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Combined organo- and gold-catalyzed enantioselective synthesis of bicyclic enones

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

By combining organocatalysis with gold catalysis highly enantioenriched bicyclic enones are available via an operationally simple one-pot procedure. Iminium-ion activation by cinchona alkaloid-derived primary amine catalysts induces the Michael addition of propargylated malononitriles and cyanoacetates to α,β-unsaturated ketones. The resulting intermediates undergo an *exo-dig* cyclization, forming a new C–C bond followed by double-bond isomerization to give highly functionalized bicyclic enones in good yields and high enantioselectivities.

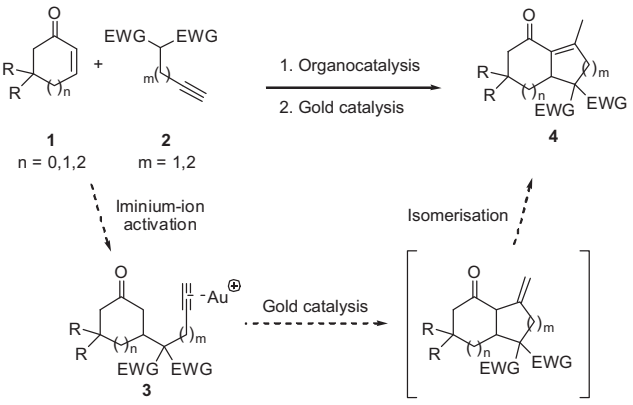
1. Introduction

Chemists remain intrigued by the ability of biological systems to transform simple compounds into a myriad of complex molecules. Cascade and tandem methods represent a possible way to mimic the efficiency of Nature, minimizing the number of required synthetic steps, and thus improving atom economy and lowering solvent use.[1] Asymmetric organocatalytic processes have become a powerful tool in the one-pot formation of multiple bonds and stereocenters without isolation of intermediates.[2] For example, the use of amine organocatalysts in iminium-ion/enamine activation sequences allows the efficient, consecutive introduction of nucleophiles and electrophiles.[3] To date these organocatalytic, asymmetric cascade reactions often rely on only one catalyst. However, the combination of two catalysts provides the opportunity of dual-activation of the substrates, and thus a more general approach.[4]

Soft transition metals such as gold and copper are capable of activating π-bonds under mild conditions using low catalyst loadings. Numerous cascade reactions utilizing this relatively recently developed chemistry have appeared.[5] Specifically, these Lewis acids have been shown to be good catalysts for the synthesis of complex carbocycles.[6] Moreover, the combination of transition-metal catalysis with organocatalysis has received increasing attention and proven to be an important strategy for the development of many unprecedented transformations.[7]

Kirsch et al. were able to combine gold- and amino-catalysis in a carbocyclization of aldehydes with alkynes.[6f] Recently, Dixon et al. combined amino- and copper-catalysis in a one-pot cascade reaction of propargylated malonates with α,β-unsaturated ketones and aldehydes forming racemic cyclopentene products.[8] These works have led to the development of asymmetric versions of these processes.[9]

Herein, we present the reaction of α,β-unsaturated ketones **1** with alkyne-tethered nucleophiles **2** to give, via intermediates **3**, bicyclic enones **4** in a highly enantioselective tandem reaction (Scheme 1).



Scheme 1. Combination of enantioselective organo- and gold-catalysis.

2. Results and discussion

The formation of bicyclic enones is based on the following reaction sequence: First, the iminium-ion activation of α,β-unsaturated ketones **1** induces the Michael addition of propargylated nucleophiles **2**. Then, the resulting intermediate **3** undergoes an *exo-dig* cyclization, forming the second C–C bond followed by double-bond isomerization to give bicyclic enones **4**.

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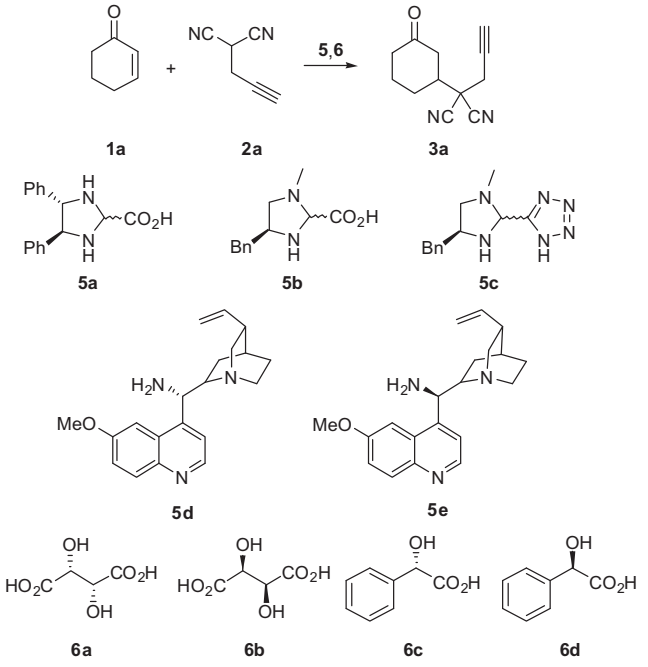
Initial screening with an alkyne-tethered malonate (EWG = CO_2Me) and 1,3-diketone (EWG = COMe) led to no satisfactory conversion in the addition step.[9a] However, switching to the more reactive and less sterically hindered propargylated malononitrile **2a** proved to be successful and allowed us to study the Michael addition reaction. Different organocatalysts were tested and the results are listed in Table 1.[10]

Table 1
Screening of organocatalysts for the Michael addition of propargylated malononitrile **2a** to cyclohexenone **1a**



