Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4419–4428

TETRAHEDRON: *ASYMMETRY*

Rh(II)-catalyzed asymmetric cyclopropenation of propargyl derivatives; synthesis of cyclopropene- and *cis*-cyclopropane-amino acids

Paul Müller * and Hassan Imogaï

Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva, Switzerland

Received 20 October 1998; accepted 17 November 1998

Abstract

The [Rh_2{(2*S*)-mepy}$_4$]-catalyzed cyclopropenation of propargylamines carrying two carboxyl or sulfonyl protecting groups with ethyl diazoacetate proceeds in high yield and with enantioselectivities in the range of 90–>97% ee. Selective deprotection of the TEOC-derivative afforded ethyl 2-aminomethylcycloprop-2-ene-1-carboxylate which was converted to several analogs of γ-aminobutyric acid (GABA) containing the cyclopropene or cyclopropane ring.

1. Introduction

While the asymmetric, transition metal-catalyzed cyclopropanation of olefins with diazoacetate esters is finding increasing applications,[1] the corresponding cyclopropenation of acetylenes is not yet established in organic synthesis. We have recently reported that the decomposition of diazoacetate esters or amides in the presence of optically active Rh(II)-carboxamidate catalysts and terminal acetylenes produces cyclopropenes in high yields with synthetically useful enantioselectivities in selected cases.[2] More recently, the cyclopropenation of 1,1-diethoxypropyne was optimized and applied to the synthesis of cyclopropene dehydroamino acids and of dictyopterene C′.[3] This article deals with the asymmetric cyclopropenation of propargyl amines and halides, and with the synthesis of enantiopure cyclopropene and cyclopropane analogs of γ-aminobutyric acid (GABA), derived from the respective cyclopropenes. GABA is an important inhibitor of neurotransmitters in the mammalian brain.[4] The incapacity of GABA to cross the blood–brain barrier has spurred interest in GABA analogs.[5] Cyclopropane analogs of GABA of high enantiomeric purity have been prepared by multistep syntheses,[6] but only one cyclopropene

* Corresponding author. E-mail: paul.muller@chiorg.unige.ch

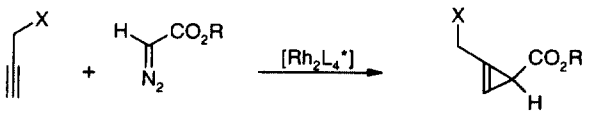
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00469-8

analog in racemic form has been described.[7] Some of the results have been reported in preliminary form.[8]

2. Results and discussion

2.1. Cyclopropenation of propargyl derivatives

Initial experiments revealed that the cyclopropenation of simple propargylamine derivatives proceeded less satisfactorily than that of the oxygen substituted counterparts such as propargyl ethers, propargyl acetate or diethoxypropyne.[3] Thus reaction of propargylacetamide or *N,N*-bis-(trimethylsilyl)propargylamine with methyl diazoacetate in the presence of $[Rh_2\{(2S)\text{-mepy}\}_4]$,[9] afforded the corresponding cyclopropene in only modest yields and with enantioselectivities far below that required for asymmetric synthesis.[10] In view of these results we investigated the cyclopropenation of propargylbromide **1a** with ethyl diazoacetate **2a** and some of the Rh(II)-carboxamidate catalysts of Doyle et al., such as $[Rh_2\{(2S)\text{-mepy}\}_4]$,[9] $[Rh_2\{(5R)\text{-phox}\}_4]$,[11] $[Rh_2\{(2S)\text{-mppim}\}_4]$,[12] and Ikegami's $[Rh_2\{(-)\text{-}(S)\text{-ptpa}\}_4]$,[13] with the expectation of synthesizing the respective aminomethyl substituted cyclopropenes by nucleophilic substitution starting from the corresponding halides. The cyclopropenations were carried out at rt in CH_2Cl_2 by slow syringe pump addition of **2a** to 10 equiv. of **1a** in the presence of 3–7% of catalyst. Reactions with propargylbromide produced the expected cyclopropene **3a** in variable yields. Although significant inductions of 40–60% ee were obtained with the mepy- and mppim-catalysts, the overall result was insufficient for our purposes. In addition, the cyclopropene **3a** proved to be highly reactive and difficult to purify and isolate. Some nucleophilic displacements were attempted with **3a**, but in vain. None of the expected cyclopropene **3b** was isolated upon attempted cyclopropenation of propargylchloride **1b**. The structure of the reaction product could not definitely be established, but the spectral evidence points to the formation of an allene, resulting from sigmatropic rearrangement of an intermediate ylide.[14] The Bu_3Sn-substituted propyne **1c**, in turn, afforded only a trace of the expected cyclopropene **3c** (see Scheme 1 and Table 1).



1a-g 2a,b 3a-h

Scheme 1.

