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Mutually Complementary Metal- and Organocatalysis with Collective Synthesis: Asymmetric Conjugate Addition of 1,3-Carbonyl Compounds to Nitroenynes and Further Reactions of the Products

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Abstract: The first metal-catalyzed 1,4-selective asymmetric addition of malonates to nitroenynes promoted by a simple chiral nickel(II)-diamine catalyst, was developed, facilitating a mild synthesis of a novel type of multifunctional chiral β-alkynyl acids bearing a nitro group. Based on this protocol, we have developed a practical and collective synthesis of a series of diverse functional molecules and building blocks including new types of chiral β-alkynyl-γ-amino acids, β-functionalized chiral δ-keto-γ-lactones, chiral γ-alkylidenelactones, alkynyl-substituted pyrrole-3-carboxylic acid derivatives, tetrasubstituted furans and chiral β-alkynyl-γ-lactams. Notably, we discovered two unusual tandem reactions leading to functionalized chiral 1,5-dicarbonyl compounds. In addition, by employing simple bifunctional organocatalysts, we have developed the first regio-, diastereo- and enantioselective conjugate addition of α-substituted β-keto esters to nitroenynes, which is poorly diastereoselective with chiral nickel(II)-diamine catalysts, providing a new entry to adjacent quaternary and tertiary stereocenters in one step. Based on this protocol, we have developed a concise asymmetric synthesis of conformationally constrained bicyclic γ^2-amino acids featuring an alkynyl side chain with an adjacent quaternary carbon stereocenter. The study described here demonstrates that the mutually complementary strategy of transition metal catalysis and organocatalysis is a powerful and promising tool in catalytic asymmetric synthesis.

Keywords: asymmetric catalysis; collective synthesis; conjugate addition; metal- and organocatalysis; nitroenynes

Introduction

The development of new catalytic chemical bond formation strategies with simple catalysts for the practical asymmetric synthesis of novel chiral multifunctional molecules with both biological and pharmacological potential as well as versatile synthetic utilities is one of the most important undertakings in modern chemical research.

Chiral β-alkynyl acids constitute an important class of pharmaceutical compounds with diverse biological activities that include PDE IV inhibitors, TNF inhibitors, GPR40 receptor agonists, and GRP receptor antagonists.[1] However, their asymmetric synthesis remains a significant challenge. The asymmetric methods that have been described to date for access to this target class involve the transition metal-mediated asymmetric conjugate addition of terminal alkynes to Meldrum's acid alkylidenes[2–4] and α,β-unsaturated thioamides,[5] respectively. While these reports stand out as pioneering efforts, they have limitations such as the requirement of the use of aromatic alkynes,[2] sterically shielded TMS (trimethylsilyl)acetylene,[3] a stoichiometric chiral mediator[4] or a complex cata-

lyst system and a relative high temperature (50 °C)[5]. Thus, the development of a new catalytic asymmetric strategy to construct chiral β-alkynyl acids,[6] especially a novel type of multifunctional chiral β-alkynyl acids with both biological and pharmacological potential as well as versatile synthetic utilities is highly desirable.

As part of our interest in developing new catalytic reactions involving alkynes,[7] and in asymmetric metal catalysis[7b,c] and organocatalysis,[8] herein we report the first metal-catalyzed 1,4-selective asymmetric addition of malonates to nitroenynes promoted by a simple chiral nickel(II)-diamine catalyst, facilitating a mild synthesis of a novel type of multifunctional chiral β-alkynyl acids bearing a nitro group[9] and an alkynyl moiety.[10] Based on this protocol, we have developed *a practical collective synthesis* of a series of diverse functional molecules and building blocks. Notably, we discovered two unusual tandem reactions. On the other hand, we have developed the first regio-, diastereo- and enantioselective organocatalytic conjugate addition of α-substituted β-keto esters to nitroenynes, which is poorly diastereoselective with chiral nickel(II)-diamine catalysts, providing a new entry to adjacent quaternary and tertiary stereocenters in one step. Based on this protocol, we have developed a concise asymmetric synthesis of conformationally constrained bicyclic γ^2-amino acids featuring an alkynyl side chain with an adjacent quaternary carbon stereocenter.

Recently, the nitroenynes have emerged as a promising class of extended Michael acceptors. Nevertheless, despite their potential utilities, catalytic asymmetric reactions involving nitroenynes are quite limited.[11] This might be due to the following two main reasons. The first reason is the competition between 1,4- and 1,6-addition of extended Michael acceptors[12] associated with the difficulties in controlling the regioselectivity. Indeed, in a recent Cu-catalyzed conjugate addition of nitroenynes, Alexakis and co-workers demonstrateded that the regioselectivity of the conjugate addition reaction was largely dependent on the types of nucleophilic reagents.[11f] The second possible reason is that, different from nitroolefins, nitroenynes have the problem of competitive bis-Michael addition probably due to the linear structure of the triple bond. Recently, we reported the first catalytic asymmetric addition of malonates to nitroenynes promoted by chiral organocatalysts.[13] However, this protocol suffers from the following significant drawbacks or limitations: (i) the reaction yield generally is not good due to the competitive bis-Michael addition; (ii) the substrate scope is limited, for example, di-*tert*-butyl malonate is not reactive; (iii) the catalyst loading is high (10 mol%). In view of its potential importance, it is highly desirable to develop a new catalytic strategy to achieve this type of asymmetric transformation with broad substrate scope and low catalyst loading without bis-Michael addition in good yields and high enantioselectivity.

On the other hand, the adjacent quaternary and tertiary stereocenters are common structural motifs in complex natural products and biologically important molecules. Significant progress has been made towards the asymmetric construction of adjacent quaternary and tertiary stereocenters.[14] While the regio-, diastereo- and enantioselective conjugate addition of α-substituted β-keto esters to nitroenynes would provide a direct approach leading to multifunctional chiral molecules containing adjacent quaternary and tertiary stereocenters in an atom-economical manner, such a process has not been reported so far.

Results and Discussion

Metal-Catalyzed Asymmetric 1,4-Addition of Malonates to Nitroenynes: A Collective Synthesis of Functional Molecules

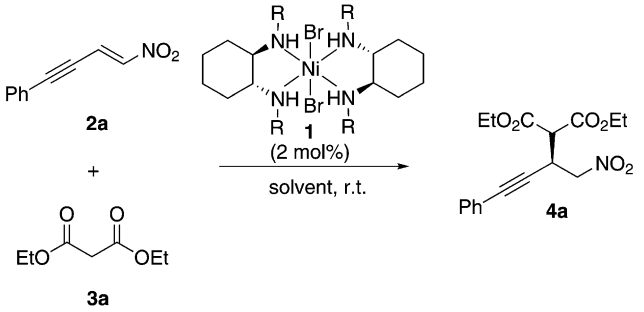
Metal-Catalyzed Asymmetric 1,4-Addition of Malonates to Nitroenynes

Considering the biological and pharmacological importance of chiral β-alkynyl acids as well as the potential synthetic versatility of asymmetric 1,4-addition adducts of malonates to nitroenynes, we turned our attention to a metal catalysis strategy and envisioned that metal catalysis could work as a complementary catalysis strategy to solve the significant problems of our previous organocatalytic version.[13] Despite the potentials of chiral nickel(II)-diamine complexes in asymmetric catalysis, the application of this class of catalysts in regioselective conjugate addition of nitroenynes has not been reported.

