, 2 equiv), and the mixture was stirred at the same temperature for 3 h. EtOAc (40 mL) was then added, and the organic phase was washed with saturated aqueous solutions of $NaHCO_3$ (40 mL), $CuSO_4$ (3×40 mL), $NaHCO_3$ (2×40 mL) and NaCl (40 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 99:1) to obtain pure compounds **10**/**11**.

General procedure for the catalytic conjugate addition of α-cyanoacetates to 1: To a solution of the corresponding α-cyanoacetate **2** (0.3 mmol, 1.5 equiv) and α′-hydroxy enone **1** (26 mg, 0.2 mmol) in 1,2-DCE (0.4 mL), catalyst **C6** (13 mg, 0.02 mmol) was added, and the resulting mixture was stirred at 50 °C until consumption of enone **1** (monitored by ^{1}H NMR spectroscopy). Then the reaction was quenched with HCl 1 N and the mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the corresponding addition/α-protonation adduct, which was purified by flash column chromatography (eluent hexane/ethyl acetate 95:5).

Catalytic conjugate addition of α-cyanoacetates 2 to chiral α′-oxy enones: To a solution of the corresponding *tert*-butyl cyanoacetate **2** (0.6 mmol) and the corresponding α′-oxy enone **8**–**11** (0.2 mmol, 1 equiv) in CH_2Cl_2 (0.4 mL), the catalyst (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α′-oxy enone (monitored by ^{1}H NMR spectroscopy; see Table 3 for reaction times). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure.

*Reactions from α′-hydroxy enone **8/9***: The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95:5).

*Reactions from α′-silyloxy enone **10/11***: The residue was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH (10 mmol, 0.2 mL) was added. The resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was basified to pH 7 with a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2×4 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The oily product was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95:5.)

Conversion of adduct 5a into carboxylic acid 20: A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of α-hydroxy ketone **5a** (69 mg, 0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 24 h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated. The product was purified by flash column chromatography (hexanes/EtOAc 80:20) to afford carboxylic acid **20** (52 mg, 86% yield, colorless oil).

Conversion of adduct 5a into aldehyde 23: BH_3·THF (1 M, 0.4 mL, 0.4 mmol) was added to a solution of α-hydroxy ketone **5a** (69 mg, 0.2 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, as above. The crude material was purified by flash column chromatography on silica gel (eluting with hexanes/EtOAc 95:5) to give compound **23** (44 mg, 76% yield, oil).

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Keywords: asymmetric organocatalysis · Brønsted bases · Michael reactions · quaternary stereocenters · stereoselective protonation

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FULL PAPER

Asymmetric Organocatalysis

I. Iriarte, S. Vera, E. Badiola, A. Mielgo, M. Oiarbide, J. M. García, J. M. Odriozola, C. Palomo**

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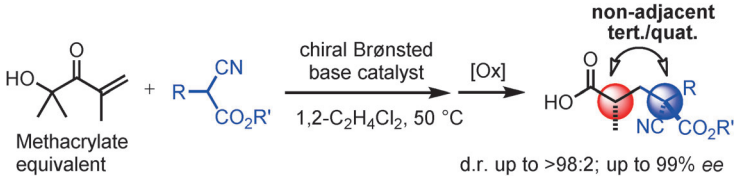
Asymmetric Assembly of All-Carbon Tertiary/Quaternary Nonadjacent Stereocenters through Organocatalytic Conjugate Addition of α-Cyanoacetates to a Methacrylate Equivalent



Michael does it again! 2,4-Dimethyl-4-hydroxypenten-3-one has been introduced as new methacrylate equivalent for the asymmetric construction of nonadjacent all carbon tertiary/quaternary stereocenters through the organocatalytic addition of α-cyanoacetates (see scheme). Direct assembly of such stereoarrays with high enantio- and diastereoselectivity has remained elusive to date.