In the end, it turned out that double protection of the amino function with electron-withdrawing carboxyl or sulfonyl groups resulted in significantly higher enantioselectivities. Propargylphthalimide **1d** and propargylsuccinimide **1e** were synthesized from propargylbromide **1a** with potassium phthalimide[15] and lithium succinimide,[16] respectively. The dinosylated propargylamine **1f**, in turn, was obtained in two steps.[17] Reaction of the amine with *p*-nitrophenylsulfonyl chloride (NsCl, 0.5 equiv.) afforded the monosulfonamide, which was deprotonated with NaH and reacted further with another 1.5 equiv. of NsCl to afford **1f**. A similar two-step procedure was applied for the diprotection of propargylamine with 2-chlorocarbonyloxy-ethyltrimethylsilane (TEOC-Cl)[18] to afford **1g**. The diamides and disulfonamides **1d–1g** were reacted with a 2–4 fold excess of **2a,b** and afforded good yields of cyclopropenes. Although the diazoester was used in excess over the acetylene derivative, no formation of bicyclobutanes, resulting from further carbene addition to the cyclopropenes was observed. The ees of the cyclopropenes were

Table 1
Cyclopropenation of propargyl derivatives

Amine	X	Diazoester	R	Catalyst	Cyclopr.	Yield, %[a]	ee,de, %
1a	Br	**2a**	Et	$[Rh_2\{(-)\text{-}(S)\text{-ptpa}\}_4]$	**3a**	12 (72)	3
1a	Br	**2a**	Et	$[Rh_2\{(5R)\text{-phox}\}_4]$	**3a**	19	7
1a	Br	**2a**	Et	$[Rh_2\{2S)\text{-mppim}\}_4]$	**3a**	61	13
1a	Br	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3a**	41	62
1b	Cl	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3b**	0	--
1c	Bu_3Sn	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3c**	trace	--
1d	PhtN[b]	**2a**	Et	$[Rh_2\{2S)\text{-mppim}\}_4]$	**3d**	7 (40)	74
1d	PhtN[b]	**2a**	Et	$[Rh_2\{5R)\text{-phox}\}_4]$	**3d**	57	64
1d	PhtN[b]	**2a**	Et	$[Rh_2\{2S)\text{-mepy}\}_4]$	**3d**	54[c]	90
1e	SuccN[d]	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3e**	79 (42)	>95
1f	$(Ns)_2N$[e]	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3f**	82 (36)	80
1g	$(TEOC)_2N$[f]	**2a**	Et	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3g**	85 (31)	>97
1g	$(TEOC)_2N$[f]	**2b**	*t*-Bu	$[Rh_2\{(2S)\text{-mepy}\}_4]$	**3h**	75	90

(a) Yield with $Rh_2(OAc)_4$ in parentheses.

(b) PhtN = phthalimido.

(c) *ca.* 50% of **1f** recovered; yield not corrected.

(d) SuccN = succinimido.

(e) $(Ns)_2N$ = *N,N*-di-*p*-nitrophenylsulfonamido.

(f) $(TEOC)_2N$ = *N,N*-di-(2-trimetylsilyl ethoxycarbonyl)-amino.

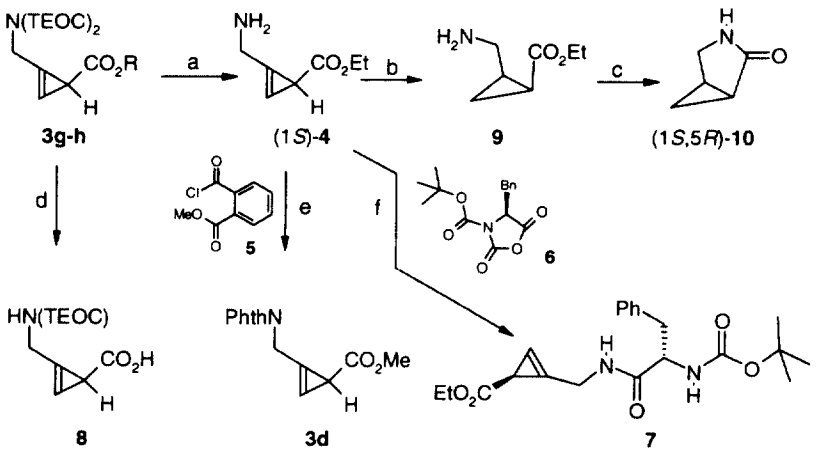
in the range of 90% and better, with the highest value for the TEOC derivative **1g**, synthesized with $[Rh_2\{(2S)\text{-mepy}\}_4]$ in 85% yield and with >97% ee.

2.2. *Transformations of protected 2-aminomethyl cycloprop-2-ene-1-carboxylates*

The search for reaction conditions for deprotection of the carboxamide and sulfonamide groups, compatible with the presence of the relatively fragile cyclopropene moiety presented major difficulties. Hydrolysis of the phthalimide **3d** with HCl (6 N) with heating,[19] exposure to sodium sulfide in THF,[20] or reaction with hydrazine in EtOH[21] resulted in decomposition of the starting cyclopropene, while only partial hydrolysis occurred with LiOH in THF. The small amount of half-deprotected

acid phthalamide was insufficient to attempt full deprotection using the recently described enzymatic procedure.[22] Attempted cleavage of the dinosyl derivative **3f** with PhSH in DMF in the presence of K_2CO_3[23] resulted in decomposition of the cyclopropene. Deprotection of the amino function was, however, possible with the TEOC derivative **3g** which reacted with tetra-*n*-butylammonium fluoride (TBAF) in THF[24] to afford the free amine **4** in 50% yield. The moderate yield of **4** is probably due to difficulties in the isolation, owing to its high solubility in water.

