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Enantioselective Synthesis of Quaternary Δ^4- and Δ^5-Dehydroprolines Based on a Two-Step Formal [3+2] Cycloaddition of α-Aryl and α-Alkyl Isocyano(thio)acetates with Vinyl Ketones

Amaiur Odriozola, Mikel Oiarbide and Claudio Palomo*

Dedication ((optional))

Abstract: A divergent synthesis of optically active quaternary both Δ^4- and Δ^5-dehydro prolines is developed based on the first catalytic enantioselective conjugate addition of α-substituted isocyano(thio)acetates to vinyl ketones that is general for both α-aryl and α-alkyl isocyano(thio)acetates. The new tetrasubstituted C–N stereocenter is formed without the need of any metal salt by the action of a bifunctional tertiary amine/squaramide catalyst featuring a bulky polyaryl sidearm and an unusually short squaramide diamide H–H interatomic distance in the solid state.

The α-carboxy-pyrrolidine units, generically referred to as prolines, are widespread within natural products and biologically active substances and bear considerable interest in peptide chemistry.[1] In this context, α-substituted (quaternary) prolines constitute a particularly relevant subclass owing to their unique structural biases and much attention has been paid to their stereoselective synthesis.[2] One major, thoroughly investigated convergent approach to the enantioselective synthesis of these heterocyclic systems relies on the catalytic [3+2] cycloaddition reaction between azomethine ylides and electrondeficient olefins (Figure 1a, left).[3] In contrast, the catalyst-controlled formal [3+2] cycloaddition involving α-isocyanoacetates and olefins (Scheme 1a, right), which also affords the pyrrolidine system through concomitant formation of the N–C_2 and C_4-C_5 bonds, has been much less developed.[4] Most studies on catalytic enantioselective cycloadditions of α-isocyanoacetates involve very reactive olefins, such as maleimides,[5] nitroalkenes,[6] β,γ-unsaturated α-keto esters,[7] methyleneindolinones[8] and allenoates,[9] and require, with a few exceptions,[6,8] combined metal/Brønsted base catalysis. Generalization of this type of cooperative catalysis is often hampered by the problem of Lewis acid/amine base self-quenching, which leads to catalyst deactivation and deleterious reaction stereocontrol, especially during formation of quaternary stereocenters.[10] In this context, a sole example of cycloaddition involving simple vinyl ketones as the reaction partner has been reported so far, affording the corresponding dehydroproline adducts with moderate (52–74% *ee*, R= H) or poor (≤36% *ee*, R= Me, Et) enantioselectivity.[11]

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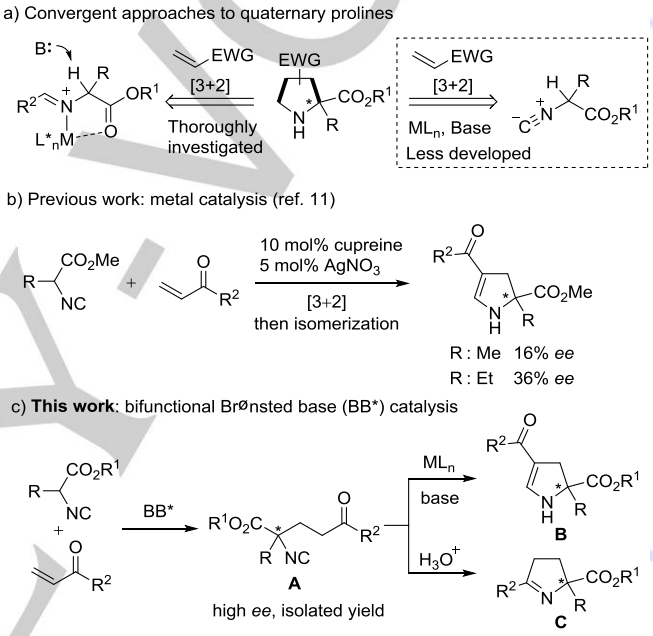

Scheme 1. Convergent approaches to enantioenriched quaternary proline derivatives.