To our delight, in the presence of only 2 mol% chiral Ni(II) catalyst **1c**,[15] the desired 1,4-addition product **4a** was obtained in excellent yield (96%) with high enantioselectivity (91% *ee*) (Table 1, entry 3). Notably, no bis-Michael addition by-product was found. The regioselectivity was perfect. A survey of solvents showed that *m*-xylene offered the best enantioselectivity (93% *ee*) (entry 4), whereas, interestingly, DMF led to complete racemization (entry 9).

Under the optimized reaction conditions, the scope of the Ni-catalyzed conjugate addition reaction was investigated. Pleasingly, di-*tert*-butyl malonate, an unreactive substrate under our previous organocatalytic conditions,[11] reacted smoothly in the presence of 2 mol% chiral Ni(II) catalyst **1c**, giving the desired 1,4-addition product **4b** in good yield (81%) with high enantioselectivity (92% *ee*) (Table 2, entry 1). After a single recrystallization, the *ee* of the product **4b** could reach 99%. Additionally, dimethyl malonate af-

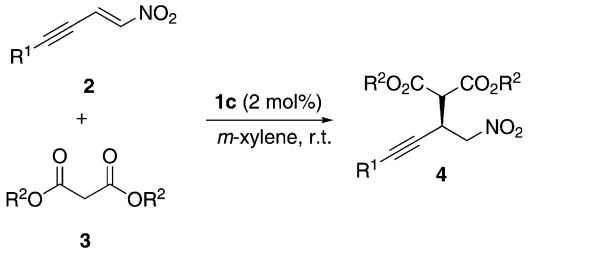
Table 1. Catalyst and solvent survey for the Ni-catalyzed 1,4-addition of diethyl malonate to phenylnitroeneyne.[a]



Entry	R	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	Bn (**1a**)	$PhCH_3$	5	90	91
2	CH_2(4-MeO-C_6H_4) (**1b**)	$PhCH_3$	5	90	90
3	CH_2(4-Br-C_6H_4) (**1c**)	$PhCH_3$	5	96	91
4	CH_2(4-Br-C_6H_4) (**1c**)	*m*-xylene	5	**96**	**93**
5	CH_2(4-Br-C_6H_4) (**1c**)	*m*-xylene	9	93	92[d]
6	CH_2(4-Br-C_6H_4) (**1c**)	Et_2O	8	82	90
7	CH_2(4-Br-C_6H_4) (**1c**)	THF	8	78	90
8	CH_2(4-Br-C_6H_4) (**1c**)	DCM	8	45	89
9	CH_2(4-Br-C_6H_4) (**1c**)	DMF	8	22	0

[a] The reaction was performed with phenylnitroeneyne **2a** (0.3 mmol) with diethyl malonate **3a** (2 equiv.) in the presence of 2 mol% catalyst **1** in solvent (0.7 mL) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis.
[d] At 0 °C.

Table 2. Regio- and enantioselective 1,4-addition of nitroenynes with malonates catalyzed by nickel(II)-diamine complex **1c**.[a]



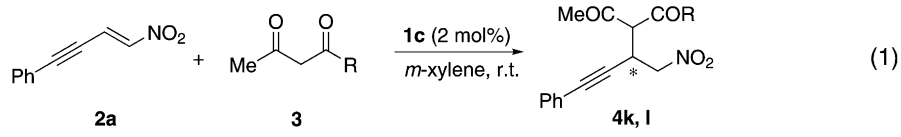
Entry	R^1	R^2	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	*t*-Bu (**3b**)	10	81	92 (99)[d]
2	Ph (**2a**)	Me (**3c**)	6	98	94
3	Ph (**2a**)	Et (**3a**)	5	96	93
4	4-Me-C_6H_4 (**2b**)	Et (**3a**)	5	96	90
5	4-MeO-C_6H_4 (**2c**)	Et (**3a**)	8	95	91
6	4-F-C_6H_4 (**2d**)	Et (**3a**)	5	95	92
7	3-F-C_6H_4 (**2e**)	Et (**3a**)	12	88	89
8	$CH_3(CH_2)_3$ (**2f**)	Et (**3a**)	10	92	>99
9	$CH_3(CH_2)_2$ (**2g**)	Et (**3a**)	10	90	>99
10	$PhCH_2CH_2$ (**2h**)	Et (**3a**)	8	89	95

[a] The reaction was performed with nitroenynes **2** (0.3 mmol) with malonates **3** (2 equiv.) in the presence of 2 mol% catalyst **1c** in *m*-xylene (0.7 mL) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis.
[d] After a single recrystallization.

forded the desired 1,4-addition product **4c** in 98% yield with 94% *ee* (entry 2) whereas this substrate gave 56% yield and 87% *ee* under our previous organocatalytic conditions.[13] For comparative purposes, diethyl malonate was employed as the nucleophile to react further with various nitroenynes. As shown in Table 1, a significant improvement in yield was observed. Moreover, generally, an improvement in *ee* was also obtained (entries 3–9). The conjugate addition worked well not only with electron-neutral (entry 3), electron-rich (entries 4 and 5), and electron-deficient aryl alkynyl substrates (entries 6 and 7), but also with alkyl-substituted alkynyl substrates (entries 8–10). The absolute configurations of **4a** and **4c–f** and **4h–j** were determined by comparing the retention time of HPLC of products with those in literature data.[13]

The asymmetric conjugate addition of other types of 1,3-dicarbonyl compounds to nitroeneyne **2a** using **1c** as the catalyst was also investigated [Eq. (1)]. For 1,3-diketone **3d**, and β-keto ester **3e**, the corresponding adducts were obtained in good yields (88–90%) and enantioselectivities (90–92% *ee*) at the β-position to the nitro group.

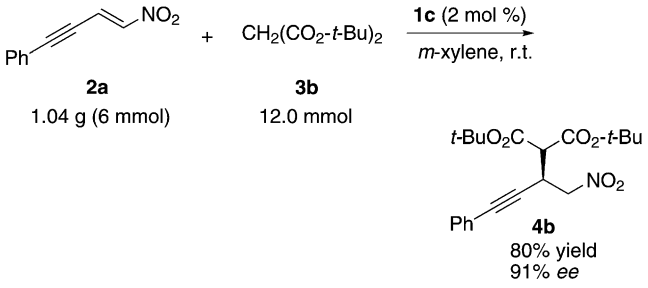
The mild reaction conditions, the easily accessible catalyst, the low catalyst loading and the synthetic potential of the 1,4-addition products offered a practical use for the present approach, thus, the reaction on a gram-scale was carried out in the presence of 2 mol% catalyst **1c** with the substrates **2a** and **3b**, affording the desired product **4b** in 81% yield with 91% *ee* (Scheme 1).