The aminocyclopropene **4** reacted with 2-methoxycarbonylbenzoyl chloride **5**[25] to yield the also independently prepared *N*-phthaloylaminomethylcyclopropene **3d**. This transformation was used for the determination of the ee of **3g**, since this could not be determined on **3g** directly (see Experimental section). Reaction of **4** with the urethane **6** derived from L-phenylalanine[26] afforded the dipeptide **7** in 82% yield. This transformation shows that the GABA analog **4** can be incorporated into peptides (Scheme 2).



(a) TBAF in THF, -10°C, 50%. (b) H_2, Pd/C, EtOH, 20°C, (c) Et_3N, THF, 65°C, 4h, 68%.

(d) CF_3COOH, 25°C, 8.3%. (e) THF, Et_3N, 20°C, 2h, 94%. (f) THF, 20°C, 82%.

Scheme 2.

Deprotection of the carboxy group was attempted with *tert*-butyl ester **3h** with trifluoroacetic acid. The reaction was accompanied by simultaneous deprotection of one of the TEOC groups and afforded **8** in the very poor yield of 8%. Attempts to generate the free amino acid were so far unsuccessful.

Catalytic hydrogenation of **4** afforded the cyclopropane **9** which, upon heating in the presence of Et_3N, cyclized to the lactam **10** (3-azabicyclo[3.1.0]hexan-2-one) This lactam had $[\alpha]_D^{22}$ −53 (*c* 1.25, $CHCl_3$), which corresponds to (1*S*,5*R*) configuration, since the reported value for (1*R*,5*S*)-**9** is $[\alpha]_D^{20}$ +49 (*c* 1.25, $CHCl_3$).[6a] It follows that the cyclopropenation of the protected propargylamine **1g** with $[Rh_2\{(2S)\text{-mepy}\}_4]$ affords the cyclopropene **3g** with (*S*) configuration. This is identical to the configuration of the cyclopropenes resulting from cyclopropenation of all other monosubstituted acetylenes investigated so far and is consistent with the previously proposed mechanistic model.[2,3] The configuration of the other cyclopropenes synthesized in this study was not investigated; however, since all of them have positive $[\alpha]_D$-values, they are probably homochiral.

3. Experimental

3.1. General methods

See Doyle et al.[11]

3.2. Synthesis of protected propargylamines

3.2.1. N-*Propargylphthalimide* **1d**

To potassium phthalimide (3.7 g, 20 mmol) in ethanol (30 mL) was added propargylbromide (2.85 g, 24 mmol). The mixture was stirred for 72 h at 60°C. After cooling, the suspension was hydrolyzed with H_2O (35 mL), and the aqueous layer was extracted with $CHCl_3$ (3×100 mL). The organic phase was concentrated in vacuo, the resulting crude product was suspended in benzene (20 mL) and filtered. The solvent was evaporated, and the crude product was purified by chromatography (SiO_2, hexane:AcOEt 80:20). Yield 2.15 g, 58% of **1d**, mp 150°C. IR ($CHCl_3$): 3019*w*, 1768*s*, 1725*w*, 1468*m*, 1343*w*, 1343*w*. ^1H NMR (200 MHz, $CDCl_3$): 2.22 (*t*, *J*=2.5, 1H); 4.44 (*d*, *J*=2.48, 2H); 7.73 (*dd*, *J*=5.2, 3.1, 2H); 7.86 (*dd*, *J*=5.2, 3.0, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 26.9 (*t*); 71.5 (*d*); 77.1 (*s*); 123.5 (*d*); 131.9 (*s*); 134.2 (*d*); 166.9 (*s*). MS: 186 (M^++1, 44), 187 (M^+, 100), 157 (70), 156 (48), 130 (35), 129 (51), 105 (22), 104 (58), 77 (24), 76 (67), 75 (25), 50 (42). HRMS: 185.0477 ($C_{11}H_7O_2N$; calc. 185.0477).

3.2.2. N-*Propargylsuccinimide* **1e**

To succinimide (990 mg, 10.0 mmol) in THF (20 mL) was added, at −20°C, LiHMDS (hexamethyldisilazane, 10 mL, 1 M in hexane). The mixture was allowed to warm up to 20°C (15 min), and was subsequently cooled to −78°C. Propargyl bromide (20 mmol) in THF (5.0 mL) was added dropwise. The mixture was stirred at 20°C overnight, then decomposed with aq. HCl (1.5 N) and saturated ammonium chloride (10 mL). The mixture was extracted with ether (3×20 mL), the extract dried ($MgSO_4$), filtered and concentrated. Chromatography of the crude product (SiO_2, hexane:AcOEt 40:60) afforded **1e** (500 mg, 37%) as colorless oil, which crystallized upon standing. Mp 52–53°C. IR (film): 3248*w*, 2932*w*, 1692*s*, 1414*m*, 1168*m*. ^1H NMR (400 MHz, $CDCl_3$): 2.17 (*t*, *J*=2.4 1H); 2.73 (*s*, 4H); 4.22 (*d*, *J*=2.5, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.6 (*t*); 28.1 (*t*); 71.2 (*s*); 76.5 (*d*); 177.6 (*s*). MS: 137 (M^+, 65), 109 (66), 96 (24), 95 (100), 80 (32), 56 (73), 55 (56), 54 (39), 53 (34), 52 (28). HRMS: 137.0477 ($C_7H_7O_2N$; calc. 137.0477).

