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# Convenient Access to Various 1-Cyclopropylcyclopropane Derivatives[‡]

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*Dedicated to Professor Wolfgang Lüttke on the occasion of his 90th birthday*

**Keywords:** Cyclopropanes / Organolithium compounds / Electrophilic substitution / Cross coupling / Cycloaddition / Small ring systems

1-Bromo-1-cyclopropylcyclopropane (**1**), which is easily accessible in two steps from methyl cyclopropanecarboxylate, does not form a stable Grignard reagent upon reaction with elemental magnesium, yet it readily undergoes bromine/lithium exchange without rearrangement upon treatment with *tert*-butyllithium in diethyl ether/pentane at –78 °C, and the resulting 1-lithio-1-cyclopropylcyclopropane can be trapped with various electrophiles to give the correspondingly 1-substituted bicyclopropyl derivatives **10** in yields ranging from 38 to over 90 % (13 examples). The (1-cyclopropylcyclopropyl)boronate **10m**, which is also obtained from the 1-lithio derivative, has been subjected to Suzuki cross couplings with a number of aryl halides to furnish 1-aryl-1,1′-bicyclopropyl compounds **11** (4 examples, 14–50 % yield), predominantly without rearrangement. Further transformations of 1-cyclopropylcyclopropanecarbaldehyde (**10e**) have provided 2-(1-cyclopropylcyclopropyl)glycine (**16**), ethyl 3-(1-cyclopropylcyclopropyl)acrylate (**17**), and its cycloadducts with the nitrone **18** and cyclopentadiene **19**, albeit the latter only in poor yield.

## Introduction

With the appearance of two recent patent applications claiming particular biological activities for certain 1- and 2-cyclopropylcyclopropane derivatives[1,2] the interest in the peculiar 1- and 2-cyclopropylcyclopropyl substituents has dramatically increased in research groups concerned with drug and agrochemical discovery and development. Since 1-bromo-1-cyclopropylcyclopropane (**1**) has been made available in two simple steps on a reasonably large scale[3] as the immediate precursor to the versatile cyclopropyl building block bicyclopropylidene,[4] we set out to probe, whether **1** would be applicable as a reagent itself to attach the 1-cyclopropylcyclopropyl substituent onto various functionalities and skeletons, and here we report our first results.

## Results and Discussion

Initial attempts to convert **1** under classical Grignard conditions into (1-cyclopropylcyclopropyl)magnesium bromide (**2**) in order to trap the latter with a variety of electrophiles and obtain the corresponding 1-substituted bicyclopropyl derivatives, only gave a mixture of 1,1′;1′,1′′;1′′,1′′′-quatercyclopropane (**4**), 1-cyclopropyl-1-(3-cyclopropylidenepropyl)cyclopropane (**5**) and 1,6-dicyclopropylidenehexane (**6**) in a ratio of 1:8:20 in 90 % yield (Scheme 1).

Apparently, the initially formed intact Grignard reagent **2**, just like (1-cyclopropylcyclopropyl)palladium intermediates[5] and simple (cyclopropylmethyl)metal derivatives,[6,7] undergoes a relatively rapid rearrangement to the homoallyl counterpart **3**. This must serve as the precursor to 3-cyclopropylidenepropyl bromide (**8**), probably by way of the Schlenk equilibrium of **3** with **7** and magnesium bromide.

The bicyclopropylyl bromide **1** does not rearrange to **8** in the presence of magnesium bromide in refluxing diethyl ether, as was proved by a control experiment. The homoallyl bromide **8** can then react with the intact Grignard reagent **2** to give **5**, and with the rearranged homoallylmagnesium bromide **3** or the bis(homoallyl)magnesium **7** to fur-

[‡] Cyclopropyl Building Blocks for Organic Synthesis, 154. Part 153: M. Limbach, A. Lygin, V. S. Korotkov, M. Es-Sayed, A. de Meijere, *Org. Biomol. Chem.* **2009**, 3338–3342; Part 152: V. A. Rassadin, A. A. Tomashevskiy, V. V. Sokolov, A. Ringe, J. Magull, A. de Meijere, *Eur. J. Org. Chem.* **2009**, 2645–2641.