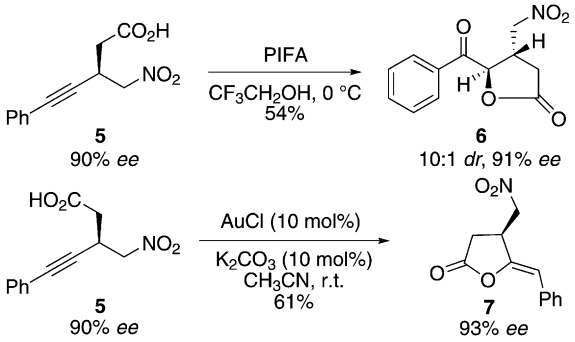
3d: R = Me
3e: R = OEt

Product	Time [h]	Yield [%]	*ee* [%]
4k	12	90	90
4l[a]	12	88	92, 92

[a] 1.2:1 diastereomeric mixture



Scheme 1. Gram-scale version of regio- and enantioselective Michael addition between **2a** and **3b**.



Scheme 3. Asymmetric construction of δ-keto-γ-lactones and γ-alkylidenelactones.

Asymmetric Synthesis of Chiral β-Alkynyl Acids

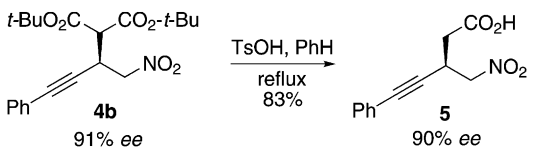
As illustrated in Scheme 2, the 1,4-addition adduct **4b** underwent a decarboxylation reaction in the presence of TsOH under reflux to afford the chiral β-alkynyl acid **5** (Scheme 2). The *ee* value of β-alkynyl acid **5** was determined by transformation into the corresponding methyl ester.

Asymmetric Synthesis of Chiral δ-Keto-γ-lactones and γ-Alkylidenelactones

δ-Functionalized γ-lactones[16] and γ-alkylidenelactones[17] represent two important types of scaffold which are frequently encountered as structural subunits in numerous biologically active products. Moreover, they are also important building blocks in natural product synthesis[18] and drug synthesis.[19]

The chiral β-alkynyl acid **5** bearing a nitro group provides an ideal platform from which to construct these chiral heterocycles. Under the catalysis of the hypervalent iodine reagent PIFA [phenyliodine(III) bis(trifluoroacetate)],[20] the chiral β-alkynyl acid **5** was transformed effectively into optically active β-functionalized δ-keto-γ-lactone **6**, which is also the core of the biologically active natural product phenatic acid B[16a] (Scheme 3). Notably, this intramolecular electrophilic cyclization is highly diastereoselective (10:1 *dr*). The relative configuration of the chiral lactone **6** was confirmed by NOESY. Despite the potential utility of PIFA-promoted intramolecular electrophilic cyclization of alkynyl carboxylic acids,[20b] the significant diastereoselectivity and enantioselectivity issues remain unknown, thus limiting its application in asymmetric synthesis.

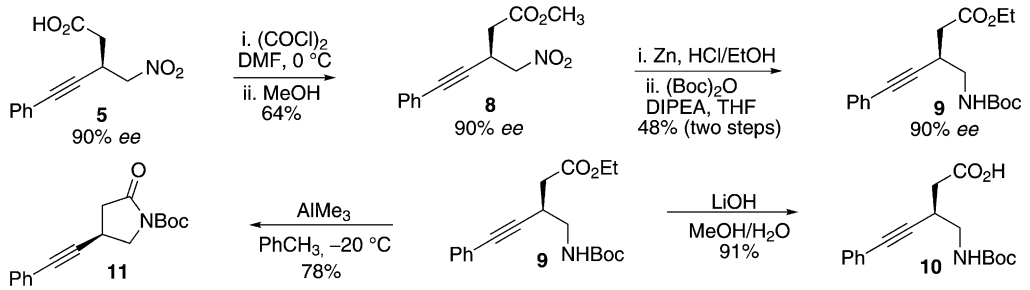
Under the catalysis of gold(I) species,[21] the chiral β-alkynyl acid **5** underwent the cyclization to provide chiral γ-alkylidenelactone **7** bearing the nitro group which can be further manipulated (Scheme 3).



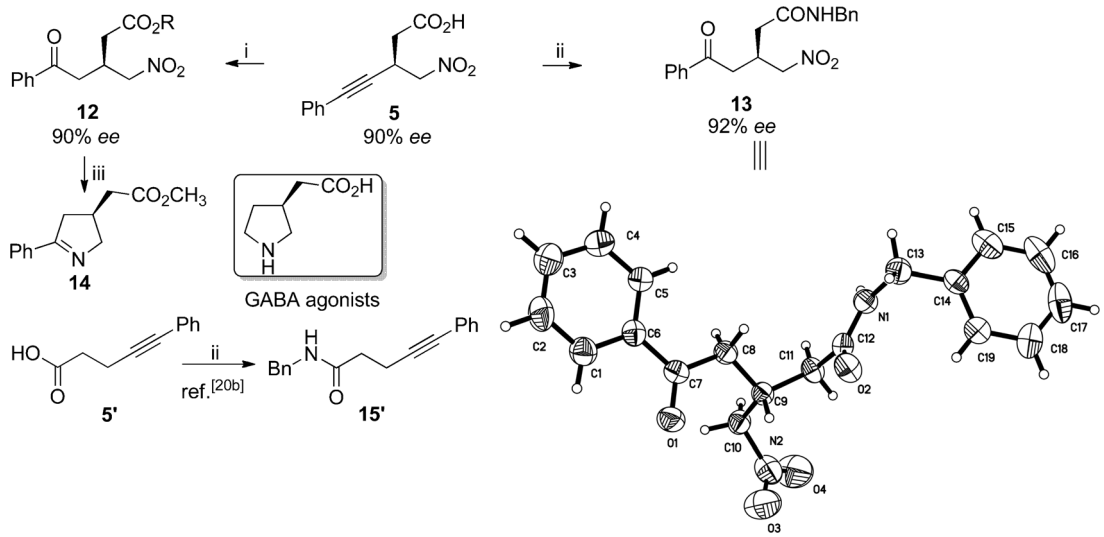
Scheme 2. Synthesis of a new type of chiral β-alkynyl acids.

Asymmetric Synthesis of Chiral β-Alkynyl-γ-amino Acids and β-Alkynylpyrrolidinones with Discovery of Unprecedented Transformations

Over the last few years, there has been increasing interest in the asymmetric design and synthesis of novel chiral γ-amino acids, in particular those bearing substituents at the β-position, which can be considered as potent drugs for the treatment of neurodegenerative disorders.[22,23] On the other hand, due to their potential biological activity as specific irreversible enzyme inhibitors,[24] the design and synthesis of amino acids with alkyne substituents (acetylenic amino acids) have received much attention.[25] Thus, chiral β-alkynyl-γ-amino acids might be attractive candidates of medicinal interest as this class of molecules merges per-



Scheme 4. Asymmetric synthesis of chiral β-alkynyl-γ-amino acids and β-alkynylpyrrolidinones.



Scheme 5. Unusual esterification and amidation of chiral β-alkynyl acid **5** to chiral 1,5-dicarbonyl compounds. *Reaction conditions:* (i) BnOH, HOBt, EDC·HCl, Et_3N, DCM, 0 °C to room temperature, 65% of compound **12a** (R = Bn); 61% of compound **12b** (R = CH_3); (ii) $BnNH_2$, HOBt, EDC·HCl, Et_3N, DCM, 0 °C to room temperature, compound **13**, 78%; compound **15′**, 82%; (iii) Zn, AcOH, 65 °C, 57%.