Entry	Organocatalyst	Acid[c]	Solvent	Yield **3a**[d] (%)	ee[e] (%)
1	**5a**[a]	—	Toluene	0	—
2	**5b**[a]	—	Toluene	58	20
3	**5c**[a]	—	Toluene	65	33
4	**5d**[a]	TFA[c]	Toluene	84	66
5	**5d**[a]	TFA[c]	CH_2Cl_2	91	76
6	**5d**[a]	—	CH_2Cl_2	86	0
7	**5d**[a]	**6a**[c]	CH_2Cl_2	68	53
8	**5d**[a]	**6b**[c]	CH_2Cl_2	80	6
9	**5d**[a]	**6c**[c]	CH_2Cl_2	97	88
10	**5d**[b]	**6d**[c]	Et_2O	90	92
11	**5e**[b]	**6c**[c]	Et_2O	95 (*ent*-**3a**)	92

Conditions: 0.3 mmol **1a** and 0.2 mmol **2a**, rt, 18 h.
[a] 20 mol %.
[b] 5 mol %.
[c] Two equivalents relative to catalyst.
[d] Isolated yield.
[e] Determined by chiral HPLC.

Table 1 shows that cinchona alkaloid-derived primary amine catalysts **5d**,**e** gave the best results, both in terms of yield and the enantioselectivity of **3a**. Furthermore, the acid additive has a very important influence on the enantioselectivity of the reaction. Protonation of the imine by the acid additive gives an iminium-ion, which is tightly ion-paired with the respective anion, responsible for the observed effect. Ion-pairing in iminium-ions has been proposed by previous calculations.[10p] If catalyst **5d** is used without additive the reaction still proceeds with good yield, but only racemic adduct **3a** is formed (entry 6). The best results, up to 92% ee, were obtained with mandelic acid **6c/d** (entries 9 and 10). The reaction proceeded efficiently at a catalyst loading of 5 mol % (entries 10 and, 11). Lower catalyst loadings (2.5 mol % and 1 mol %) gave also good results, but required prolonged reaction times. Non-polar solvents, such as CH_2Cl_2, toluene, or Et_2O, were found to be best suited for the reaction and could be used without affecting the yields or enantioselectivities of the reaction. Lowering the temperature to 4 °C increased the enantioselectivity only marginally; however, the reaction rate was reduced considerably. Finally, utilizing the quasienantiomeric combination of **5e** and **6c** under the optimal conditions gave the opposite enantiomer of the product with nearly identical results (entry 11). The absolute configuration of the product **3a** was assigned to be (*S*) by single-crystal analysis (Fig. 1).[11] The stereochemistry of the product formed indicates that the nucleophile attacks from the *Si*-face of the iminium-ion intermediate.

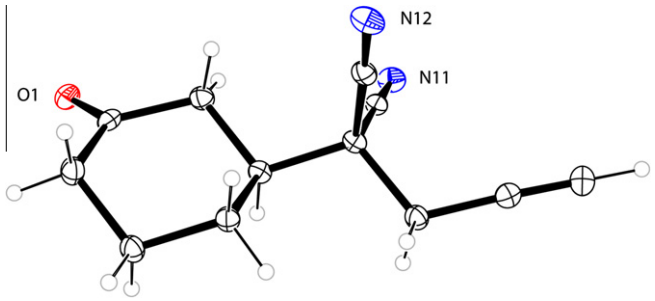
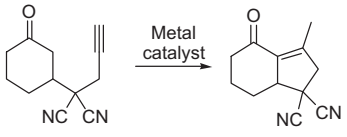


Figure 1. Ortep plot at 30% ellipsoid probability of **3a**.

Having found the optimal conditions for the first step of the cascade reaction, the second step was investigated. Several transition metals such as Cu, Ag, Au, Pt, and Pd are known to activate alkynes toward nucleophilic attack.[5,6] A variety of transition metal salts and additives were tested in the *5-exo-dig* cyclization reaction of **3a** to **4a** and some representative results are presented in Table 2. It was found that gold complexes showed promising reactivities (entries 4–11), and thus the Lewis-acid catalyst [bis(trifluoromethanesulfonyl)imidate](PPh$_3$)Au(I) (2:1) toluene adduct (Au(NTf$_2$)PPh$_3$)

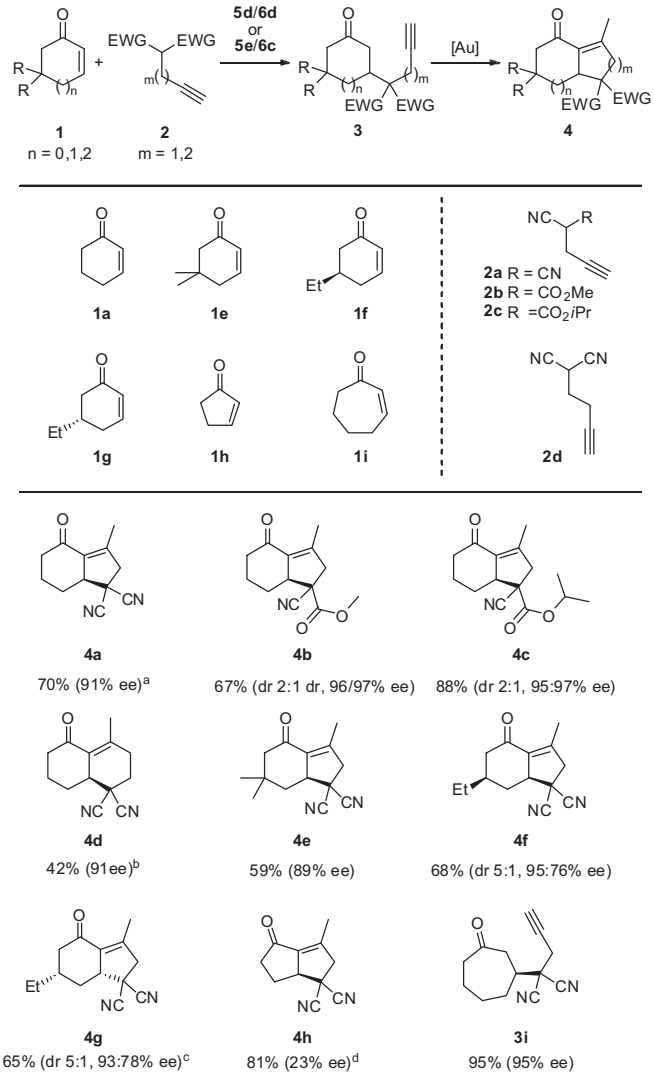
Table 2
Screening of different Lewis-acid catalysts for the cyclization