We were intrigued by the possibility of triggering the α-isocyanoacetate-olefin addition reaction through an alternative organocatalytic activation mode whereby the bifunctional catalyst would activate both the donor and acceptor reaction components in a manner similar to that assumed for the metal-mediated process (model **II** vs. **I**, Figure 1). Eventually, the absence of a metal catalyst might also slow down the subsequent intramolecular cyclization step[12] (**III**) thus allowing α-protonation to occur preferentially (**IV**) leading to adduct **A**. Upon these assumptions, a divergent access to 4,5- and 1,5-dehydroprolines **B** and **C** from the common intermediate **A** would be conceivable (Scheme 1c), resulting in a substantial enlargement of product scope. The challenge here is to perform the 1,4-addition reaction leading to **A** efficiently and with good enantiocontrol.[13] Indeed, the relatively low carbon acidity of most α-substituted isocyanoacetates has caused that catalytic conjugate additions have been carried out with highly reactive acceptors only,[14] remaining the conjugate addition to simple vinyl ketones undocumented so far. Another serious limitation in scope concerns the isocyanoacetate component, with

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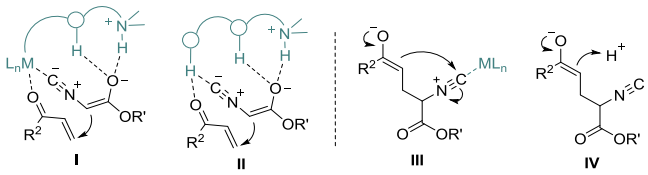
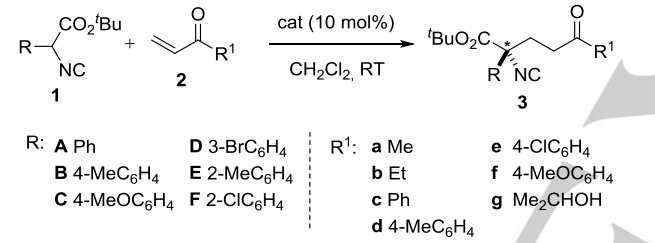
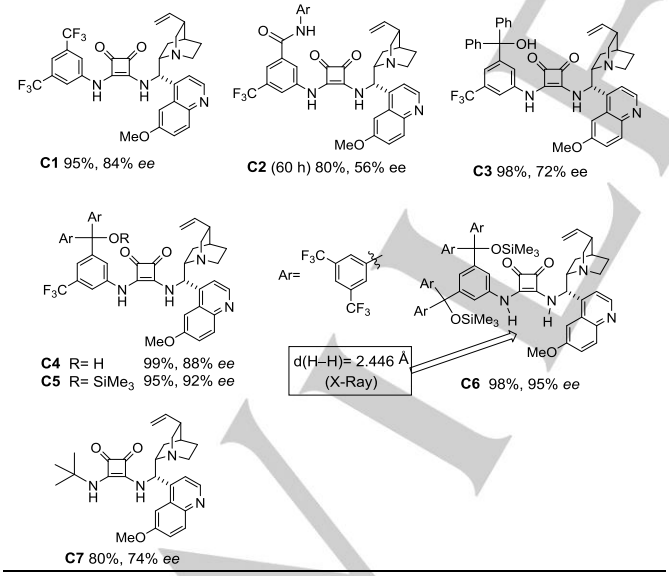


Figure 1. Idealized dual activation modes (left) and reaction pathways (right) in the presence or absence of a metal.

essentially all asymmetric organocatalytic reactions hitherto reported dealing with α-aryl substituted isocyanoacetates.[15] Besides these deficiencies, another significant challenge concerns the control of stereochemistry during the generation of the quaternary carbon center.[16] Herein we report the first enantioselective conjugate addition of both α-aryl and α-alkyl isocyano(thio)acetates to vinyl ketones enabled by bifunctional Brønsted base catalysts, ultimately resulting in a new approach to enantioenriched quaternary dehydroproline products of type **B** and **C**.