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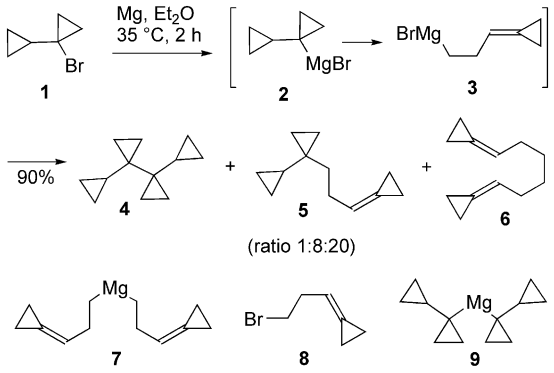


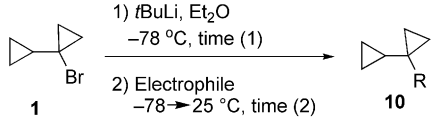

Scheme 1. Reaction of 1-bromo-1-cyclopropylcyclopropane (**1**) with magnesium turnings.

nish **6**. The latter can also be formed by reductive elimination from **7**. The quatercyclopropyl **4** must arise by reductive elimination from bis(1-cyclopropylcyclopropyl)-magnesium (**9**), which is formed in the Schlenk equilibrium with **2** and magnesium bromide.

Treatment of **1** in tetrahydrofuran with magnesium turnings in the presence of benzaldehyde, i.e. under conditions of the so-called Barbier reaction,[8] furnished the same hydrocarbons **5** and **6**, but none of the tertiary alcohol that would have resulted from the addition of **2** to benzaldehyde. The formation of the bicyclopropyl coupling products **4** and **5** indicates that the rearrangement of (bicyclopropyl-1-yl)magnesium bromide (**2**) is not extremely rapid even at 35 °C. One would therefore expect that a (bicyclopropyl-1-yl)metal derivative, when generated at lower temperature, would survive long enough to be trapped by appropriate electrophiles before undergoing rearrangement to the corresponding (homoallyl)metal species. An attempt to achieve a bromine/magnesium exchange by treatment of **1** with isopropylmagnesium chloride in the presence of lithium chloride (so-called turbo-Grignard) according to Knochel et al.,[9] was not successful. An attempted bromine/lithium exchange on **1** with *n*-butyllithium at –78 °C also failed.

However, treatment of 1-bromobicyclopropyl (**1**) in diethyl ether with *tert*-butyllithium in pentane at –78 °C and subsequent quenching with trimethylsilyl chloride gave 1-(trimethylsilyl)-1-cyclopropylcyclopropane (**10a**) in 53% yield. Analogously, various 1-substituted bicyclopropyl derivatives **10b**–**m** were obtained in yields ranging from 38 to approx. 92% (Scheme 2 and Table 1). Among them are the (1-cyclopropylcyclopropyl)stannane **10b**, the carboxylic acid **10d**,[10] the aldehyde **10e**, the diphenylphosphanyl derivative **10l** as a potentially interesting new ligand for transition metals, and the boronate **10m**. This access to **10m** is far superior to a previously published preparation of 2-(bicyclopropyl-1-yl)-1,3,2-dioxaborinane from bicyclopropylidene.[11]