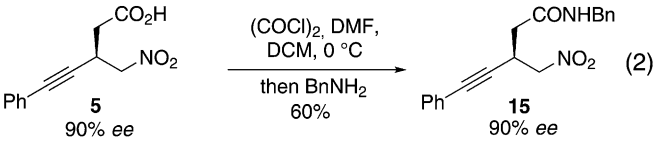
fectly γ-amino acids and β-side chains containing an alkyne functionality.

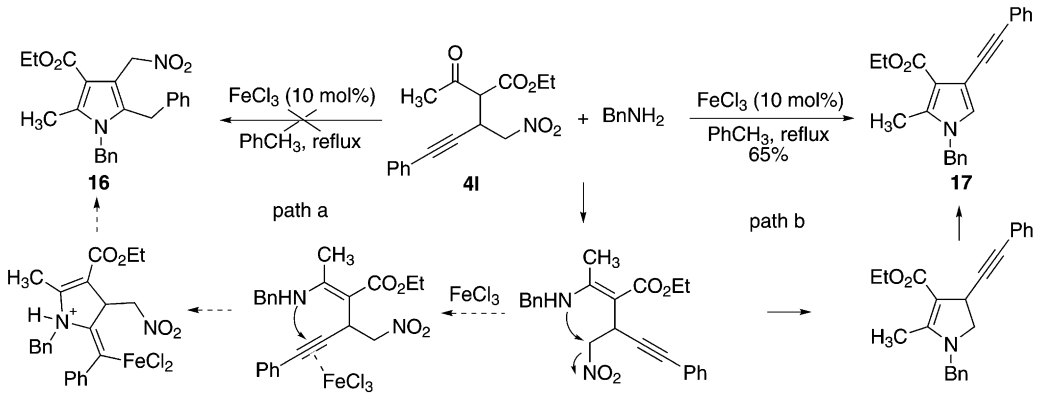
Starting from the the chiral β-alkynyl acid **5**, the chiral β-alkynyl-γ-amino acid **10** was synthesized (Scheme 4). Also, from the chiral β-alkynyl acid **5** as the common intermediate, the β-alkynylpyrrolidinone **11** was obtained *via* a three-step transformation (Scheme 4).

While the above route (Scheme 4) seems to be routine, the esterification reaction of the chiral β-alkynyl acid **5** to the corresponding chiral β-alkynyl ester **8** is unusual.

Initially, we used HOBt and EDC·HCl as activating reagents to perform the esterification reaction of chiral β-alkynyl acid **5**. Surprisingly, the desired esterification product **8** was not obtained, instead, the chiral 1,5-dicarbonyl compound **12** (CCDC 863799) bearing a nitro group was unexpectedly obtained (Scheme 5). This transformation can be also extended to the synthesis of the functionalized chiral 1,5-dicarbonyl compound **13** (Scheme 5). Interestingly, under the identical conditions, the unsubstituted β-alkynyl acid **5′**, was reported to afford the corresponding amide **15′** in 82% yield.[20b] While the accurate reaction mechanism is not clear at this stage, these results seem to indicate that the nitro group of chiral β-alkynyl acid **5** might participate in the reaction, giving the unexpected functionalized chiral 1,5-dicarbonyl compounds. Notably, these functionalized chiral 1,5-dicarbonyl compounds bearing a nitro group are potential precursors to pharmaceutically active molecules such as conformationally restricted homo-β-proline analogues, which are inhibitors of $GABA_A$ as well as $GABA_B$ receptor binding.[26]

The normal chiral β-alkynyl amide **15** bearing the nitro group can be achieved by using the following method [(Eq. (2)].





Scheme 6. Synthesis of alkynyl-substituted pyrrole-3-carboxylic acid derivative **17**.

Synthesis of Alkynyl-Substituted Pyrrole-3-carboxylic Acid Derivatives

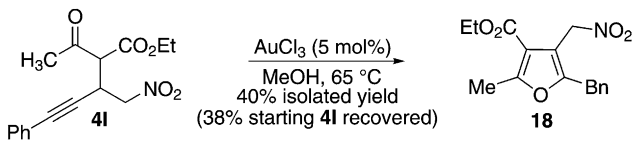
The pyrrole framework is a ubiquitous structural motif found in a wide range of biologically active natural products and pharmaceutically active agents.[27]

To derive the substituted pyrroles, the 1,4-conjuagte addition product **4l** of phenylnitroeneyne with ethyl acetoacetate was subjected to the conditions ($FeCl_3$, toluene, reflux) recently reported by Bi and Zhang.[28] Interestingly, the normal pyrrole product **16** was not obtained, instead, the alkynyl-substituted pyrrole-3-carboxylic acid ethyl ester **17** was achieved, which is of medicinal interest as it combines a pyrrole-3-carboxylic acid moiety[27d] and the alkyne functionality[24] (Scheme 6). To account for the current results, we proposed a possible mechanism depicted in Scheme 6 (path b).

Synthesis of Multisubstituted Furans

Multisubstituted furans are of importance because numerous compounds bearing such a heterocyclic ring exhibit a wide range of biological activities and are also building blocks for organic synthesis.[29,30] The development of new and efficient syntheses of multisubstituted furans having specific substitution patterns is an important objective.[31]

Under the catalysis of $AuCl_3$, the 1,4-conjugate addition product **4l** underwent cycloisomerization[32] to provide the new tetrasubstituted furan **18** (Scheme 7). While the yield is moderate, this is the first example of an $AuCl_3$-catalyzed cycloisomerization of β-alkynyl-β-keto ester to generate a tetrasubstituted furan.

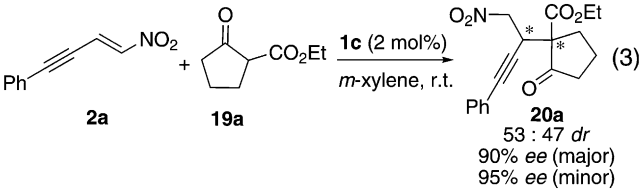


Scheme 7. Synthesis of tetrasubstituted furans.

Organocatalytic Asymmetric 1,4-Addition of α-Substituted β-Keto Esters to Nitroenynes: A Concise Syntheis of Bicyclic γ^2-Amino Acids Featuring an Alkynyl Side Chain

Organocatalytic Asymmetric 1,4-Addition of α-Substituted β-Keto Esters to Nitroenynes

Under identical reaction conditions as for the Ni-catalyzed conjugate addition of malonates to nitroenynes, we explored the conjugate addition reaction of 2-oxocyclopentanecarboxylate **19a** to phenylnitroeneyne **2a**. Unfortunately, although the enantioselectivity of this reaction was good, the diastereoselectivity was quite poor (53:47 *dr*) [Eq. (3)]. It is interesting to note that



with NaH as the only base or catalyst, the racemic reaction can be achieved in 80:20 *dr*. We turned our attention to organocatalysis again, hoping that organocatalysis could also serve as a complementary strategy to impart both high diastereoselectivity and enantioselectivity.