Table 1. Reaction of α-cyanoacetates **1** with enones **2** and catalyst screening for the reaction of **1A** with **2a** to give **3Aa**.[a]

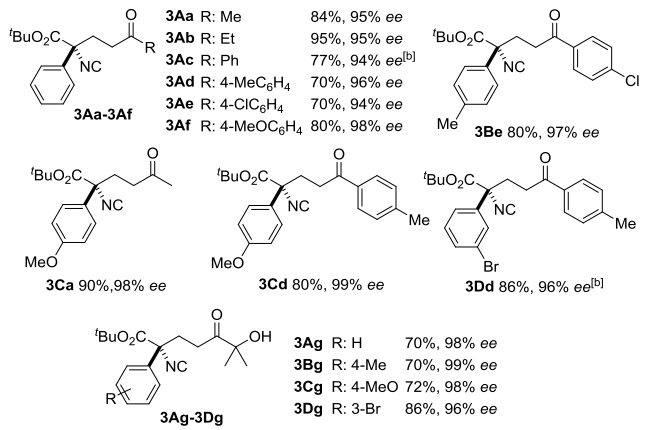




[a] Reactions conducted on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio of **1A**/**2a**/catalyst 1:2:0.1). Data refer to reaction conversion at 14 h unless otherwise specified. Ee´s determined by chiral HPLC.

The investigation was initiated by studying the reaction of α-phenyl *tert*-butyl isocyanoacetate **1A** with methyl vinyl ketone **2a** in the presence (10 mol%) of a selection of benchmark bifunctional Brønsted base organocatalysts.[17] From this initial screening,[18] the known catalyst **C1**[19] proved to be superior in terms of reaction conversion and enantioselectivity. As shown in Table 1, attempts to improve the result using catalysts **C2**, which has proven to be effective in difficult to control stereoselective reactions,[20] were unfruitful giving adduct **3Aa** in good yield but a poor 56% *ee*. We then decided to explore the more sterically demanding gem-diaryl catalysts **C3**, **C4** and **C5**, and the gem,gem-(bis)diaryl congener **C6**, which could be easily prepared through modification of the *meta* mono- and diester group(s) of the aniline fragment via Grignard technology.[18] We presumed that the bulky polyaryl moiety near the squaramide framework might prevent catalyst self-aggregation, a phenomenon that affects hydrogen-bond accepting substrate recognition.[21] Gratifyingly, each catalyst provided clean reaction with essentially complete conversion, while the highest selectivities were obtained with the bulkiest catalysts **C5** and **C6** (92% and 95% *ee*, respectively). In this respect, the X-ray structure analysis data of crystallized **C6** are worth of mention. The interatomic diamide H…H distance in **C6** is unusually short (2.446 Å) as compared with the typical values previously reported for related squaramide catalysts (≈2.85 Å[19c, 21]), and get closer to that found for the parent thiosquaramides.[22] On the other hand, squaramide units in the solid structure of **C6** do not self-aggregate through dual hydrogen bonding as is generally assumed. Instead, both N—H bonds of each squaramide unit point toward the quinoline nitrogen of a contiguous molecule.[18] It is likely that these features, probably induced by the bulky polyaryl sidearm in **C6**, would also prevail in solution and impact the catalytic behaviour. For comparison, catalyst **C7**[23] was also tested, resulting in lower reactivity and efficiency (14 h, 80% conversion, 74% *ee*) probably due to its lower solubility. Further experiments involving **1A** and catalyst **C6** showed that the stereochemical outcome of the reaction appears to be independent of the enone partner. As data in Table 2 show, both