Entry	Metal catalyst	Additive	Yield[d] (%)	ee[e] (%)
1	$Pd(OAc)_2$[a]	—	—	—
2	$Pd(PPh_3)_4$[a]	—	—	—
3	$Cu(MeCN)_4OTf$[a]	—	—	—
4	Au(NTf$_2$)(PPh$_3$)[a]	—	89 (100)	90
5	Au(NTf$_2$)(PPh$_3$)[b]	PPh$_3$	—	—
6	Au(NTf$_2$)(PPh$_3$)[b]	1 equiv Pyrrolidine	85 (100)	0
7	Au(NTf$_2$)(PPh$_3$)[b]	5 mol % **5d**	—	—
8	Au(NTf$_2$)(PPh$_3$)[b]	5 mol % **5d**, 10 mol % **6d**	22 (35)	89
9	Au(NTf$_2$)(PPh$_3$)[b]	5 mol % **5d**, 10 mol % **6d** 10 mol % pTSA	45 (74)	91
10	Au(NTf$_2$)(PPh$_3$)[b]	5 mol % **5d**, 10 mol % **6d** 20 mol % pTSA	56 (100)	91
11	Au(NTf$_2$)(PPh$_3$)[b,c]	5 mol % **5d**, 10 mol % **6d** 20 mol % pTSA	70 (100)	91

Conditions: 0.1 mmol **3a**, 0.4 mL CH_2Cl_2, 45 °C.
[a] 20 mol %.
[b] 5 mol %.
[c] 0.4 mL Et_2O was used instead of CH_2Cl_2.
[d] Isolated yield, conversion given in parenthesis.
[e] Determined by HPLC on a chiral stationary phase.

was chosen for this work. Application of this complex allowed us to perform the cyclization reaction with full retention of the stereocenter, which was obtained in the first step. Pyrrolidine was also found to accelerate the reaction as observed in previous work[8] but led to racemization of the product obtained (entry 6). In contrast to this, it was found that organocatalysts **5d/e** impede the reaction (entries 7 and 8). By ^{31}P NMR spectroscopy, coordination of the organocatalyst to the gold cation was observed. To overcome this problem 20 mol % *para*-toluenesulfonic acid (pTSA) was added to block the organocatalyst and keep the gold catalyst sufficiently active (entries 9–11). Diethylether was found to be a good solvent for the carbocyclization reaction and 70% yield from isolated intermediate **3a** was obtained in the presence of the organocatalyst **5d** (entry 11). With this information in hand, a two-step protocol for the cascade reaction was elaborated. First, organocatalyst **5d**/**6d** or **5e**/**6c** activates enone **1a** for the attack of nucleophile **2a** to give **3a** or *ent*-**3a**, respectively. After full conversion, pTSA and gold salt were added and the mixture was heated to 45 °C to cause the carbocyclization to give **4a** or *ent*-**4a**, respectively, in a one-pot reaction. Lowering the amount of cyclohexenone **1a** from 2 equiv to 1.5 equiv was important in order to minimize side product formation and thus increase the yield of **4a** to 70% in one-pot (see Scheme 2).

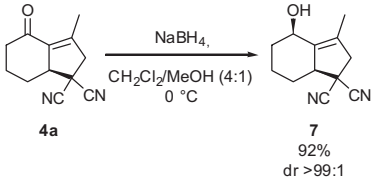


Scheme 2. Scope and limitations of the cascade reaction. [a] Both **4a** and *ent*-**4a**, [b] two-pot procedure, [c] **5e/6c** was used as organocatalyst, [d] two-pot procedure; Au(Cl)(IPr)/AgOTf was used as metal catalyst.

Furthermore, we investigated the scope of the cascade reaction for different cycloalkenones **1** with propargylated malononitriles **2a**,**d** and cyanoacetates **2b**,**c** (Scheme 2). For cyclohexenone **1a** reacting with propargylated malononitrile **2a**, bicyclic enone **4a** was obtained in 70% yield and 91% ee. Compound **1a** reacted with the propargylated cyanoacetates **2b**,**c** to give optically active products **4b** and **4c** as a 2:1 diastereomeric mixture with high enantioselectivity (up to 97% ee). The addition of homo-propargylated malononitrile **2d** proceeded smoothly. However, to effect the *6-exo-dig* cyclization, intermediate **3d** had to be isolated and reacted separately in order to obtain an acceptable yield of **4d** (42%) with 91% ee. 5,5-Dimethyl cyclohexenone **1e** reacted cleanly with the chosen reaction conditions giving **4e** in a moderate yield (59%) and with 89% ee. The 5-ethyl substituted cyclohexenones **1f** and **1g** were prepared in enantioenriched form (90% ee) with a known absolute configuration.[12] As anticipated, a matched/mismatched situation was found. Whereas **1f** gave a 1:5 diastereoselectivity in the addition to **2a** with catalyst **5d**/**6d**, **1g** gave a 1:1 mixture of diastereoisomers. Using the pseudo-enantiomeric catalyst **5e**/**6c** with **1g** and **2a**, comparable results were obtained (dr 5:1). The relative configurations **4f**/**g** were assigned assuming reagent control by the organocatalyst.