To our delight, in the presence of bifunctional organocatalyst **21a** (Figure 1), the desired addition product **20a** was obtained in good yield (91%) with good enantioselectivity (90% *ee*) and diastereoselectivity (95:5 *dr*) (Table 3, entry 1). Decreasing the temperature to −30 °C led to 97% *ee* and 93:7 *dr* but 77%

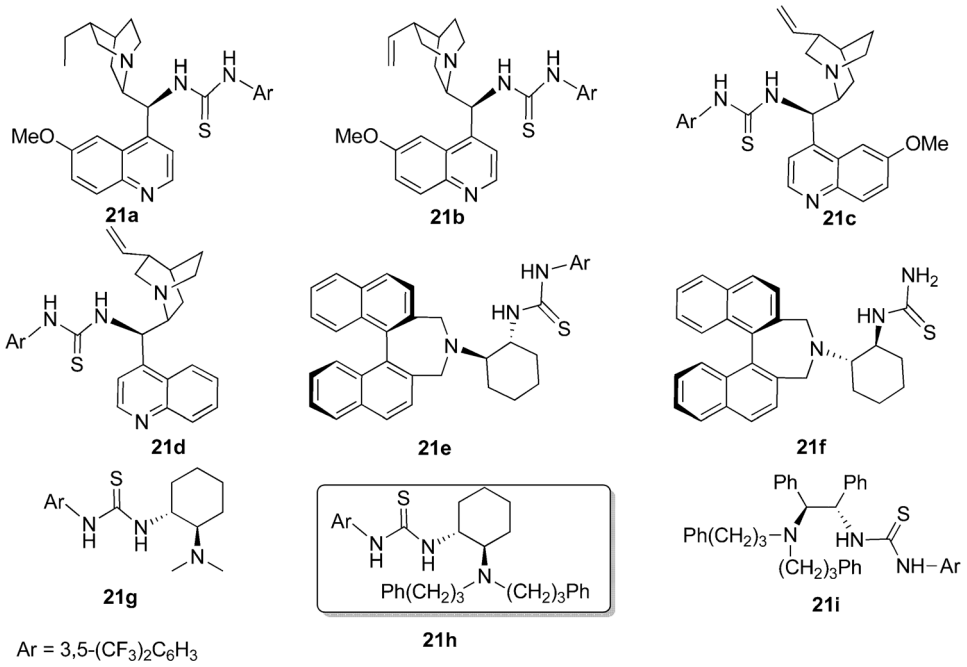


Figure 1. Bifunctional organocatalysts tested in this study.

yield (entry 2). To examine the effect of catalyst structure on the diastereo- and enantioselectivity as well as to further improve these two parameters, a series of other types of organocatalysts was subsequently investigated (Figure 1). The *Cinchona* alkaloid-derived catalysts[33] **21b–d** proved to be promising, affording 82–91% *ee* and 95:5–98:2 *dr* (entries 3–5). The widely used 1,2-cyclohexanediamine-derived catalyst **21g**, Takemoto's catalyst,[34] resulted in −69% *ee* and 91:8 *dr* (entry 8). The catalyst **21e** bearing central and axial chiral elements[8d] afforded −71% *ee* and 94:6 *dr* (entry 6), whereas its diastereomer **21f** offered 87% *ee* and 87:13 *dr* (entry 7). The differences observed in *dr* and *ee* suggested that the structure of the base had an effect on these two parameters. The further tunablility of the structure of the base led to the catalyst **21h**, giving −93% *ee* and 97:3 *dr* (entry 9). The 1,2-diphenylethanediamine-derived organocatalyst **21i** afforded moderate *ee* (57%) but excellent *dr* (99:1) (entry 10). These results indicated that the diamine scaffolds of the catalysts have a significant impact on both diastereo- and enantioselectivity. Subsequently, a series of solvents was examined. Et_2O provided the best results (95% *ee*, 98:2 *dr* and 92% yield) (entry 13).

With the optimized reaction conditions in hand, we investigated the scope of the reaction (Table 4). Various aromatic and aliphatic nitroenynes reacted smoothly with five-membered cyclic β-keto esters to give the desired adducts containing diverse alkynyl, nitro, ketone and ester groups, featuring adjacent quaternary and tertiary stereocenters, in good yields with high to excellent diastereoselectivity and enantioselectivity (entries 1–6).

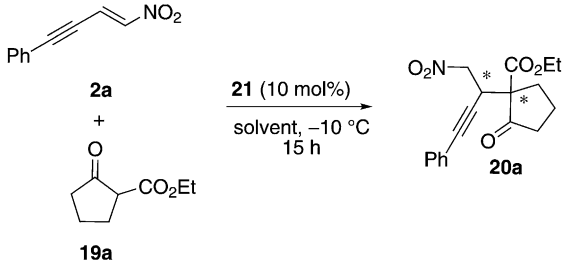
In addition to five-membered cyclic β-keto esters, the six-membered cyclic β-keto ester **19b** was also a good nucleophile, leading to the addition product in 97:3 *dr* and 84% *ee* (entry 7). The 2-acetylbutyrolactone **19c** also reacted with nitroenyne providing the desired product in 98: 2 *dr* and 78% *ee* (entry 8). In view of the importance of fluorinated compounds in medicinal chemistry[35a] and material chemistry,[35b] the acyclic α-fluorinated β-keto ester **19d** was examined, affording high enantioselectivity (96% *ee*) but moderate diastereoselectivity (63:37 *dr*) (entry 9). The relative and absolute configurations of the products of Michael reactions of nitroenynes with α-substituted β-keto esters were assigned on the basis of an X-ray crystal structural analysis of the product of **20a** [Flack parameter 0.03(15), Figure 2].[36]

High diastereoselectivity and enantioselectivity could be explained *via* the transition state models shown in Figure 3.

Asymmetric Synthesis of Constrained Bicyclic γ^2-Amino Acid Featuring an Alkynyl Side Chain

γ^2-Amino acids represent potential building blocks for γ-peptide[37] and heterogeneous backbone foldamers.[38] On the other hand, bicyclic unnatural amino acids have been developed as reverse turn mimetics and dipeptide isosteres, and the constraint imposed by their structures has been reported as a tool for controlling the conformational preferences of modified

Table 3. Catalyst and solvent survey for the regio-, diastereo- and enantioselective 1,4-addition of **2a** with **19a** catalyzed by organic catalysts.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**21a**	toluene	91	90	95:5
2	**21a**	toluene	77	97	93:7[e]
3	**21b**	toluene	82	91	95:5
4	**21c**	toluene	86	−87	96:4
5	**21d**	toluene	87	−82	98:2
6	**21e**	toluene	85	−71	94:6
7	**21f**	toluene	89	87	87:13
8	**21g**	toluene	88	−69	91:8
9	**21h**	toluene	90	−93	97:3
10	**21i**	toluene	75	57	99:1
11	**21h**	*m*-xylene	85	−88	98:2
12	**21h**	THF	87	−92	97:3
13	**21h**	Et_2O	**92**	**−95**	**98:2**
14	**21h**	DCM	88	−81	97:3
15	**21h**	$CHCl_3$	90	−84	96:4
16	**21h**	DCE	85	−90	98:2

[a] The reaction was performed with **2a** (0.3 mmol) and **19a** (0.15 mmol) in the presence of 10 mol% catalyst **21** in solvent (0.5 mL) at −10 °C.
[b] Isolated yield.
[c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR analysis or HPLC.
[e] At −30 °C.

peptides.[39] In addition, due to their potential biological activity as specific irreversible enzyme inhibitors[24], the amino acids with alkyne substituents (acetylenic amino acids) have aroused much interest.[24,25] In view of these factors, as a novel type of conformationally constrained bicyclic γ^2-amino acid derivatives, the chiral bicyclic γ^2-amino acid derivatives bearing an alkynyl side chain such as **23** might have potential in peptide foldamer research and pharmaceutical synthesis.