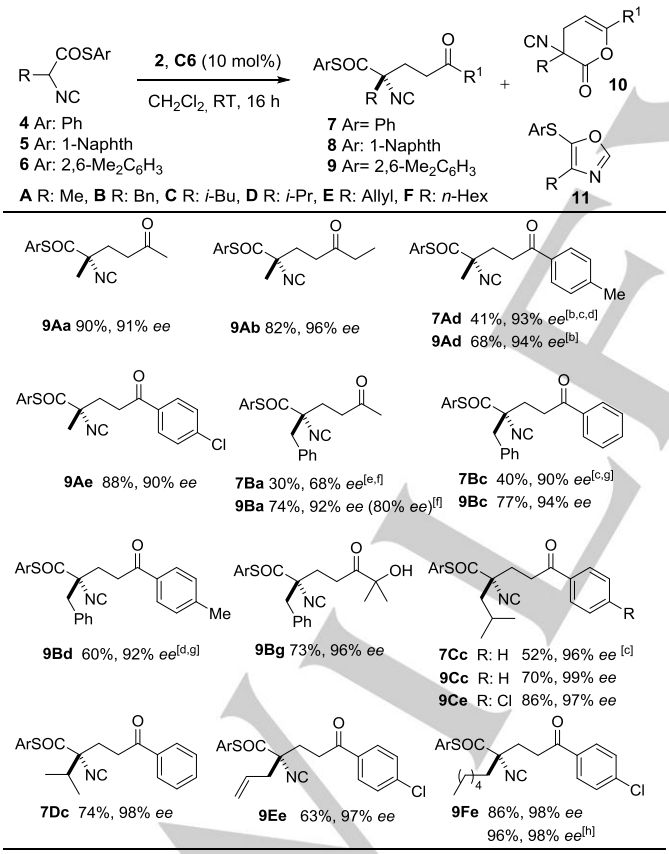
Table 2. Scope of the conjugate addition of **1** to vinyl ketones **2** catalyzed by **C6**.[a]



[a] Reactions conducted on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio of **1**/**2**/catalyst 1:2:0.05) at room temperature, unless otherwise stated. Yields of isolated product after column chromatography. Enantioselectivity determined by chiral HPLC. [b] 2 mol% of **C6** used (reaction run for 36 h).

alkyl- and aryl-vinyl ketones **2a–f** upon reaction with **1A** provided adducts **3Aa–f** with good isolated yields and ee's up to 98%. The reaction also worked quite well with respect the isocyanoacetate component. Thus, each **1B**, **1C** and **1D** reacted with the corresponding vinyl enone **2** to give products **3Be**, **3Ca**, **3Cd**, and **3Dd** with yields within the 80–90% range and ee values greater than 96%. Nonetheless, *o*-substituted aryl isocyanoacetates **1E**/**1F** as well as α–alkyl isocyanoacetates were not competent reaction partners. On the other hand, methyl acrylate, a less reactive Michael acceptor as compared to vinyl ketones, was not effective in this reaction regardless the catalyst employed. However, reactions of α'-hydroxy enone **2g**, an acrylate surrogate recently introduced by us,[24] with **1A–D** proceeded smoothly to give the corresponding adducts **3Ag**, **3Bg**, **3Cg** and **3Dg** in good yields and excellent enantioselectivity. For these reactions a 5 mol% catalyst loading was systematically employed, although both selectivity and yield remained essentially the same using 2 mol% catalyst only (products **3Ac** and **3Dd**).

Table 3. Conjugate addition of α-alkylisocyanothioacetates **4–6** to vinyl ketones **2** catalyzed by **C6**.[a]