3.2.3. N,N-*Di-(4-nitrophenylsulfonyl)propargylamine* **1f**

To propargylamine (440 mg, 8.0 mmol) in anhydrous ether (20 mL) was added dropwise at 0°C, 4-nitrophenylsulfonyl chloride (NsCl, 887 mg, 4.0 mmol) in ether (16 mL). After vigorous stirring during 2 h, the mixture was filtered, the solid residue was extracted with AcOEt, and the crude product was purified by column chromatography (SiO_2, hexane:AcOEt 70:30) to afford *N*-(4-nitrophenylsulfonyl)propargylamine (580 mg, 61%) as a white solid, mp >230°C. (IR, KBr): 3302*m*, 3269*w*, 1529*m*, 1349*m*, 1163*s*, 1065*w*, 859*m*, 733*m*, 616*m*. ^1H NMR (200 MHz, DMSO-d_6): 3.01 (*dd*, *J*=2.5, 2H); 3.77 (*d*, *J*=2.5, 2H); 8.05 (*d*, *J*=9.1, 2H); 8.38 (*d*, *J*=9.0, 2H); 8.51 (*s*, broad), 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 31.7 (*t*); 74.9 (*d*); 76.7 (*d*); 124.1 (*d*); 128.2 (*d*); 146.2 (*s*); 149.9 (*s*). MS: 241 (M^+, 1.8), 186 (36), 170 (42), 122 (65), 92 (41), 75 (67), 50 (61).

To a suspension of NaH (58 mg, 1.2 mmol) in THF (5.0 mL) was added dropwise at 0°C, *N*-(4-nitrophenylsulfonyl)propargylamine (240 mg, 1.0 mmol) in THF (5.0 mL). The mixture was stirred at 20°C during 20 min, then cooled to −10°C. NsCl (300 mg, 1.35 mmol) in THF (5.0 mL) was added

dropwise. After 1 h of stirring, aq. HCl (1.5 N, 3.5 mL) and satd ammonium chloride (3.5 mL) were added. The aqueous layer was extracted with AcOEt (4×20 mL), the combined organic phases dried ($MgSO_4$) and concentrated. The crude product decomposed on SiO_2. It was suspended in AcOEt (3.0 mL), filtered, and the residue was washed with AcOEt (1.0 mL). The dinosylamide **1f** (240 mg, 55%) was isolated as a white solid, mp 168°C. IR (KBr): 3292*m*, 3106*w*, 1534*s*, *large*, 1371*m*, *large*, 1162*m*, 1065*m*, 1000*m*, 789*m*, 744*m*. ^{1}H NMR (200 MHz, DMSO-d_6): 3.37–3.39 (*m*, 1H); 4.84 (*d*, *J*=2.3, 2H); 8.30–8.32 (*m*, 4H); 8.43–8.55 (*m*, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): 38.8 (*s*); 77.2 (*d*); 77.4 (*t*); 124.8 (*d*); 129.9 (*d*); 143.5 (*s*); 150.9 (*s*). MS: 425 (M^+, 0.3), 239 (68), 223 (22), 186 (60), 122 (100), 92 (36), 76 (70), 75 (68). HRMS: 424.9974 ($C_{15}H_{11}O_8N_3S_2$; calc. 424.9988).

3.2.4. N,N-*Di-(trimethylsilyl-2-ethoxycarbonyl)propargylamine* **1g**

2-Chlorocarbonyloxyethyl-trimethylsilane (TEOC-Cl) was prepared from 2-(trimethylsilyl)ethanol and phosgene in toluene (CAUTION) according to Shute and Rich.[18] To propargylamine (486 mg, 8.5 mmol) in CH_2Cl_2 (15 mL) was added, at −10°C, diisopropylethylamine (1.72 g, 17 mmol) followed by TEOC-Cl (3.06 g, 17 mmol) in CH_2Cl_2, and finally, dimethylaminopyridine (DMAP, 30 mg). The mixture was stirred overnight, then hydrolyzed with satd $NaHCO_3$, and extracted with CH_2Cl_2 (3×30 mL) at 0°C and satd Na_2CO_3. After drying and evaporation of the solvent, the crude product was purified by chromatography (SiO_2; hexane:AcOEt 85:5) and afforded *N*-(trimethylsilyl-2-ethoxycarbonyl)propargylamine (1.49 g, 88%) as a colorless liquid. IR ($CHCl_3$): 3324*s*, *large*, 2953*m*, 2899*m*, 1703*s*, *broad*, 1512*s*, 1240*m*, 1240*m*, 831*s*. ^{1}H NMR (200 MHz, $CDCl_3$): 0.02 (*s*, 9H); 0.93–1.02 (*m*, 2H); 2.20 (*t*, *J*=2.5, 1H); 3.95 (*dd*, *J*=5.6, 2.5, 2H); 4.12–4.21 (*m*, 2H); 4.90 (*s*, broad, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): −1.5 (*q*); 17.7 (*t*); 30.7 (*t*); 63.5 (*t*); 71.4 (*d*); 79.9 (*s*); 156.2 (*s*). HRMS: 184.0799 [$C_8H_{14}O_2NSi$ (M–CH_3); calc. 184.0794].