Isolated compound **3h** from cyclopentenone **1h** was successfully cyclized using a combination of Au(IPr)Cl/AgOTf (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as the catalyst.[13] Unfortunately, the cyclization of addition product **3i**, derived from cycloheptenone **1i** and **2a**, was not observed under all conditions tested.

Additionally, we were able to reduce product **4a** with $NaBH_4$ in CH_2Cl_2/MeOH (Scheme 3). Alcohol **7** was obtained in a highly diastereoselective manner (dr >99:1) and with an excellent yield (92%). The relative stereochemistry of **7** (4*R*,7a*R*) was assigned by an NOE experiment and is in agreement with the stereochemical expectation.



Scheme 3. Reduction of **4a** with $NaBH_4$.

3. Conclusion

We have shown a tandem reaction sequence, combining the iminium-ion activation of cyclic α,β-unsaturated ketones with gold-catalyzed carbocyclization of the generated addition products. Highly enantioenriched bicyclic enones **4** have been formed. Despite limitations in the scope, the reaction can be useful in the construction of highly functionalized, versatile molecules.

4. Experimental

4.1. General methods

The NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz and 100 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ ^1H NMR: 7.26 ppm; ^{13}C NMR (77.0 ppm). The following abbreviations are used to indicate the multiplicity in ^1H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br s, broad signal. Mass spectra were recorded on a micromass LCT

spectrometer using electrospray ionization (ESI) techniques. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary-phase HPLC (Daicel Chiralpak AD column) or GC (Agilent Cyclosil B). Analytical grade solvents and commercially available reagents, including gold catalysts [bis(trifluoromethanesulfonyl)imidate](PPh$_3$)Au(I) (2:1) toluene adduct and chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]Au(I), were purchased from Aldrich and used without further purification. Nucleophiles **2a**–**d**[14a] and ketones **1e**–**g**[12,14b] were synthesized according to the literature procedures.

4.2. General procedures

4.2.1. Addition

Nucleophile **2** (0.2 mmol) and the salt of **5d** and 2 equiv **6d** (3.1 mg, 5 mol %) were dissolved in Et$_2$O (0.8 mL). Ketone **1** (0.3 mmol) was added and the resulting mixture stirred at room temperature for 16 h. Adduct **3** was isolated by FC with a gradient of 10–30% Et$_2$O in pentane.

4.2.2. Carbocyclization

Adduct **3** (0.2 mmol), pTSA·H$_2$O (3.8 mg, 20 mol %), and Au(NTf$_2$)(PPh$_3$)(C$_7$H$_8$)$_{0.5}$ (4 mg, 5 mol %) were dissolved in Et$_2$O (0.8 mL). The mixture was warmed to 45 °C for 16 h in a tightly closed screw-capped vial and the cyclopentene product **4** was isolated by FC with a gradient of 10–30% Et$_2$O in pentane.

4.2.3. Combination

Nucleophile **2** (0.2 mmol) and the pre-formed salt of **5d** and 2 equiv **6d** (3.1 mg, 5 mol %) were dissolved in Et$_2$O (0.8 mL). Ketone **1** (0.3 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. pTSA·H$_2$O (3.8 mg, 20 mol %) and [Au(NTf$_2$)(PPh$_3$)] (C$_7$H$_8$)$_{0.5}$ (4 mg, 5 mol %) were added and the mixture was warmed to 45 °C for 16 h. Product **4** was isolated by FC with a gradient of 10–30% Et$_2$O in pentane.

4.2.3.1. (*S*)-2-(3-Oxocyclohexyl)-2-(prop-2-ynyl)malononitrile 3a. Colorless solid; mp: 78 °C; R_f = 0.26 (Et$_2$O/pentane = 2:1); $[\alpha]_D^{25} = -17.1$ (*c* 1, CH$_2$Cl$_2$); 92% ee; GC: t_R = 48.5 and 48.8 min (1 min at 70 °C heated to 160 °C at 10 °C/min, hold 30 min, then heated to 180 °C at 10 °C/min., hold 10 min.; flow: 1 mL/min); ^{1}H NMR (CDCl$_3$): δ = 1.67–1.80 (m, 2H), 2.24–2.40 (m, 4H), 2.47–2.57 (m, 2H), 2.65–2.71 (m, 1H), 2.92 (dd, *J* = 17.0, 2.7 Hz, 1H), 3.00 (dd, *J* = 17.0, 2.7 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 23.8, 26.4, 27.1, 40.6, 41.7 (C$_q$), 42.7, 42.7, 73.9 (C$_q$, alkyne), 76.1 (CH, alkyne), 113.3 (C$_q$, CN), 113.7 (C$_q$, CN), 206.4 (C$_q$, C=O); HRMS: calcd for C$_{12}$H$_{12}$N$_2$NaO [M+Na]: 223.0847; found: 223.0842.