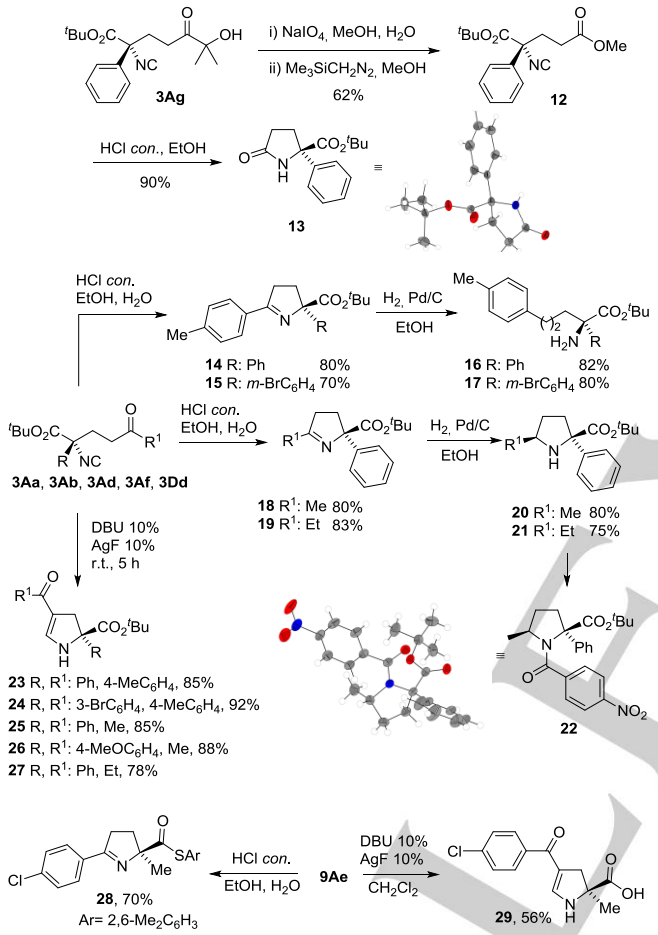


[a] Reactions conducted on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio of thioester/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. Enantioselectivity determined by chiral HPLC. [b] reaction run for 3 days. [c] about 30% of product **10** formed. [d] 3 equiv. of **2d** used. [e] About 35% of product **11** formed. [f] with catalyst **C1**.[g] Reaction run for 2 days. [h] Reaction run at 3 mmol scale using 1.3 equiv of **2e**.

Next, the inability of α-alkyl isocyanoacetates to react under the above conditions was addressed by using the corresponding thioesters instead, and assuming that thioesters are generally more acidic than oxoesters. At the outset, however, it was not clear whether α-alkyl isocyanoacetate thioesters would be effective donor substrates in this reaction. In fact, a few classes of thioesters only, with inherently acidic character, e.g. arylacetic,[25] β,γ-unsaturated carboxylic acid,[26] and malonic acid thioesters,[27] have been successfully employed in catalytic asymmetric carbon-carbon bond forming reactions and, as far as we know, α-substituted isocyanoacetic thioesters have never been reported.[28] In initial attempts, we observed that the **C6**-catalyzed reactions of various α-alkyl isocyanoacetate thioesters 4 (Ar: Ph) with enones **2** provided the Michael adducts **7** in good *ee´*s, but with formation of considerable amounts (20%–40%) of undesired byproducts such as **10**, **11** and sulfa-Michael products.[29] In case of using thioester **5** (Ar= 1-naphthyl) and methyl vinyl ketone, compound **11Aa** was the major product formed with no even traces of **8Aa** detected. In view of these complications,[30] some precursors of α-isocyanothioesters, such as α-substituted α-formamido thioesters and N-Boc α-amino acid thioesters, were also evaluated for the above reactions, but these substrates resulted totally unreactive under the above catalytic conditions. After some screening,[18] it was finally found that α-alkyl isocyanoacetate thioester **6A**, with a di-ortho substituted phenyl group installed (Ar= 2,6-$Me_2C_6H_3$), reacted cleanly to furnish the corresponding adduct **9A** essentially as the sole reaction product. This reactivity pattern was quite general for an array of isocyanoacetates **6** bearing short, medium, and longer α-alkyl linear as well as branched chains. As data in Table 3 show, upon reaction with enones **2** the corresponding products **9** were obtained in isolated yields from good to very good and excellent enantioselectivity, without traces of accompanying byproducts.[31] Furthermore, as production of compound **9Fe** illustrates, the reaction can be run at 3 mmol scale without any detriment in yield or selectivity.

The synthetic utility of the method was briefly explored as shown in Scheme 2. For example, the oxidative cleavage of the acyloin moiety in adduct **3Ag** provided, after methylation of the intermediate carboxylic acid, ester **12**. This product is difficult to obtain enantioselectively from a direct addition to methyl acrylate *vide supra*. Of practical interest, acetone is the only carbon by-product formed during this two-step transformation. Product **12** could be transformed into the pyroglutamate ester **13** in good yield. On the other hand, mild acid hydrolysis of adducts **3Ad** and **3Dd**, followed by spontaneous cyclisation, provided the 1,5-dehydroproline esters **14** and **15** in yields of 80% and 70%, respectively. Exposure of these adducts to H_2 over Pd on charcoal proceeded with concomitant cleavage of the benzylic C–N bond to give the corresponding α,α-disubstituted α-amino esters **16** and **17**. Conversely, when 1,5-dehydroproline esters **18** and **19**, obtained from **3Aa** and **3Ab** as above, were submitted to the same hydrogenation conditions, pyrrolidines **20** and **21** were produced with almost perfect stereocontrol at the newly generated stereocenter (dr>20:1).[32] The absolute configuration of compounds **13** and **22** was determined by X-ray single crystal structure analysis[33] and that of the remaining adducts by analogy assuming a uniform reaction mechanism.