To NaH (99 mg, 18.9 mmol) in THF (18 mM) was added, at −20°C *N*-(trimethylsilyl-2-ethoxycarbonyl)propargylamine (2.51 g, 12.6 mmol) in THF (12 mL). The mixture was allowed to reach 20°C (15 min), and was then cooled to −20°C. TEOC-Cl (4.50 g, 25.2 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at 20°C overnight, and was then decomposed with satd $NaHCO_3$ (20 mL) and water (10 mL). The mixture was extracted with ether (3×20 mL), which was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography (SiO_2, hexane:AcOEt 90:10) or by Kugelrohr distillation (127–140°C/0.3 torr). **3g** (4.11 g, 95%) was isolated as a colorless liquid. IR (film): 3280*w*, 2953*m*, 2899*m*, 1790*s*, 1746*s*, 1697*s*, 1098*s*, 695*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 0.05 (*s*, 18H); 1.06–1.15 (*m*, 4H); 2.20 (*t*, *J*=2.4, 1H); 4.29–4.38 (*m*, 4H); 4.45 (*d*, *J*=2.4, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −1.6 (*q*); 17.5 (*t*); 35.8 (*t*); 66.0 (*t*); 71.1 (*d*); 79.1 (*s*); 152.9 (*s*). MS: 343 (M^+, abs.), 328 (8), 272 (18), 228 (14), 198 (10), 147 (62), 101 (28), 73 (100), 58 (35), 59 (30), 45 (30). HRMS: 328.1423 ($C_{14}H_{28}O_4NSi_2$ {M–CH_3} calc. 328.1411).

3.3. *Cyclopropenation of propargyl derivatives*

3.3.1. *Cyclopropenation of propargyl bromide* **1a**. *Ethyl 2-bromomethylcycloprop-2-ene-1-carboxylate* **3a**

To propargyl bromide **1a** (10 mmol) and [$Rh_2(OAc)_4$] (20 mg, 0.040 mmol, activated by heating to 200°C with a heat-gun) in CH_2Cl_2 (15 mL) was added the diazoester **2** (1.0 mmol) in CH_2Cl_2 (15 mL) within 15 h at 20°C. When the addition was completed, the reaction mixture was filtered through a column of SiO_2 (7.0 g, hexane:AcOEt 70:30). After evaporation of the solvent, the crude product was subjected to column chromatography (SiO_2, hexane:AcOEt 90:10) and afforded 149 mg (72%) of cyclopropene **3a**. IR (film): 1714*s*, 1191*m*, 902*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (*t*, *J*=7.1, 3H);

2.35 (*d*, *J*=1,3, 1H); 4.10 (*qd*, *J*=7.1, 0.8, 2H); 4.28 (*dd*, *J*=13.1, 1.0, 2H); 6.68 (*ddd*, *J*=1.18, 1.19, 1.32, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.2 (*q*); 22.5 (*d*); 60.6 (*t*); 99.7 (*t*); 111.8 (*s*); 129.8 (*d*); 174.7 (*s*). Reaction with [Rh_2\{(2*S*)-mepy\}$_4$]: $[\alpha]_D^{20}$ −27 (*c* 2.6, $CHCl_3$) for 62% ee {by GC with LIPODEX E column (90°C, H_2 carrier gas, 70 kPa)}. For results with other optically active catalysts, see Table 1.

3.3.2. Cyclopropenation of diprotected propargylamines

The cyclopropenations were carried out as with propargyl bromide **1**, but with the amine derivative as a limiting reagent (0.5–1.0 mmol) and a two- to fourfold excess of diazo ester.