4.2.3.2. (*R*)-3-Methyl-4-oxo-5,6,7,7a-tetrahydro-1*H*-indene-1,1(2*H*,4*H*)-dicarbonitrile 4a. Colorless oil; R_f = 0.34 (Et$_2$O/pentane 2:1), $[\alpha]_D^{25} = -7.6$ (*c* 0.44, CH$_2$Cl$_2$), 90% ee; *ent*-**4a**: $[\alpha]_D^{25} = +7.2$ (*c* 0.56, CH$_2$Cl$_2$), 90% ee; HPLC: t_R = 13.1 min, 16.8 min (AD, 90:10 hexane/isopropanol, flow: 1 mL/min); ^{1}H NMR (CDCl$_3$): δ = 1.74–1.91 (m, 2H), 2.18 (s, 3H), 2.19–2.22 (m, 1H), 2.27–2.36 (m, 2H), 2.52–2.59 (m, 1H), 3.01–3.14 (m, 1H), 3.21–3.26 (m, 1H), 3.46–3.50 (m, 1H); ^{13}C NMR (CDCl$_3$): δ = 15.9, 22.2, 26.9, 38.3 (C$_q$), 40.4, 48.7, 54.9, 114.4 (C$_q$, CN), 115.0 (C$_q$, CN), 130.9 (C$_q$, C=C), 148.4 (C$_q$, C=C), 196.9 (C$_q$, C=O); HRMS: calcd for C$_{12}$H$_{12}$N$_2$NaO [M+Na]: 223.0847; found: 223.0842.

4.2.3.3. (*S*)-Methyl 2-cyano-2-(3-oxocyclohexyl)pent-4-ynoate 3b. Colorless oil; R_f = 0.29 (both diastereoisomers, Et$_2$O/pentane 2:1); dr = 1:2; major diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.60–1.75 (m, 2H), 1.78–1.83 (m, 1H), 2.11–2.17 (m, 1H), 2.22 (t, *J* = 2.6 Hz, 1H), 2.27–2.41 (m, 3H), 2.42–2.48 (m, 2H), 2.53–2.58 (m, 1H), 2.74 (dd, *J* = 16.5, 2.6 Hz, 1H), 2.80 (dd, *J* = 16.5, 2.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (CDCl$_3$): δ = 24.0, 25.3, 27.5, 40.7, 43.0 (CH$_3$, OMe), 42.5, 53.8 (CH), 53.9 (C$_q$), 73.6 (CH, alkyne), 76.1 (C$_q$, alkyne), 116.5 (C$_q$, CN), 167.3 (C$_q$, COO), 207.6 (C$_q$, C=O); minor diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.60–1.75 (m, 2H), 1.78–1.83 (m, 1H), 2.11–2.17 (m, 1H), 2.23 (t, *J* = 2.7 Hz, 1H), 2.27–2.41 (m, 3H), 2.42–2.48 (m, 2H), 2.53–2.58 (m, 1H), 2.79 (dd, *J* = 16.7, 2.7 Hz, 1H), 2.86 (dd, *J* = 16.7, 2.7 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (CDCl$_3$): δ = 23.9, 25.5, 26.2, 40.5, 43.2 (CH$_3$, OMe), 43.5, 53.9 (CH), 53.9 (C$_q$), 73.6 (CH, alkyne), 76.2 (C$_q$, alkyne), 116.7 (C$_q$, CN), 167.1 (C$_q$, COO), 207.5 (C$_q$, C=O); HRMS: calcd for C$_{13}$H$_{15}$NNaO$_3$ [M+Na]: 256.0950; found: 256.0948.

4.2.3.4. (*S*)-Methyl-1-cyano-3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1*H*-indene-1-carboxylate 4b. Colorless oil; R_f = 0.49 and 0.48 (major/minor diastereoisomer, Et$_2$O/pentane 2:1); $[\alpha]_D^{25} = +7.7$ (*c* 0.5, CH$_2$Cl$_2$), 96% ee major diastereoisomer, 97% ee minor diastereoisomer, dr = 1:2; HPLC: t_R = 25.3/34.6 and 27.8/36.0 min. (major/minor diastereoisomer, AD, 97:3 hexane/isopropanol, flow: 1 mL/min); major diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.20–1.27 (m, 1H), 1.70–1.89 (m, 2H), 2.09–2.17 (m, 2H), 2.14 (s, 3H), 2.18–2.33 (m, 1H), 2.45–2.53 (m, 1H), 2.88–2.92 (m, 1H), 3.24–3.29 (m, 1H), 3.35–3.40 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (CDCl$_3$): δ = 14.9, 21.7, 26.5, 29.3 (C$_q$), 39.5, 46.7, 52.3, 52.9, 117.2 (C$_q$, CN), 130.1 (C$_q$, C=C), 147.7 (C$_q$, C=C), 167.5 (C$_q$, COO), 197.0 (C$_q$, C=O); minor diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.20–1.27 (m, 1H), 1.70–1.89 (m, 2H), 2.09–2.17 (m, 2H), 2.14 (s, 3H), 2.18–2.33 (m, 1H), 2.45–2.53 (m, 1H), 3.02–3.14 (m, 2H), 3.61–3.66 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (CDCl$_3$): δ = 14.6, 21.8, 25.9, 28.7 (C$_q$), 39.3, 46.3, 52.0, 56.0, 119.0 (C$_q$, CN), 129.5 (C$_q$, C=C), 149.1 (C$_q$, C=C), 166.7 (C$_q$, COO), 196.8 (C$_q$, C=O); HRMS: calcd for C$_{13}$H$_{15}$NNaO$_3$ [M+Na]: 256.0950; found: 256.0948.