Finally, it was gratifying to observe that adducts **3Aa**, **3Ab**, **3Af**, **3Ca** and **3Dd** upon treatment with 10 mol% each DBU and AgF led to 4,5-dehydroprolines **23**–**27** in very good yields through a clean cyclization and isomerization process. Other bases examined for this process, i.e. Et_3N and iPr_2EtN, were also effective but longer reaction times were required for completion, whereas in the absence of silver salts the reactions did not proceed.[34] Importantly, using this approach prolines with an α-alkyl substituent may now be produced, as illustrated with compounds **28** and **29** derived from **9Ae**.



Scheme 2. Elaboration of adducts.

In conclusion, we report here a new divergent synthesis of quaternary Δ^4- and Δ^5-dehydroprolines with broad substitution patterns based on a catalytic enantioselective two-step formal [3+2] cycloaddition of α-substituted isocyano(thio)acetates with vinyl ketones. Key for success is the development, for the first time, of isocyanoacetic acid thioesters as donor reagents in asymmetric synthesis and the design of a new subtype of squaramide/tertiary amine catalyst featuring a sterically congested polyaryl side-arm. We anticipate that these two key elements will find future applications in the realm of asymmetric catalysis.

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Keywords: asymmetric synthesis • organocatalysis • prolines • Brønsted bases • conjugate additions.

[1] a) A. Pérez-Luna, C. Butuha, F. Ferreira, F. Chemla, *New J. Chem.* **2008**, *32*, 594-606; b) L. Demange, A. Ménez, C. Dugave, *Tetrahedron Lett.* **1998**, *39*, 1169-1172.

[2] Recent reviews on quaternary α-amino acids: a) K. Bera, I. N. N. Namboothiri, *Asian J. Org. Chem.* **2014**, *3*, 1234-1260. A review on quaternary prolines: b) M. I. Calaza, C. Cativiela, *Eur. J. Org. Chem.* **2008**, 3427-3448.

[3] Selected recent reviews, see: a) J. Adrio, J. C. Carretero, *Chem. Commun*. **2014**, *50*, 12434-12446; b) K. Jiang, Y.-C. Chen, *Tetrahedron Lett.* **2014**, *55*, 2049-2055; c) R. Narayan, M. Potowski, Z.-J. Ja, A. P. Antonchick, H. Waldman, *Acc. Chem. Soc.* **2014**, *47*, 1296-1310. b) C. Nájera, J. M. Sansano, M. Yus, *Org. Biomol. Chem*. **2015**, *13*, 8596. For general reviews on 1,3-dipolar cycloadditions, see: d) J. Adrio, J. C. Carretero, *Chem. Commun*. **2014**, *50*, 12434-12446; e) T. Hashimoto, K. Maruoka, *Chem. Rev*. **2015**, *115*, 5366-5412; f) M. S. Singh, S. Choudhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603-1644.

[4] For recent reviews, see: a) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235-5331; b) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal.* **2014**, *356*, 2135-2196; c) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698-2779.

[5] a) M.-X. Zhao, D.-K. Wei, F.-H. Ji, X.-L. Zhao, M. Shi, *Chem. Asian J.* **2012**, *7*, 2777-2781; b) S. Padilla, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2012**, *77*, 4161-4166.

[6] C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 3462-3465; *Angew. Chem. Int. Ed.* **2008**, *47*, 3414-3417.

[7] J. Song, C. Guo, P.-H. Chen, J. Yu, S.-W. Luo, L.-Z. Gong, *Chem. Eur. J.* **2011**, *17*, 7786-7790.

[8] L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2012**, *48*, 5175-5177.

[9] J.-Y. Liao, P.-L. Shao,Y. Zhao, *J. Am. Chem. Soc*. **2015**, *137*, 628-631.