3.3.2.1. *Ethyl 2-phthalimidomethylcycloprop-2-ene-1-carboxylate* ***3d***. Purification by column chromatography (SiO_2, hexane:AcOEt 60:40). Yield: 54%. Colorless solid, mp 91°C. $[\alpha]_D^{22}$ +38 (*c* 0.75, $CHCl_3$) for 90% ee (by HPLC, Chiracel OD.H column with hexane:isopropanol 95:5) from reaction with [Rh_2\{(2*S*)-mepy\}$_4$]. IR ($CHCl_3$): 1774*s*, 1714*s*, 1415*m*, 1398*m*, 1208*m*. ^{1}H NMR (400 MHz, $CDCl_3$): 1.16 (*t*, *J*=7.2, 3H); 2.28 (*d*, *J*=2.28, 1H); 4.03 (*q*, *J*=7.2, 2H); 4.79 (*d*, *J*=1.2, 2H); 6.63 (*d*, *J*=1.2, 1H); 7.26–7.36 (*m*, 2H); 7.85–7.88 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (*q*); 20.7 (*d*); 32.9 (*t*); 60.4 (*t*); 98.6 (*d*); 110.8 (*s*); 123.3 (*d*); 131.9 (*s*); 133.9 (*d*); 167.2 (*s*); 174.7 (*s*). MS: 271 (M^+, 2), 243 (18), 198 (100), 160 (13), 130 (7), 104 (11), 96 (13), 51 (4). HRMS: 271.0845 ($C_{15}H_{13}O_4N$; calc. 271.0845).

3.3.2.2. *Ethyl 2-succinimidomethylcycloprop-2-ene-1-carboxylate* ***3e***. Column chromatography (SiO_2, hexane:AcOEt 50:50) afforded **3e** (79%) as a pale yellow oil, $[\alpha]_D^{20}$ +34 (*c* 1.0, $CHCl_3$) for >95% ee (by ^{1}H NMR, using [Eu(hfc)$_3$] from reaction with [Rh_2[(2*S*)-mepy\}$_4$]. IR ($CHCl_3$): 3017*w*, 1771*s*, 1396*m*, 1194*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (*t*, *J*=7.2, 3H); 2.25 (*d*, *J*=1.2, 1H); 2.73 (*s*, 4H); 4.10 (*q*, *J*=7.2, 2H); 4.61 (*s*, 2H); 6.62 (*d*, *J*=0.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3 (*q*); 20.5 (*d*); 28.3 (*t*); 33.4 (*t*); 60.4 (*t*); 98.8 (*d*); 110.1 (*s*); 174.8 (*s*); 176.1 (*s*). MS: 224 (M^++1, 3); 195 (100), 112 (21), 96 (33), 86 (77), 84 (99), 55 (86). HRMS: 224.0876 ($C_{11}H_{14}O_4N$; calc. 224.09229).

3.3.2.3. *Ethyl 2-(*N,N*-bis-4-nitrophenylsulfonylamino)methylcycloprop-2-ene-1-carboxylate* ***3f***. Purification by column chromatography (SiO_2, hexane:AcOEt 80:20). Yield: see Table 1. Mp 116°C, $[\alpha]_D^{20}$ +57 (*c* 0.95, $CHCl_3$) for 80% ee from reaction with [Rh_2\{(2*S*)-mepy\}$_4$] (via cycloadduct **11**). IR ($CHCl_3$): 1703*m*, 1536*s*, *large*, 1392*m*, 1346*m*, 1171*w*. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (*t*, *J*=6.9, 3H); 2.16 (*d*, *J*=1.0, 1H); 4.15 (2×*q*, *J*=6.9, 2H); 4.85 (*dd*, *J*=19, 9.7, 1H); 5.08 (*dd*, *J*=18.9, 1.0, 1H); 6.35–6.37 (*m*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (*q*); 21.6 (*d*); 60.8 (*t*); 100.7 (*s*); 110.7 (*s*); 124.4 (*d*); 130.1 (*s*); 144.4 (*s*); 151.0 (*s*); 174.2 (*s*). MS: 511 (M^+, 0.3), 438 (100), 241 (20), 247 (19), 189 (38), 170 (65), 141 (22), 127 (43), 61 (51), 59 (86).

3.3.2.4. *(1*S*)-Ethyl 2-{*N,N*-bis-(2-trimethylsilylethoxycarbonyl)amino}methylcycloprop-2-ene-1-carboxylate* ***3g***. 10 mmol scale with [Rh_2\{(2*S*)-mepy\}$_4$]. Column chromatography (SiO_2, hexane:AcOEt 90:10) gave **3g** (85%) as a colorless oil. $[\alpha]_D^{20}$ +19 (*c* 0.60, $CHCl_3$) for >97% ee (via conversion to **3d**). IR (film): 3008*w*, 2942*w*, 1779*s*, 1741*s*, 1719*s*, 1213*s*, 853*m*, 842*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 0.03 (*s*, 18H); 1.02–1.11 (*m*, 4H); 1.23 (*t*, *J*=7.1, 3H); 2.24 (*d*, *J*=1.5, 1H); 4.10 (*qd*, *J*=7.1, 1.0, 2H); 4.24–4.33 (*m*, 4H); 4.78 (*d*, *J*=1.4, 2H); 6.53–6.55 (*m*, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): −1.6 (*q*); 14.3 (*q*); 17.5 (*t*); 20.5 (*d*); 41.6 (*t*); 60.3 (*t*); 65.9 (*t*); 97.1 (*d*); 112.2 (*s*); 153.0 (*s*); 175.1 (*s*). MS: 429 (M^+, 0.6), 358 (2), 300 (7), 256 (6), 147 (10), 101 (10), 73 (100), 45 (72). HRMS: 358.1157 ($C_{14}H_{24}O_6NSi_2$, ($M-2CH_3$); calc. 358.1142).