Starting from the organocatalytic 1,4-addition product **20a**, a concise synthesis of the conformationally constrained bicyclic γ^2-amino acid derivative **23** featuring a chiral alkynyl side chain with an adjacent quaternary carbon stereocenter was developed (Scheme 8).

Conclusions

We developed the first metal-catalyzed 1,4-selective asymmetric addition of malonates to nitroenynes promoted by a simple chiral nickel(II)-diamine catalyst, facilitating a mild synthesis of novel types of multifunctional chiral β-alkynyl acids bearing the nitro group. Based on this protocol, we developed a practical collective synthesis of a series of diverse functional molecules and building blocks including new types of chiral β-alkynyl-γ-amino amino acids, β-functionalized chiral δ-keto-γ-lactones, chiral γ-alkylidenelactones, alkynyl-substituted pyrrole-3-carboxylic acid derivatives, tetrasubstituted furans and chiral β-alkynyl-γ-lactams. Notably, we discovered two unusual tandem reactions leading to functionalized chiral 1,5-dicarbonyl compounds. In addition, by employing simple bifunctional organocatalysts, we have developed the first regio-, diastereo- and enantioselective conjugate addition of α-substituted β-keto esters to nitroenynes, which is poorly diastereoselective with chiral nickel(II)-diamine catalysts, providing a new entry to adjacent quaternary and tertiary stereocenters in one step. Based on this protocol, we developed a concise asymmetric synthesis of conformationally constrained bicyclic γ^2-amino acids featuring an alkynyl side chain with an adjacent quaternary carbon stereocenter. The study described here demonstrates that the mutually complementary strategy of transition metal catalysis and organocatalysis is a powerful and promising tool in catalytic asymmetric synthesis.

Experimental Section

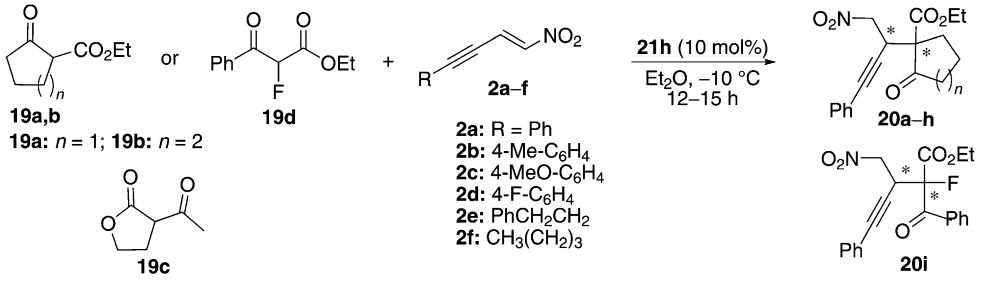
General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrophotometer. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. The enantiomeric excess was determined by HPLC using Chiralpak AD-H, Chiralcel OD-H and Chiralcel OJ-H column with *n*-hexane and 2-propanol as eluents. High resolution mass spectrometry (HR-MS) was recorded on a VG Auto Spec-3000 spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (230–400 mesh).

General Procedure for Ni-Catalyzed Regio- and Enantioselective Conjugate Addition of Malonates to Nitroenynes

To a solution of catalyst **1c** (2 mol%) in *m*-xylene (0.7 mL) was added malonate **3** (0.6 mmol, 2 equiv.) and nitroenyne **2** (0.3 mmol). The resulting solution was stirred at room temperature until the reaction was complete (monitored by TLC). The volatile components were removed under re-

Table 4. Regio-, diastereo- and enantioselective 1,4-addition of nitroenynes with α-substituted β-keto esters catalyzed by bifunctional organocatalyst **21h**.[a]



Entry	19	2	Product	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**19a**	**2a**	**20a**	92	95	98:2
2	**19a**	**2b**	**20b**	84	96	94:6
3	**19a**	**2c**	**20c**	93	92	95:5
4	**19a**	**2d**	**20d**	80	94	95:5
5	**19a**	**2e**	**20e**	87	95	99:1
6	**19a**	**2f**	**20f**	85	95	99:1
7	**19b**	**2a**	**20g**	80	84	97:3
8	**19c**	**2a**	**20h**	66	78	98:2
9	**19d**	**2a**	**20i**	73	96	63:37

[a] The reaction was performed with nitroenynes **2** (0.3 mmol) with α-substituted β-keto esters **19** (0.15 mmol) in the presence of 10 mol% catalyst **21h** in Et_2O (0.5 mL) at −10 °C.
[b] Isolated yield.
[c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis.
[d] Determined by ^1H NMR analysis or HPLC.

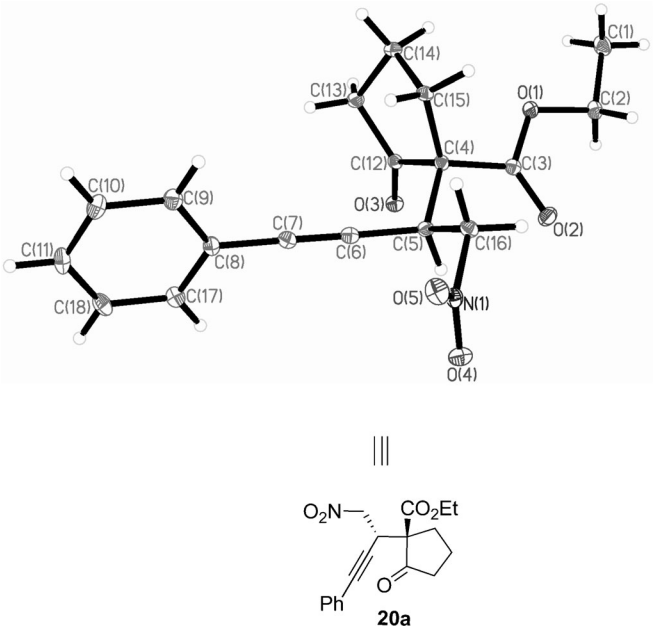


Figure 2. X-ray structure of compound **20a**.