4.2.3.5. (*S*)-Isopropyl 2-cyano-2-(3-oxocyclohexyl)pent-4-ynoate 3c. Colorless oil; R_f = 0.34 and 0.32 (major/minor diastereoisomer, Et$_2$O/pentane 2:1); dr = 1:2; major diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.34 (d, *J* = 6.3 Hz, 3H), 1.35 (d, *J* = 1.3 Hz, 3H), 1.60–1.76 (m, 2H), 1.80–1.85 (m, 1H), 2.12–2.17 (m, 1H), 2.20 (t, *J* = 2.7 Hz, 1H), 2.27–2.39 (m, 3H), 2.41–2.48 (m, 1H), 2.53–2.56 (m, 1H), 2.72 (dd, *J* = 16.7, 2.7 Hz, 1H), 2.78 (dd, *J* = 16.7, 2.7 Hz, 1H), 5.17 (sept, *J* = 6.3 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 21.8 (CH$_3$), 24.3, 25.5, 27.6, 41.0, 42.8, 43.3 (CH, OCH), 54.1 (C$_q$), 72.0 (CH), 73.8 (CH, alkyne), 76.5 (C$_q$, alkyne), 116.9 (C$_q$, CN), 166.3 (C$_q$, COO), 208.0 (C$_q$, C=O); minor diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.34 (d, *J* = 6.3 Hz, 3H), 1.35 (d, *J* = 1.3 Hz, 3H), 1.60–1.76 (m, 2H), 1.80–1.85 (m, 1H), 2.12–2.17 (m, 1H), 2.20 (t, *J* = 2.7 Hz, 1H), 2.27–2.39 (m, 3H), 2.41–2.48 (m, 1H), 2.53–2.56 (m, 1H), 2.76 (dd, *J* = 16.5, 2.6 Hz, 1H), 2.85 (dd, *J* = 16.5, 2.6 Hz, 1H), 5.17 (sept, *J* = 6.3 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 21.8 (CH$_3$), 24.2, 25.8, 26.4, 40.8, 43.4 (CH, OCH), 43.8, 53.9 (C$_q$), 72.1 (CH), 73.7 (CH, alkyne), 76.6 (C$_q$, alkyne), 117.1 (C$_q$, CN), 166.5 (C$_q$, COO), 207.9 (C$_q$, C=O); HRMS: calcd for C$_{15}$H$_{19}$NNaO$_3$ [M+Na]: 284.1263; found: 284.1263.

4.2.3.6. (*S*)-Isopropyl 1-cyano-3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1*H*-indene-1-carboxylate 4c. Colorless oil; R_f = 0.64 and 0.59 (major/minor diastereoisomer, Et$_2$O/pentane 2:1); $[\alpha]_D^{25} = +14.0$ (*c* 0.5, CH$_2$Cl$_2$), 95% ee major diastereoisomer, 97% ee minor diastereoisomer, dr = 1:2; HPLC: t_R = 13.9/17.0 and 23.2/25.7 min (major/minor diastereoisomer, AD, 97:3 hexane/isopropanol, flow: 1 mL/min). major diastereoisomer: ^{1}H NMR (CDCl$_3$): δ = 1.32 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.72–1.90 (m, 2H), 2.08–2.14 (m, 2H), 2.14 (s, 3H), 2.24–2.34 (m, 1H), 2.47–2.53 (m, 1H), 2.86–2.91 (m, 1H), 3.23–3.28 (m, 1H), 3.32–3.38 (m, 1H), 5.11 (sept, *J* = 6.2 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 15.9 (CH$_3$), 21.5 (CH$_3$), 21.6 (CH$_3$), 22.7, 27.5, 40.5, 47.5, 53.2 (CH),

53.4 (C_q), 71.3 (C_q), 118.4 (C_q, CN), 131.1 (C_q, C=C), 148.8 (C_q, C=C), 167.3 (C_q, COO), 198.1 (C_q, C=O); minor diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 1.29–1.36 (m, 1H), 1.33 (d, J = 6.2 Hz, 6H), 1.66–1.79 (m, 1H), 2.09–2.25 (m, 3H), 2.13 (s, 3H), 2.45–2.51 (m, 1H), 3.01–3.14 (m, 2H), 3.60–3.66 (m, 1H), 5.09 (sept, J = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.9 (CH_3), 21.9 (CH_3), 22.0 (CH_3), 23.2, 27.0, 40.6, 47.7, 48.7, 57.2 (CH), 71.6 (C_q), 120.4 (C_q, CN), 130.9 (C_q, C=C), 150.5 (C_q, C=C), 166.8 (C_q, COO), 198.2 (C_q, C=O); HRMS: calcd for $C_{15}H_{19}NNaO_3$ [M+Na]: 284.1263; found: 284.1262.

4.2.3.7. (*S*)-2-(But-3-ynyl)-2-(3-oxocyclohexyl)malononitrile 3d. Colorless oil; R_f = 0.22 (Et_2O/pentane 2:1); ^{1}H NMR ($CDCl_3$): δ = 1.55–1.75 (m, 2H), 2.06 (t, J = 2.6 Hz, 1H), 2.10–2.35 (m, 7H), 2.37–2.47 (m, 1H), 2.55 (td, J = 7.88, 2.57 Hz, 2H), 2.62–2.68 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.8, 23.8, 27.4, 33.9, 40.7, 42.3 (C_q), 43.1, 44.1, 71.5 (CH, alkyne), 80.0 (C_q, alkyne), 113.6 (C_q, CN), 114.0 (C_q, CN), 206.5 (C_q, C=O); HRMS: calcd for $C_{13}H_{14}N_2NaO$ [M+Na]: 237.1004; found: 237.1007.

4.2.3.8. (*R*)-4-Methyl-5-oxo-2,3,6,7,8,8a-hexahydronaphthalene-1,1(5*H*)-dicarbonitrile 4d. From **3d**. Colorless oil; R_f = 0.23 (Et_2O/pentane 2:1); $[\alpha]_D^{25} = -29.0$ (c 0.5, CH_2Cl_2), 91% ee; HPLC: t_R = 11.6 and 13.4 min (AD, 90:10 hexane/isopropanol, flow: 1 mL/min); ^{1}H NMR ($CDCl_3$): δ = 1.70–1.76 (m, 1H), 1.80 (dd, J = 12.1, 2.6 Hz, 1H), 1.86 (dd, J = 12.1, 3.0 Hz, 1H), 1.92 (d, J = 1.83 Hz, 3H), 2.09 (dd, J = 11.9, 5.3 Hz, 1H), 2.10–2.16 (m, 1H), 2.27–2.57 (m, 5H), 2.79–2.86 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 22.2 (CH_3), 22.3, 28.7, 29.9, 30.6, 37.3 (C_q), 42.2, 45.6, 113.7 (C_q, CN), 116.1 (C_q, CN), 128.7 (C_q, C=C), 145.1 (C_q, C=C), 200.5 (C_q, C=O); HRMS: calcd for $C_{13}H_{14}N_2NaO$ [M+Na] calcd: 237.1004; found: 237.1004.