3.3.2.5. tert-*Butyl 2-{*N,N-*bis-(2-trimethylsilylethoxycarbonyl)amino}methylcycloprop-2-ene-1-carboxylate* ***3h***. Reaction with 1.0 mmol of **1g** and 3.0 mmol of **2b**[27] in the presence of $[Rh_2\{(2S)\text{-mepy}\}_4]$. Chromatography ($SiO_2$, hexane:AcOEt 85:15) afforded **3h** (75%) as a colorless oil. $[\alpha]_D^{20}$ +15 (*c* 1.0, $CHCl_3$) for 90% ee (by HPLC, Chiracel AD column, with hexane:isopropanol 119:1). IR (film): 2947*w*, 1739*s*, 1731*s*, 1602*m*, 1381*m*. ^{1}H NMR (400 MHz, $CDCl_3$): 0.04 (*s*, 18H); 1.43 (*s*, 9H); 1.07–1.11 (*m*, 4H); 2.16 (*d*, *J*=1.5, 1H); 4.27–4.33 (*m*, 4H); 4.79 (*ddd*, *J*=18, 16.7, 1.2, 2H); 6.52–6.54 (*m*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 1.6 (*q*); 17.6 (*t*); 21.5 (*d*); 28.1 (*q*); 41.6 (*t*); 65.9 (*t*); 79.9 (*s*); 97.5 (*s*); 112.6 (*s*); 153.0 (*s*); 174.5 (*s*). MS: 457 (M^+, abs.) 401 (0.8), 300 (27), 256 (25), 212 (16), 186 (23), 184 (10), 169 (11), 147 (53), 141 (17), 101 (33), 100 (20), 75 (78), 74 (62), 73 (100), 59 (24), 58 (15), 57 (74), 52 (36), 45 (28). HRMS: 401.1680 ($C_{17}H_{31}O_6NSi_2$ ($M^+-C_4H_8$); calc. 401.1689).

3.4. Transformation of substituted cycloprop-2-ene-1-carboxylates

3.4.1. Deprotection of ***3g****. (1S)-Ethyl 2-aminomethylcycloprop-2-ene-1-carboxylate* ***4***

To **3g** (3.00g, 7.0 mmol) in THF (20 mL) was added dropwise, at −10°C, tetra-*n*-butylammonium fluoride (TBAF, 1 M in THF, 28 mL, 28 mmol) under argon. After 16 h of stirring at 20°C the mixture was hydrolyzed with satd $NaHCO_3$ (20 mL). The aqueous phase was extracted with $CHCl_3$ (10×40 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo (60 torr). Chromatography (SiO_2, hexane:AcOEt, MeOH (16% NH_3) 60:40:10 yielded **4** (490 mg, 50%) as a transparent oil. $[\alpha]_D^{20}$ +59 (*c* 1.5, $CHCl_3$) for >97% ee (via conversion to **3d**). IR (film): 3150–2400*m*, *large*, 3000*w*, 2980*w*, 1724*s*, 1040*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 1.23 (*t*, *J*=7.1, 3H); 1.42 (*s*, broad, 2H); 2.24 (*d*, *J*=1.5, 1H); 3.76 (*d*, *J*=1.6, 2H); 4.12 (*qd*, *J*=7.1, 1.3, 2H); 6.74 (*td*, *J*=1.6, 1.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2 (*q*); 20.2 (*d*); 41.7 (*t*); 60.2 (*t*); 95.0 (*d*); 116.3 (*s*); 176.0 (*s*). MS: 141 (M^+, 10), 113 (15), 112 (20), 96 (30), 95 (12), 83 (20), 69 (16), 68 (100), 67 (17), 58 (18). HRMS: 141.0795 ($C_7H_{11}O_2N$; calc. 141.0790).

3.4.2. Conversion of ***4*** *into* ***3d***

To **4** (14 mg, 0.10 mmol) in THF (3 mL) was added, at 0°C, Et_3N (20 mL) and 2-methoxycarbonylbenzoyl chloride (**5**) (30 mg, 1.5 mmol) in THF. The mixture was stirred during 2 h, then poured onto ice (2 g). After stirring overnight, the mixture was extracted with AcOEt (2×15 mL). The organic phase was dried ($MgSO_4$), concentrated, and the crude product purified by chromatography (SiO_2, hexane:AcOEt 60:40). The cyclopropene **3d** (27 mg, 94%) was isolated as a white solid, $[\alpha]_D^{20}$ +40 (*c* 1.2, $CHCl_3$). For spectral data see Section 3.3.2.1.