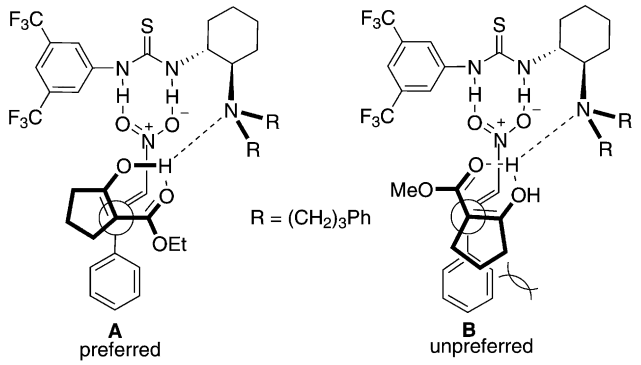


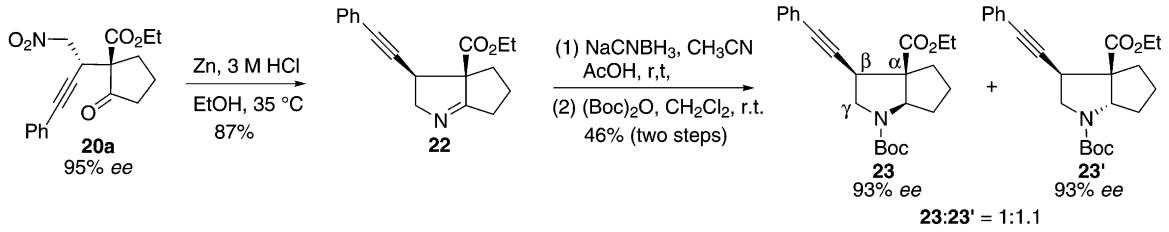
Figure 3. Transition-state models of organocatalytic asymmetric 1,4-addition of α-substituted β-keto esters.

duced pressure and the crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (*R*)-di-*tert*-butyl 2-(1-nitro-4-phenylbut-3-yn-2-yl)malonate (4b): Yellow solid; $[\alpha]_D^{20}$: −6.3 (*c* 1.0 $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$ (m, 2H), 7.28 (m, 3H), 4.78 (m, 2H), 4.05 (m, 1H), 3.60 (m, 1H), 1.49 (brs, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 165.8, 131.8, 128.6, 128.3, 122.1, 85.3, 83.8, 83.1, 82.9, 76.5, 55.0, 30.7, 27.9, 27.8. HR-MS: $m/z =$ 389.1824, calcd. for $C_{21}H_{27}NO_6$ $[M]^+$: 389.1838; HPLC (Chiralpak AD-H, 2–propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): $t_{major} = 7.9$ min, $t_{minor} = 10.4$ min.

Asymmetric Synthesis of Chiral β-Alkynyl Acid 5

To a solution of compound **4b** (30 mg, 0.077 mmol) in PhH (2.5 mL) was added TsOH (3 mg, 0.2 equiv.). The resulting solution was stirred for 3 h under reflux. After removal of



Scheme 8. Asymmetric synthesis of constrained bicyclic γ^2-amino acid derivative **23** bearing the alkynyl side chain.

solvent, the crude product was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **5;** yield: 15 mg (83%); $[\alpha]_D^{20}$: −17.4 (*c* 0.8 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.51 (m, 1H), 7.44 (m, 2H), 7.28 (m, 3H), 4.65 (m, 2H), 3.89 (m, 1H), 2.82 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 131.8, 128.7, 128.3, 128.1, 122.0, 84.8, 84.6, 76.6, 36.4, 27.5; HR-MS: m/z = 233.0687, calcd. for $C_{12}H_{11}NO_4$ $[M]^+$: 233.0688.

Asymmetric Synthesis of β-Functionalized δ-Ketolactone 6

To a solution of compound **5** (56 mg, 0.24 mmol) in CF_3CH_2OH (2 mL) was added PIFA (155 mg, 0.36 mmol, 1.5 equiv.) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The solution was extracted with CH_2Cl_2 and the separated organic phase was washed by saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **6**; yield: 32 mg (54%); $[\alpha]_D^{20}$: −5.1 (*c* 0.6 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.2 Hz, 2H), 7.68 (m, 1H), 7.54 (m, 2H), 5.62 (d, J = 4.5 Hz, 1H), 4.71 (m, 1H), 4.57 (m, 1H), 3.35 (brs, 1H), 2.96 (m, 1H), 2.47 (dd, J = 5.4, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.9, 173.1, 134.9, 133.5, 129.3, 129.1, 79.3, 75.8, 35.7, 31.0. HR-MS: m/z = 249.0654, calcd. for $C_{12}H_{11}NO_5$ $[M]^+$: 249.0637; HPLC (Chiralpak AD-H, 2-propanol/hexane = 20/80, flow rate 0.7 mL min^{-1}, λ = 210 nm): t_{minor} = 30.9, t_{major} = 37.0 min.

Asymmetric Synthesis of Chiral γ-Alkylidenelactone 7

To a solution of compound **5** (23 mg, 0.1 mmol) in acetonitrile (0.5 mL) at room temperature was added gold chloride (10 mol%) and K_2CO_3 (0.1 equiv.). The reaction mixture was stirred until disappearance of the starting material **5** (TLC monitoring). The reaction solution was extracted with DCM and the combined organic layers were dried over Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **7**; yield: 14 mg (61%); $[\alpha]_D^{20}$: −7.4 (*c* 0.3 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.5 Hz, 2H), 7.36 (m, 3H), 5.62 (m, 1H), 4.71 (m, 1H), 4.57 (m, 1H), 4.02 (m, 1H), 3.08 (m, 1H), 2.71 (dd, J = 4.8, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 145.8, 132.6, 128.7, 128.6, 127.8, 107.2, 77.0, 37.0, 31.6. HR-MS: m/z = 233.0683, calcd. for $C_{12}H_{11}NO_4$ $[M]^+$: 233.0688; HPLC (Chiralcel OD-H, 2-propanol/hexane = 20/80, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_{minor} = 8.2, t_{major} = 17.4 min.

Asymmetric Synthesis of Chiral β-Alkynyl-γ-amino Acid 10

To a solution of compound **5** (93 mg, 0.40 mmol) in DCM (5 mL) was added $(COCl)_2$ (52 mg, 0.40 mmol) followed by DMF (1 drop) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. Then MeOH (19 mg, 0.6 mmol, 1.5 equiv.) was added at 0 °C. The reaction solution was stirred for 2 h at 0 °C and extracted with EtOAc. The separated organic phase was washed by saturated aqueous $NaHCO_3$. The combined organic phase was dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **8**; yield: 63 mg (64%); $[\alpha]_D^{20}$: −4.7 (*c* 0.8 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5H), 4.67 (m, 2H), 3.88 (m 1H), 3.75 (s, 3H), 2.77 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 131.8, 128.6, 128.3, 122.1, 84.9, 84.6, 76.6, 52.1, 36.4, 27.7; HR-MS: m/z = 270.0739, calcd. for $C_{13}H_{13}NO_4Na$ $[M+Na]^+$: 270.0742; HPLC (Chiralcel OD-H, 2-propanol/hexane = 15/85, flow rate 0.7 mL min^{-1}, λ = 210 nm): t_{minor} = 21.8, t_{major} = 27.2 min.

To a solution of compound **8** (49 mg, 0.20 mmol) in EtOH (2 mL) was added Zn powder (195 mg, 15 equiv.). The resulting mixture was stirred for 10 min at 35 °C. 4M HCl (1.25 mL) was added. The reaction mixture was stirred overnight. After filtration, the filtrate was evaporated under vacuum. Then 2M NaOH was added to the residue, and the resulting solution was stirred for 5 min. The reaction mixture was extracted with DCM and the combined organic phase was dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was used for next step without further purification.