4.2.3.9. (*S*)-2-(3,3-Dimethyl-5-oxocyclohexyl)-2-(prop-2-ynyl) malononitrile 3e. The addition was performed at 45 °C. Colorless solid; mp: 85 °C; R_f = 0.43 (Et_2O/pentane 2:1), ^{1}H NMR ($CDCl_3$): δ = 0.94 (s, 3H), 1.18 (s, 3H), 1.71 (t, J = 12.8 Hz, 1H), 1.88–1.94 (m, 1H), 2.21 (dt, J = 13.0, 1.8 Hz, 1H), 2.27 (t, J = 13.9 Hz, 2H), 2.41 (t, J = 2.8 Hz, 1H), 2.61–2.74 (m, 2H), 2.94 (dd, J = 17.1, 2.8 Hz, 1H), 3.01 (dd, J = 17.0, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 25.7 (CH_3), 26.5 (CH_3), 31.9, 34.5 (C_q), 39.3, 40.1, 41.7, (C_q), 41.8, 53.9, 73.8 (C_q, alkenyl), 76.1 (CH, alkenyl), 113.4 (C_q, CN), 113.6 (C_q, CN), 206.5 (C_q, C=O); HRMS: calcd for $C_{14}H_{16}N_2NaO$ [M+Na]: 251.1160; found: 251.1165.

4.2.3.10. (*R*)-3,6,6-Trimethyl-4-oxo-5,6,7,7a-tetrahydro-1*H*-indene-1,1(2*H*,4*H*)-dicarbonitrile 4e. The addition was performed at 45 °C. Colorless oil; R_f = 0.44 (Et_2O/pentane 2:1); $[\alpha]_D^{25} = -11.0$ (c 0.39, CH_2Cl_2), 89% ee; HPLC: t_R = 6.6 and 8.5 min (AD, 90:10 hexane/isopropanol, flow: 1 mL/min); ^{1}H NMR ($CDCl_3$): δ = 0.95 (s, 3H), 1.10 (s, 3H), 1.78 (t, J = 12.7 Hz, 1H), 1.96 (ddd, J = 12.7, 5.6, 2.2 Hz, 1H), 2.08–2.11 (m, 3H), 2.15 (d, J = 16.5 Hz, 1H), 2.25 (dd, J = 16.5, 2.2 Hz, 1H), 3.08 (d, J = 17.2 Hz, 1H), 3.15–3.23 (m, 1H), 3.48–3.57 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 26.1 (CH_3), 29.9, 31.5 (CH_3), 33.9, 39.1 (C_q), 39.6 (CH_3), 49.2, 52.3 (C_q), 54.5, 114.7 (C_q, CN), 115.2 (C_q, CN), 130.3 (C_q, C=C), 148.3 (C_q, C=C), 197.1 (C_q, C=O); HRMS: calcd for $C_{14}H_{17}N_2O$ [M+H$^+$]: 229.1341; found: 229.1342.

4.2.3.11. 2-((1*S*,3*R*)-3-Ethyl-5-oxocyclohexyl)-2-(prop-2-ynyl)-malononitrile 3f and 2-((1*S*,3*S*)-3-ethyl-5-oxocyclohexyl)-2-(prop-2-ynyl)malononitrile 3g. The addition was performed at 45 °C. Colorless oil; R_f = 0.40 (Et_2O/pentane 2:1), dr = 1:5; major diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, J = 7.5 Hz, 3H), 1.35–1.50 (m, 3H), 1.60–1.73 (m, 2H), 1.98 (t, J = 13.6 Hz, 1H), 2.19 (m, 1H), 2.27 (d, J = 13.6 Hz, 1H), 2.32–2.36 (m, 1H), 2.45–2.52 (m, 1H), 2.56–2.63 (m, 1H), 2.86 (dd, J = 17.2, 2.6 Hz, 1H), 2.96 (dd, J = 17.2, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_3), 26.5, 29.6, 29.9, 33.5, 38.0 41.8, 42.2, 46.8, 73.9 (C_q, alkyne), 76.2 (CH, alkyne), 113.3 (C_q, CN), 113.8 (C_q, CN), 206.4 (C_q, C=O); HRMS: calcd for $C_{14}H_{16}N_2NaO$ [M+Na] calcd: 251.1160; found: 251.1158.