*3.4.3. Synthesis of dipeptide 7, (*S*)-ethyl 2-{*N-tert-*butoxycarbonyl-(*S*)-phenylalanyl}-aminomethylcycloprop-2-ene-1-carboxylate*

To *N*-butoxycarbonyl-L-phenylalanine anhydride **5** (38 mg, 1.05 equiv.) in anhydrous THF (3.0 mL) was added, successively, the amine **4** (17.7 mg, 0.125 mmol, 1.0 equiv.) in THF (2.0 mL) and Et_3N (9.0 μL, 0.5 equiv.). After 3 h of stirring, the reaction mixture was concentrated in vacuo. Chromatography of the crude product (SiO_2, hexane:AcOEt 60:40) afforded **7** (40 mg, 82%) as a viscous oil. $[\alpha]_D^{20}$ +36 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3428*w*, 2985*w*, 1705*s*, *broad*, 1677*s*, 1492*s*, 1365*m*, 1030*m*. ^{1}H NMR (200 MHz, $CDCl_3$): 1.23 (*t*, *J*=6.3, 3H); 1.38 (*s*, 9H); 2.22 (*d*, *J*=1.5, 1H); 3.04 (*dd*, *J*=6.9, 4.8, 2H); 4.10 (*qd*, *J*=7.0, 0.8, 2H); 4.26–4.32 (*m*, 2H); 4.35–4.38 (*m*, 1H); 5.1 (*d*, broad, *J*=8.0, 1H); 6.44–6.46 (*m*, 1H); 6.53 (*t*, *J*=6.0, 1H); 7.16–7.29 (*m*, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2 (*q*); 20.4 (*d*); 28.2 (*q*); 35.2 (*t*); 38.5 (*t*); 55.7 (*d*); 60.5 (*t*); 80.2 (*s*); 97.4 (*s*); 112.0 (*s*); 126.9 (*d*); 128.6 (*d*); 129.2 (*d*); 136.6 (*s*);

155.4 (*s*); 171.4 (*s*); 175.7 (*s*). MS: 388 (M^+, 8), 332 (46), 271 (21), 259 (14), 241 (11), 197 (14), 57 (97). HRMS: 388.1989 ($C_{21}H_{28}O_5N_2$; calc. 388.1998).

3.4.4. Hydrolysis of ***3h****. 2-{(N-2-Trimethylsilylethoxycarbonyl)amino}-methylcyclo-prop-2-ene-1-carboxylic acid* ***8***

To **3h** (300 mg, 0.75 mmol) in CH_2Cl_2 (15 mL) was added CF_3COOH (200 μL). The mixture was stirred at 25°C during 24 h, then concentrated in vacuo. Chromatography (SiO_2, hexane:AcOEt 50:50 afforded **8** (16 mg, 8.3%) as a transparent oil. $[\alpha]_D^{20}$ +29 (*c* 1.0, $CHCl_3$) for >97% ee (from **3g**). IR (film): 3500–3300*w*, *large*, 2947*w*, 1703*s*, 1506*m*, 1247*m*, 904*s*. ^1H NMR (200 MHz, $CDCl_3$): 0.37 (*s*, 3H); 0.95–1.03 (*m*, 2H); 2.28 (*s*, 1H); 4.12–4.23 (*m*, 2H); 4.30 (*d*, broad, *J*=5.4, 2H); 5.10 (*s*, broad, 1H); 6.57 (*s*, 1H); 8.60 (*s*, broad, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): −1.51 (*q*); 17.7 (*t*); 20.0 (*d*); 36.8 (*t*); 63.7 (*t*); 96.7 (*d*); 112.5 (*d*); 156.6 (*s*); 180.0 (*s*). MS: 184 (M^+–$SiMe_3$, 7), 152 (7), 96 (17), 77 (23), 75 (85), 73 (100), 68 (22) , 67 (13), 59 (12), 52 (13), 45 (29). HRMS: 184.0610 ($C_8H_{10}O_4N$; calc. 184.1720).

3.4.5. Catalytic hydrogenation of ***4*** *and synthesis of lactam* ***10****. (1S,5R)-3-Azabicyclo[3.1.0]hexan-2-one*

To Pd/C (5.0 mg) in EtOH (6.0 mL) under H_2 was added, by means of a syringe, the amine **4** (10.7 mg, 0.076 mmol) in EtOH at 20°C. After 90 min of stirring, the mixture was filtered through Celite. The filtrate was dried (Na_2SO_4) and concentrated at 100 torr. The crude cyclopropane **9** was dissolved in THF (5.0 mL) to which 3 drops of Et_3N were added. The mixture was heated to reflux during 4 h, then concentrated in vacuo (60 torr), and the residue was subjected to chromatography (SiO_2, AcOEt:MeOH 90:10) to afford **10** (5.0 mg, 68%) as a white solid. $[\alpha]_D^{20}$ −53 (*c* 1.25, $CHCl_3$). {Lit.:[6a] $[\alpha]_D^{20}$ +49 (*c* 1.25, $CHCl_3$) for (1*R*,5*S*)-**10**.} Spectral data identical to those reported by Galeazzi et al.[6a]

Acknowledgements

This work was supported by the Swiss National Science Foundation (Grant No. 20-45255.95 and 20-48156.96. The authors are indebted to Mrs. A. Pinto and J.-P. Saulnier for the routine NMR spectra and to Ms. G. Klink for the mass spectra.

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