Since the boronate **10m** was obtained in higher yield (71%) than the stannane **10b** (61%) and Suzuki couplings[12] are more popular than Stille couplings,[13,14] the palladium-catalyzed cross coupling of **10m** with some aryl halides was tested. Suzuki cross couplings of simple cyclopropylboronates are known,[15] and an analogous cross coupling of a (*trans*-2-cyclopropylcyclopropyl)boronate to yield (*trans*-2-cyclopropylcyclopropyl)arenes has previously been developed in our laboratory.[16] However, **10m** is a tertiary and at the same time neopentyl-type alkylboronate, and couplings of such substrates are unknown. Yet, when **10m** and phenyl iodide were subjected to typical Suzuki coupling conditions, 1-phenyl-1,1′-bicyclopropyl (**11n**) was obtained in 50% yield (Scheme 3). Analogously, the reactions of **10m** with 1-bromo-4-(trifluoromethyl)benzene and 4-iodoanisol gave the corresponding bicyclopropyl derivatives **11o** and **11p** each in 45% yield. 1,4-Dibromobenzene furnished the twofold coupling product **12** in poor yield (14%) along with the monocoupling/monoreduction product **11n** (25%) and 1-iodo-2,4,6-trimethylbenzene only provided the product **13** with a rearranged $C_6$ unit (17% yield), the formation of which is not understood. Attempted coupling of **10m** with 1-bromo-2-(trifluoromethyl)benzene, 2-bromoaniline, 2-bromo-*N*-(*tert*-butoxycarbonyl)aniline as well as 3-iodopyridine did not lead to any identifiable products, and 2-iodopyridine in the presence of **10m** only led to 2,2′-bipyridyl (**14**). Although all the yields in the successful couplings of **10m** are not very high, it is remarkable that the products **11n**–**p** were obtained without rearrangement (Table 2), as previously developed cross couplings proceeding via (1-cyclopropylcyclopropyl)palladium intermediates




Scheme 2. Bromine/lithium exchange on 1-bromobicyclopropyl (**1**) and subsequent electrophilic substitution. For details see Table 1.

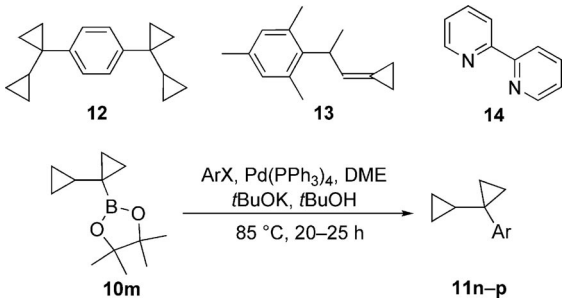
Table 1. Bromine/lithium exchange on 1-bromobicyclopropyl (**1**) and subsequent electrophilic substitution (see Scheme 2).

| Electrophile | Time (1) [min] | Time (2) [min] | Product | R | Isolated yield [%] |
|---|---|---|---|---|---|
| $Me_3SiCl$ | 50 | 60 | **10a** | $Me_3Si$ | 53 |
| $Bu_3SnCl$ | 50 | 60 | **10b** | $Bu_3Sn$ | 61 |
| PhSSPh | 50 | 60 | **10c** | PhS | 63 |
| $CO_2$ | 50 | 120 | **10d** | $CO_2H$ | 89 |
| $Me_2NCHO$ | 50 | 60 | **10e** | CHO | ca. 92[a] |
| $(CH_2O)_n$ | 120 | 60 | **10f** | $CH_2OH$ | 61 |
| PhCHO | 60 | 60 | **10g** | PhCHOH | 63 |
| 3,5-$Cl_2C_6H_3CHO$ | 35 | 125 | **10h** | 3,5-$Cl_2C_6H_3CHOH$ | 63 |
| *c*PrCOMe | 35 | 180 | **10i** |  | 66 |
| *c*PrCO*c*Pr | 35 | 185 | **10j** |  | 64 |
| $MeCO_2Me$ | 50 | 23 h | **10k** |  | 38 |
| $Ph_2PCl$ | 35 | 135 | **10l** | $Ph_2P$ | 64[b] |
| *i*PrOB(O)O | 60 | 6 h | **10m** | B(O)O | 71 |

[a] The aldehyde was not completely purified, but further transformed as a 1:1 mixture with $Et_2O$. [b] Isolated as the air-stable borane complex.

gave rearrangement products only.[5] Attempts to improve the yields in the Suzuki couplings of **10m** by using the more advanced protocol by Buchwald et al.,[17] failed completely. Under two types of conditions as reported, only traces of the product **11n** could be detected, when bromo- and iodobenzene were employed.