[10] For advances in this area, see: a) L. Stegbauer, F. Sladojevich, D. Dixon, *Chem. Sci.* **2012**, *3*, 942-958; b) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999-3025.

[11] C. Arroniz, A. Gil-González, V. Senak, C. Escolano, J. Bosch, M. Amat, *Eur. J. Org. Chem.* **2011**, 3755-3760.

[12] Cycloadditions catalyzed by bifunctional thioureas and squaramide organocatalysts, see: F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, *6*, 645-667.

[13] For reviews on organocatalytic conjugate additions, see: a) Y. Zhang, W. Wang, *Catal. Sci. Tech.* **2012**, *2*, 42-53; b) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselecive Conjugate Addition Reactions*; RSC Publishing: Cambridge, **2010**; c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701-1716; d) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299-365; e) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065-2092; f) Y. Zhang, W. Wang in *Stereoselective Organocatalysis* (Ed.: R. Ríos), Wiley, New Jersey, **2013**, pp. 147-203.

[14] (β-Trifluoromethyl α,β-enones) a) M.-X. Zhao, H.-K. Zhu, T.-L. Dai, M. Shi, *J. Org. Chem.* **2015**, *80*, 11330-11338. (Maleimides) b) J.-F. Bai, L.-L. Wang, L. Peng, Y.-L- Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu,

L.-X. Wang, *J. Org. Chem.* **2012**, *77*, 2947-2953; c) M.-X. Zhao, F.-H. Ji, D.-K- Wei, M. Shi, *Tetrahedron* **2013**, *69*, 10763-10771. (Vinylselenones) d) T. Buyck, Q. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 12946-12950; *Angew. Chem. Int. Ed.* **2013**, *52*, 12714-12718. (α-Pyridyl acrylonitriles) e) C. D. Fiandra, M. Moccia, V. Cerulli, M. F. A. Adamo, *Chem. Commun.* **2016**, *52*, 1697-1700.

[15] While α-aryl isocyanoacetate esters are common substrates in the reported organocatalytic methods (ref. 13), the α-alkyl analogues are recalcitrant, leading to no reaction at all (ref.13a,c) or poor selectivities (two entries in ref. 13b: *dr* 55:45, *ee* <60%). Also, see: ref. 5a, 7, 8, and 11.

[16] Reviews on tetrasubstituted carbon stereocenters: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem*. **2013**, 2745-2759; b) J. P. Das, I. Marek, *Chem. Commun*. **2011**, *47*, 4593-4623; c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583-1614; d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem*. **2007**, 5969-1614; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369-396; f) *Quaternary Stereocenters* (Ed.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; g) C. J. Douglas, L. E. Overman, *Proc. Nat. Acad. Sci*. **2004**, *101*, 5363-5367. For a review on metal-catalyzed conjugate additions leading to all-carbon quaternary stereocenters, see: h) C. Hawner, A. Alexakis, *Chem. Commun*. **2010**, *46*, 7295-7306.

[17] Reviews on Brønsted base catalysis: a) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev*. **2009**, *38*, 632-653; b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, 2012; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem*. **2010**, *291*, 145-200.

[18] See the Supporting Information for details.

[19] a) W. Yang; D.-M. Du, *Org. Lett*. **2010**, *12*, 5450-5453; b) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137-2141. Pionering work on squaramide catalysts, see: c) J. P. Malerich, K. Hagihama, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417; d) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157-160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156;

[20] a) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem.* **2017**, *129*, 2091-2095; *Angew. Chem. Int. Ed.* **2017**, *56*, 2059-2063; b) E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185-8195.

[21] For reviews on squaramide catalysts, see: a) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330-2346; b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890-6899; c) P. Chauahn, S. Mahahan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253-281.

[22] Recently, bifunctional thiosquaramides have been described as efficient catalysts with the two NH hydrogen atoms positioned for the two rotamers 2.43 Å and 2.64 Å apart, respectively. See: M. Rombola, C. S. Sumaria, T. D. Montgomery, V. H. Rawal, *J. Am. Chem. Soc.* **2017**, *139*, 5297−5300.