To a solution of the crude product obtained in THF (2 mL) was added $(Boc)_2O$ (25 mg, 0.18 mmol) followed by DIPEA (15 mg, 0.18 mmol) at 0 °C. The resulting solution was stirred for 30 min. After removal of solvent, the residue was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **9**; yield: 32 mg (48% over two steps); $[\alpha]_D^{20}$: −1.5 (*c* 0.4 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (m, 2H), 7.27 (m, 3H), 4.90 (brs, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.32 (m, 3H), 2.58 (d, J = 6.6 Hz, 2H), 1.40 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 155.8, 131.7, 128.2, 128.1, 123.0, 88.9, 83.1, 79.6, 60.7, 44.0, 37.4, 30.1, 28.4, 14.2; HR-MS: m/z = 354.1680, calcd. for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$: 354.1681; HPLC (Chiralcel OD-H,

2-propanol/hexane = 10/90, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_{major} = 9.5 min, $_{tminor}$ = 11.3 min.

To a solution of compound **9** (17 mg, 0.05 mmol) in MeOH/H_2O (2:1) (1.5 mL) was added LiOH (6 mg, 0.25 mmol, 5 equiv.). The resulting mixture was stirred for 2 h at room temperature, acidified with 10% citric acid and extracted with EtOAc. The combined organic phase was evaporated under vacuum. The residue was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **10**; yield: 14 mg (91%); $[\alpha]_D^{20}$: −4.4 (*c* 0.2 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (m, 2H), 7.28 (m, 3H), 4.98 (brs, 1H), 3.28 (m, 3H), 2.65 (brs, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 156.2, 131.8, 128.2, 128.1, 122.9, 88.6, 83.2, 78.0, 43.7, 37.1, 29.9, 28.3. HR-MS: *m/z* = 303.1480, calcd. for $C_{17}H_{21}NO_4$ $[M]^+$: 303.1471.

Asymmetric Synthesis of Chiral β-Alkynyl-γ-lactam 11

The compound **9** (23, 0.07 mmol) was dissolved in dry PhMe (1.5 mL). The solution was cooled to −20 °C. Then a solution of $AlMe_3$ (0.055 mL, 0.11 mmol, 2.0 M in PhMe) was added dropwise slowly under the atmosphere of N_2. The reaction was stirred at −20 °C for 2 h and then quenched with saturated aqueous Rochelle's salt (2.0 mL). The mixture was warmed to room temperature and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **11**;[6] yiele: 16 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (m, 2H), 7.32 (m, 3H), 4.09 (t, *J* = 8.1 Hz, 1H), 3.78 (t, *J* = 7.5 Hz, 1H), 3.37 (t, *J* = 8.1 Hz, 1H), 2.87 (m, 1H), 2.73 (m, 1H), 1.56 (brs, 9H).

General Procedure for Asymmetric Synthesis of Chiral 1,5-Dicarbonyl Compounds

To a solution of compound **5** (39 mg, 0.17 mmol) in dry DCM (5 mL) was added EDC·HCl (48 mg, 0.26 mmol, 1.5 equiv.), HOBt (34 mg, 0.26 mmol, 1.5 equiv.) and BnOH (28 mg, 0.26 mmol, 1.5 equiv.). The resulting solution was cooled to 0 °C and Et_3N (25 mg, 0.26 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 6 h at room temperature. Then the reaction solution was washed by 1 M HCl and saturated aqueous $NaHCO_3$. After removal of solvent, the residue was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **12a**; yield: 38 mg (65%).

Characterization of a representative compound – (*S*)-benzyl 3-(nitromethyl)-5-oxo-5-phenylpentanoate (12a): $[\alpha]_D^{20}$: −1.9 (*c* 0.5 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 7.28 (m, 5H), 5.14 (s, 2H), 4.67 (d, *J* = 4.8 Hz, 2H), 3.33 (m, 1H), 3.28 (brs, 2H), 2.67 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 171.1, 135.5, 133.6, 128.8, 128.6, 128.3, 128.0, 127.0, 77.4, 66.7, 39.0, 35.4, 28.0; HR-MS: *m/z* = 341.3054, calcd. for $C_{19}H_{19}NO_5$ $[M]^+$: 341.3056; HPLC (Chiralpak AD-H, 2-propanol/hexane = 10/90, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_{major} = 35.7 min, t_{minor} = 37.8 min.

Synthesis of Substituted Pyrrole-3-carboxylic Acid 17

To a solution of compound racemic **4l** (30 mg, 0.10 mmol) and $BnNH_2$ (13 mg, 0.12 mmol) in toluene (2 mL) was added $FeCl_3$ (2 mg, 10 mol%) under an atmosphere of N_2. The resulting mixture was stirred for 3 h under reflux. After removal of solvent, the crude product was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **17** as a yellow solid; yield: 22 mg (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 6.9 Hz, 2H), 7.30 (m, 6H), 7.03 (d, *J* = 6.6 Hz, 2H), 6.90 (s, 1H), 5.04 (s, 2H), 4.33 (t, *J* = 6.9 Hz, 2H), 2.46 (s, 3H), 1H), 1.39 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 136.5, 136.2, 131.3, 129.0, 128.2, 128.0, 127.5, 126.5, 126.1, 124.3, 113.5, 105.0, 89.9, 84.1, 59.7, 50.7, 14.5, 11.3; HR-MS: *m/z* = 343.1567, calcd. for $C_{23}H_{21}NO_2$ $[M]^+$: 343.1572.

Synthesis of Tetrasubstituted Furan 18

To a solution of compound racemic **4l** (30 mg, 0.10 mmol) in MeOH (2 mL) was added $AuCl_3$ (1.5 mg, 5 mol%). The resulting mixture was stirred for 26 h at 65 °C. After removal of solvent, the crude product was purified through column chromatography on silica gel (petroleum ether/ethyl acetate as eluents) to afford the compound **18** as a yellow solid; yield: 12 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 3H), 7.17 (m, 2H), 5.42 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 2.55 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 159.4, 153.5, 136.3, 128.9, 128.4, 127.1, 110.5, 69.1, 60.5, 32.2, 14.1, 14.0; HR-MS: *m/z* = 303.1109, calcd. for $C_{16}H_{17}NO_5$ $[M]^+$: 303.1107.

General Procedure for Organocatalytic Asymmetric Conjugate Addition of α-Substituted β-Keto Esters to Nitroenynes

To a solution of catalyst **21h** (10 mol%) in Et_2O (0.5 mL) was added α-substituted β-keto ester **19** (0.15 mmol) and nitroenyne **2** (0.3 mmol) at −10 °C. The resulting solution was stirred at −10 °C until the reaction was complete (monitored by TLC). The volatile components were removed under reduced pressure and the crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (*R*)-ethyl 1-[(*S*)-1-nitro-4-phenylbut-3-yn-2-yl]-2-oxocyclopentanecarboxylate (20a): $[\alpha]_D^{20}$: −7.0 (*c* 1.0 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 5H), 4.85 (dd, *J* = 4.2, 4.2 Hz, 1H), 4.53 (t, *J* = 12.3 Hz, 1H), 4.31 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.53 (m, 2H), 2.26 (m, 2H), 2.17 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.4, 168.5, 131.8, 128.8, 128.3, 121.8, 86.0, 83.7, 76.0, 62.4, 61.1, 38.1, 35.3, 30.4, 20.1, 14.0; HR-MS: *m/z* = 329.1268, calcd. for $C_{18}H_{19}NO_5$ $[M]^+$: 329.1263; HPLC (Chiralcel OJ-H, 2-propanol/hexane = 10/90, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_{minor} = 39.2 min, t_{major} = 44.8 min.

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