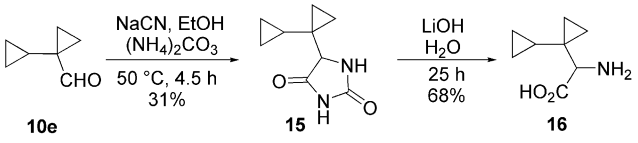

Scheme 3. Suzuki cross coupling of (1-cyclopropylcyclopropyl)-boronate **10m** with some aryl halides. For details see Table 2.

Table 2. Suzuki cross coupling of (1-cyclopropylcyclopropyl)-boronate **10m** with some aryl halides (see Scheme 3).

| ArX | Time [h] | Product | Yield [%] |
|---|---|---|---|
| PhI | 20 | **11n** | 50 |
| 4-$F_3CC_6H_4Br$ | 25 | **11o** | 45 |
| 4-$MeOC_6H_4Br$ | 25 | **11p** | 45 |
| 4-$BrC_6H_4Br$ | 25 | **12** | 14[a] |
| 2,4,6-$Me_3C_6H_2I$ | 25 | **13** | 17 |
| 2-Py-I | 20 | **14** | 67 |

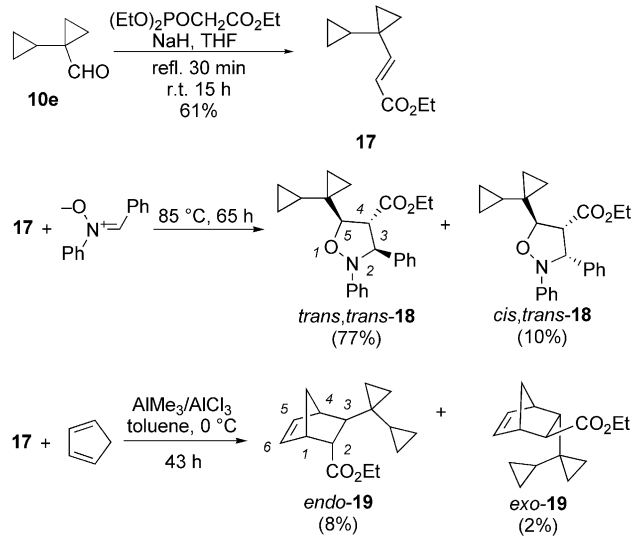
[a] In addition, 25% of **11n** was isolated.

The aldehyde **10e** could be converted into the unusual amino acid **16** via the (1-cyclopropylcyclopropyl)-substituted hydantoin **15** (Scheme 4) by employing an established procedure[18] in 21% overall yield (not optimized).




Scheme 4. Preparation of 2-amino-2-(1-cyclopropylcyclopropyl)-acetic acid (**16**).

The versatility of **10e** was also demonstrated by its conversion to the 2-(1-cyclopropylcyclopropyl)-substituted ethyl acrylate **17** and further transformations of the latter to additional new bicyclopropyl derivatives (Scheme 5). Wittig–Horner–Emmons alkenation of **10e** with ethyl (diethoxyphosphoryl)acetate gave the acrylate **17** in approximately 61% yield. For a test, this α,β-unsaturated ester **17** was employed in a 1,3-dipolar cycloaddition as well as a Diels–Alder reaction (Scheme 5). Thus, upon heating of a mixture of diphenyl nitrone with a twofold excess of **17** at 85 °C for 65 h, a 7:1 mixture of the two diastereomeric cycloadducts *trans,trans*- and *cis,trans*-**18** was obtained. The individual diastereomers were isolated in 77 and 10% yield, respectively, by column chromatography, and the structure including the relative configuration of the major isomer was proven by an X-ray crystal-structure analysis to be (3*RS*,4*SR*,5*SR*), i.e. *trans,trans*-**18** (Figure 1). This is consistent with the interactions 3-H/$CH_2O$, 3-H/5-H, 4-H/*o*-H(3-Ph), 4-H/cPr-H, observed in the 2D-NOESY $^1$H-NMR spectrum.