4.2.3.12. (6*R*,7a*R*)-6-Ethyl-3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1*H*-indene-1,1-dicarbonitrile 4f and (6*S*,7a*S*)-6-ethyl-3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1H-indene-1,1-dicarbonitrile 4g. The addition was performed at 45 °C. Colorless oil; R_f = 0.41 (Et_2O/pentane 2:1), **4f:** $[\alpha]_D^{25} = +5.1$ (c 0.55, CH_2Cl_2), 94% ee major diastereoisomer, 76% ee minor diastereoisomer, dr = 1:5; **4g:** $[\alpha]_D^{25} = -4.1$ (c 0.32, CH_2Cl_2), 93% ee major diastereoisomer, 77% ee minor diastereoisomer, dr = 1:5; HPLC: t_R = 15.2/23.3 and 14.5/17.7 min (major/minor diastereoisomer, AD, 97:3 hexane/isopropanol, flow: 1 mL/min); major diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, J = 7.3 Hz, 3H), 1.50 (q, J = 12.5 Hz, 2H), 1.72–1.82 (m, 1H), 1.92 (d, J = 12.8 Hz, 1H), 1.97 (d, J = 12.5 Hz, 1H), 2.11 (br s, 3H), 2.21–2.29 (m, 1H), 2.54 (ddd, J = 17.3, 3.9, 2.2 Hz, 1H), 3.07 (d, J = 17.6 Hz, 1H), 3.19 (d, J = 17.6 Hz, 1H), 3.38–3.47 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 11.4 (CH_3), 29.2, 29.9 (CH_3), 33.1, 36.7, 38.6 (C_q), 47.2, 49.2, 54.8, 114.7 (C_q, CN), 115.3 (C_q, CN), 130.9 (C_q, C=C), 148.4 (C_q, C=C), 196.9 (C_q, C=O); HRMS: calcd for $C_{14}H_{16}N_2NaO$ [M+Na] calcd: 251.1160; found: 251.1156.

4.2.3.13. ((*S*)-2-(3-Oxocyclopentyl)-2-(prop-2-ynyl)malononitrile 3h. Colorless solid; mp: 95 °C; R_f = 0.20 (Et_2O/pentane 2:1); ^{1}H NMR ($CDCl_3$): δ = 1.98 (qd, J = 11.7, 8.7 Hz, 1H), 2.22–2.39 (m, 2H), 2.43 (t, J = 2.7 Hz, 1H), 2.42–2.50 (m, 1H), 2.53–2.64 (m, 2H), 2.91–3.04 (m, 1H), 2.94 (dd, J = 16.9, 2.7 Hz, 1H), 3.01 (dd, J = 16.9, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 25.6, 27.3, 38.0, 40.3, 40.7 (C_q), 41.9, 73.8 (C_q, alkyne), 75.8 (CH, alkyne), 113.1 (C_q, CN), 113.2 (C_q, CN), 212.1 (C_q, C=O); HRMS: calcd for $C_{11}H_{10}N_2NaO$ [M+Na]: 209.0691; found: 209.0689.

4.2.3.14. (*R*)-3-Methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1(2*H*)-dicarbonitrile 4h. Cyclization was done using isolated **3h** with [Au(Cl)(IPr)] (5 mol %) and AgOTf (10 mol %). Colorless oil; R_f = 0.25 (Et_2O/pentane 2:1); $[\alpha]_D^{25} = -11.3$ (c 0.5, CH_2Cl_2), 23% ee; HPLC: t_R = 15.0 min, 16.7 min (AD, 90:10 hexane/isopropanol, flow: 1 mL/min); ^{1}H NMR ($CDCl_3$): δ = 2.00–2.11 (m, 1H), 2.06 (s, 3H), 2.34–2.41 (m, 1H), 2.55–2.72 (m, 2H), 3.32–3.36 (m, 1H), 3.58–3.64 (m, 1H), 3.86–3.92 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.9, 25.0, 29.9 (C_q), 44.1, 54.9, 56.9, 114.3 (C_q, CN), 115.1 (C_q, CN), 136.8 (C_q, C=C), 144.7 (C_q, C=C), 198.6 (C_q, C=O); HRMS: calcd for $C_{11}H_{10}N_2NaO$ [M+Na]: 209.0691; found: 209.0690.

4.2.3.15. (*S*)-2-(3-Oxocycloheptyl)-2-(prop-2-ynyl)malononitrile 3i. Colorless oil; R_f = 0.32 (Et_2O/pentane 2:1); ^{1}H NMR ($CDCl_3$): δ = 1.43–1.72 (m, 3H), 1.98–2.06 (m, 1H), 2.11–2.18 (m, 1H), 2.22–2.26 (m, 1H), 2.42 (t, J = 2.7 Hz, 1H), 2.43–2.55 (m, 2H), 2.58–2.64 (m, 1H), 2.68–2.72 (m, 2H), 2.96 (dd, J = 17.1, 2.7 Hz, 1H), 3.02 (dd, J = 17.1, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 23.8, 26.4, 27.7, 32.3, 40.9, 41.9 (C_q), 43.4, 44.6, 73.8 (C_q, alkyne), 75.8 (CH, alkyne), 113.4 (C_q, CN), 113.7 (C_q, CN), 208.9 (C_q, C=O); HRMS: calcd for $C_{13}H_{14}N_2NaO$ [M+Na]: 237.1004; found: 237.1005.

4.2.3.16. (4*R*,7a*R*)-4-Hydroxy-3-methyl-5,6,7,7a-tetrahydro-1*H*-indene-1,1(2*H*,4*H*)-dicarbonitrile 7. To a solution of **4a** (80 mg, 0.4 mmol) in CH_2Cl_2/MeOH (4:1; 1 mL) $NaBH_4$ (45 mg, 1.2 mmol) was added at 0 °C and the mixture was stirred for 40 min. Usual workup and FC (CH_2Cl_2) provided **7** in 92% yield as a colorless oil and single diastereoisomer (dr >99:1); $[\alpha]_D^{25} = +9.1$ (c 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.23–1.50 (m, 3H), 1.94 (s, 3H), 1.96–2.09 (m, 4H), 3.02–3.11 (m, 3H), 4.28 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.0, 22.9, 29.4, 35.9 (C_q), 36.0, 49.6, 55.9, 71.2, 115.0 (C_q, CN), 116.8 (C_q, CN), 127.2 (C_q, C=C), 134.4 (C_q, C=C); HRMS: calcd for $C_{12}H_{14}N_2NaO$ [M+Na$^+$]: 225.1004; found: 225.0994.

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