[23] F. Manoni, S. J. Connon *Angew. Chem*. **2014**, *126*, 2666-2670; *Angew. Chem. Int. Ed*. **2014**, *53*, 2628-2632.

[24] a) E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881; For a review on masked unsaturated esters in organocatalysis, see b) D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. Eur. J.* **2015**, *21*, 4494-4504.

[25] a) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem*. **2008**, *120*, 4664-4667; *Angew. Chem. Int. Ed*. **2008**, *47*, 4588-4591; b) M. C. Kohler, J. M. Yost, M. R. Garnsey, D. M. Coltart, *Org. Lett*. **2010**, *12*, 3376-3379; c) J. Guang, A. J. Larson, J. C. G. Zhao, *Adv. Synth. Catal*. **2015**, *357*, 523-529; d) S. Duce, M. Jorge, I. Alonso, J. L. García Ruano, M. B. Cid *Eur. J. Org. Chem.* **2013**, 7067-7075.

[26] I. Iriarte, O. Olaizola, S. Vera, I. Ganboa, M. Oiarbide, C. Palomo, *Angew. Chem*. **2017**, *129*, 8986-8990; *Angew. Chem. Int. Ed*. **2017**, *56*, 8860-8864.

[27] E. Cosimi, O. D. Engl, J. Saadi, M.-O. Ebert, H. Wennemers *Angew. Chem.* **2016**, *128*, 13321-13325; *Angew. Chem. Int. Ed.* **2016**, *55*, 13127-13131.

[28] B. H. Rotstein, D. J. Winternheimer, L. M. Yin, C. M. Deber, A. K. Yudin, *Chem. Commun.* **2012**, *48*, 3775-3777.

[29] Sulfa-Michael adducts may arise from traces of arylthiol realeased via base-promoted ketene formation. The identity of byproducts was confirmed by comparison with authetic samples.

[30] Potential problems arising from the use of thioesters, such as ketene formation and acyl transfer processes, have been previously noted. See reference 25b.

[31] This reactivity pattern appears to be independent of the acceptor. For example, whilst *N*-phenyl maleimide hardly reacts with α-benzyl isocyanoacetate methyl ester under Brønsted base catalysis (ref 14c), the reaction with isocyanothioacetate **6B** proceeded smoothly (10 mol% **C6**, RT, overnight) to provide the corresponding adduct in 70% isolated yield, albeit as a mixture of diastereomers (dr= 70:30, 68%/80% *ee*).

[32] For a previous study on reducing agents of the imine moiety on related compounds, see: M. Lee, Y.-J. Lee, E. Park, Y. Park, M. W. Ha, S. Hong, Y. J. Lee, T.-S. Kim, M.-h. Kim, H.-g. Park, *Org. Biomol. Chem.* **2013**, *11*, 2039-2046.

[33] CCDC 1555683 (catalyst **C6**), CCDC 1555682 (compound **13**) and CCDC 1555684 (compound **22**) contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

[34] $AgNO_3$, AgOTf and AgOAc were also tested as alternative silver source, but among them only the latter was effective.

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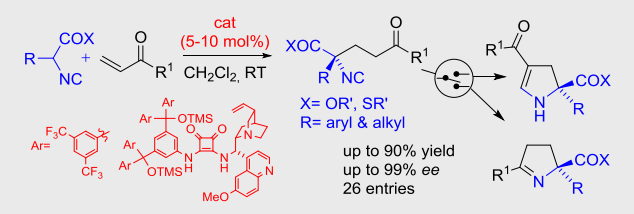

Double game: A bifunctional Brønsted base catalyst promotes the reaction of both α-aryl and α-alkyl isocyano(thio)acetates with vinyl ketones, opening a divergent access to quaternary either Δ^4- or Δ^5-dehydroprolines with high enantioselectivity.

*Amaiur Odriozola, Mikel Oiarbide, Claudio Palomo**

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Enantioselective Synthesis of Quaternary Δ^4- and Δ^5-Dehydroprolines Based on a Two-Step Formal [3+2] Cycloaddition of α-Aryl and α-Alkyl Isocyano(thio)acetates with Vinyl Ketones.