Scheme 5. Preparation of ethyl (*E*)-3-(1-cyclopropylcyclopropyl)-acrylate (**17**) and its employment in cycloaddition reactions.

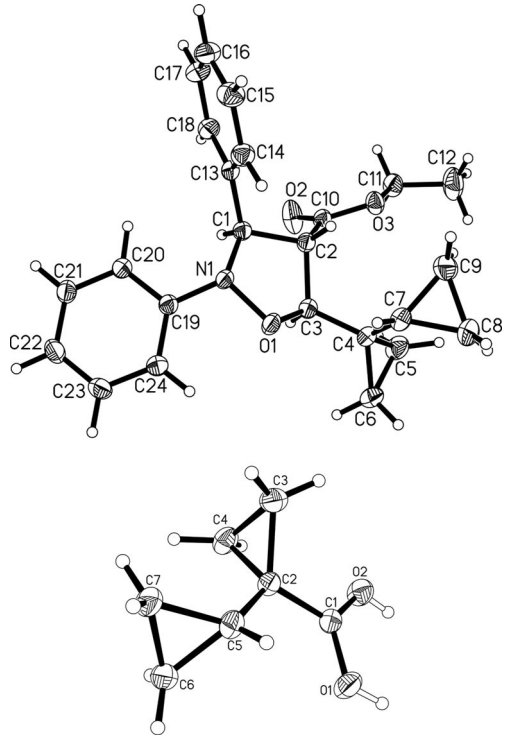



Figure 1. Structures of ethyl (3*RS*,4*SR*,5*SR*)-5-(1-cyclopropylcyclopropyl)-2,3-diphenylisoxazolidine-4-carboxylate (*trans,trans*-**18**) (top) and 1-cyclopropylcyclopropanecarboxylic acid (**10d**) (bottom) in the crystal.[19]

The bicyclopropyl substituent in *trans,trans*-**18** adopts the same *synclinal* (*gauche*) conformation as that in 1-cyclopropylcyclopropanecarboxylic acid (Figure 1). This is typical for 1-substituted bicyclopropyl derivatives,[11]

whereas bicyclopropyl itself in the crystal assumes an *anti-periplanar* (*s-trans*) orientation.[20] The carboxy group of the acid **10d** is in a plane bisecting the adjacent three-membered ring. This conformation as well as the bond-length alteration in the carboxy-substituted cyclopropane ring is typical for cyclopropanes with an electron-withdrawing substituent.[21] The molecules **10d** in the crystal form centrosymmetrical dimers as is typical for carboxylic acids.[22]

The 2-substituted acrylate **17** turned out to be a poor dienophile. Heating of a mixture of **17** and cyclopentadiene at 42 °C for 10 h did not furnish any of the expected cycloadduct. Only under conditions that have been put forward for Diels–Alder reactions to be carried out at low temperatures,[23] i.e. in the presence of $AlMe_3/AlCl_3$ in toluene at 0 °C, could the cycloadducts *endo*-**19** and *exo*-**19** be isolated in 8 and 2% yield, respectively (Scheme 5). The *endo* – with respect to the orientation of the methoxycarbonyl group – configuration of the major diastereomer was assigned on the basis of 1D-NOE NMR measurements showing strong interactions between 7-$H_{syn}$ and 2-H as well as between 7-$H_{syn}$ and some cyclopropyl protons, but none between 7-$H_{syn}$ and 3-H.

## Conclusions

Bromine/lithium exchange on 1-bromo-1,1-bicyclopropyl (**1**) with *tert*-butyllithium generates an electrophilic reagent that allows one to attach the 1-cyclopropylcyclopropyl substituent to various substructures by way of building blocks like the carboxylic acid **10d**, the aldehyde **10e**, the boronate **10m**, the acrylate **17** and others, that are conveniently accessible from 1-lithiobicyclopropyl. The interest in the 1- and 2-cyclopropylcyclopropyl substituents is growing,[1,2] and this must have to do with the peculiar electronic properties of cyclopropyl substituents in general[24] and the added steric features of substituted bicyclopropyl units, which have a preferred *synclinal* (*gauche*) orientation.[11,25]

## Experimental Section

**General Remarks:** All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aqueous solvents were carried out by using standard Schlenk techniques under dry nitrogen. Solvents were purified and dried according to conventional methods prior to use. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AM 250 (250 MHz for $^1H$ and 62.9 MHz for $^{13}C$), a Varian UNITY-300 (300 MHz for $^1H$ and 75.5 MHz for $^{13}C$) or an Inova-500 (125.7 MHz for $^{13}C$) instrument. Chemical shifts $\delta$ are given in ppm relative to residual resonances of solvents ($^1H$: $\delta$ = 7.26 ppm for $CHCl_3$, 2.50 ppm for [$D_6$]-DMSO; $^{13}C$: $\delta$ = 77.0 ppm for $CDCl_3$, 39.52 for [$D_6$]DMSO) or tetramethylsilane ($^1H$: $\delta$ = 0.00 ppm; $^{13}C$: $\delta$ = 0.0 ppm); coupling constants *J* are presented as absolute values in Hz. The multiplicities of $^{13}C$ signals were determined by the DEPT or the APT technique. IR: Bruker IFS 66 (FTIR) spectrometer, measured as KBr pellets or oils between KBr plates. EI-MS: Finnigan MAT 95, 70 eV. ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). TLC: Macherey–Nagel, TLC plates Alugram® Sil G/UV254. Detection under UV light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid, solution in ethanol). Melting points: Büchi 540 capillary melting point apparatus, uncorrected values. The elemental analyses were performed on an HP185B CHN analyzer.

**Reaction of 1-Bromobicyclopropyl (1) with Magnesium:** A 100 mL round-bottomed Schlenk flask, fitted with a reflux condenser as well as a rubber septum and equipped with a magnetic stirring bar, was charged with magnesium turnings (0.34 g) and anhydrous $Et_2O$ (20 mL). The magnesium was activated by addition of a few drops of 1,2-dibromoethane from a syringe; then bromide **1** (2.0 g, 12.4 mmol) was added dropwise at room temp. The mixture was heated under reflux for 2 h, then cooled to 0 °C, and the reaction was quenched with satd. aq. $NaHCO_3$ solution (14 mL). The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated in a rotary evaporator at 0 °C/150 Torr to give 900 mg (90%) of a mixture of 1,1′;1′,1′′;1′′,1′′′-quatercyclopropyl (**4**), 1-cyclopropyl-1-(3-cyclopropylidenepropyl)cyclopropane (**5**) and 1,6-dicyclopropylidenehexane (**6**) in a ratio of 1:8:20. The isomers were separated by preparative-scale gas-liquid chromatography on a 3 m × 0.63 cm glass column with 15% FFAP on Chromosorb W/AW/DMCS 60–80 mesh and helium as carrier gas at 150 °C.

**Compound 4:** Colorless oil. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = –0.05 to –0.02 (m, 4 H, cPr-H), 0.01–0.04 (m, 4 H, cPr-H), 0.05–0.08 (m, 4 H, cPr-H), 0.28–0.31 (m, 4 H, cPr-H), 1.28–1.33 (m, 2 H, cPr-H) ppm. $^{13}C$ NMR (125.7 MHz, $CDCl_3$, additional DEPT): $\delta$ = 2.3 (–, cPr-C), 7.0 (–, cPr-C), 15.1 (+, cPr-C), 25.1 ($C_q$, cPr-C) ppm. EI-MS: *m*/*z* (%) = 147 (2) $[M - 15]^+$, 134 (22), 119 (27), 105 (19), 93 (18), 91 (55), 84 (27), 79 (46), 67 (24), 55 (24), 53 (20), 41 (100). DCI: *m*/*z* (%) = 180 (18) $[M + NH_4]^+$, 163 (100) $[M + H]^+$, 134 (22), 121 (10), 93 (8).

**Compound 5:** Colorless oil. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = –0.09 to –0.06 (m, 2 H, cPr-H), 0.10–0.12 (m, 4 H, cPr-H), 0.26–0.29 (m, 2 H, cPr-H), 0.97–1.01 (m, 4 H, cPr-H), 1.02–1.06 (m, 1 H, cPr-H), 1.47–1.49 (m, 2 H, $CH_2$), 2.33–2.38 (m, 2 H, $CH_2$), 5.75–5.79 (m, 1 H, =CH) ppm. $^{13}C$ NMR (125.7 MHz, $CDCl_3$, additional DEPT): $\delta$ = 1.9 (–, cPr-C), 2.1 (–, cPr-C), 2.2 (–, cPr-C), 9.3 (–, cPr-C), 14.4 (+, cPr-C), 20.3 ($C_q$, cPr-C), 29.5 (–, $CH_2$), 39.6 (–, $CH_2$), 118.7 (+, =CH), 120.4 ($C_q$, =C) ppm. EI-MS: *m*/*z* (%) = 147 (3) $[M - 15]^+$, 133 (10), 119 (26), 105 (34), 93 (46), 91 (73), 79 (100), 67 (70), 55 (47), 53 (42), 41 (96). DCI: *m*/*z* (%) = 180 (54) $[M + NH_4]^+$, 163 (100) $[M + H]^+$, 134 (22), 121 (43), 107 (36), 95 (46), 93 (32).

**Compound 6:** Colorless oil. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 0.98–1.02 (m, 8 H, cPr-H), 1.43–1.47 (m, 4 H, $CH_2$), 2.15–2.20 (m, 4 H, $CH_2$), 5.72–5.76 (m, 1 H, =CH) ppm. $^{13}C$ NMR (125.7 MHz, $CDCl_3$, additional DEPT): $\delta$ = 1.9 (–, cPr-C), 2.3 (–, cPr-C), 29.1 (–, $CH_2$), 31.8 (–, $CH_2$), 118.3 (+, =CH), 120.8 ($C_q$, =C) ppm. EI-MS: *m*/*z* (%) = 161 (0.3) $[M - H]^+$, 147 (3) $[M - 15]^+$, 133 (7), 119 (22), 105 (37), 93 (37), 91 (70), 79 (100), 67 (50), 55 (24), 53 (21), 41 (75). DCI: *m*/*z* (%) = 180 (33) $[M + NH_4]^+$, 163 (22) $[M + H]^+$, 147 (43), 134 (38), 121 (60), 107 (70), 93 (100).

**General Procedure for the Bromine/Lithium Exchange on 1-Bromo-1,1′-bicyclopropyl (1) and Subsequent Trapping with Electrophiles (GP1):** A solution of *t*BuLi (1.5–1.7 M in pentane or hexane, 1.05–2.10 equiv.) was added dropwise at –78 °C within 5 min to a solution of 1-bromobicyclopropyl (**1**) (1 equiv.) in $Et_2O$ (10 mL). After the given time (1) (see Table 1), the respective electrophile (1.05 equiv.) was added from a syringe (5 min), and the mixture was warmed slowly to room temp. over the given time (2) (see

Table 1). The reaction was quenched with $H_2O$, if not stated otherwise; the aqueous layer was extracted with diethyl ether (3 × 20 mL) and then with pentane (2 × 10 mL); the combined organic phases were washed with brine, dried ($Na_2SO_4$) and concentrated in a rotary evaporator at 0 °C/80 Torr. The residue was purified by column chromatography (silica gel, pentane), if not stated otherwise.

**1-Cyclopropylcyclopropanecarboxylic Acid (10d):**[10] A solution of *t*BuLi (1.6 M in pentane, 8.16 mL, 13.04 mmol) was added dropwise at –78 °C within 30 min to a solution of 1-bromobicyclopropyl (**1**) (2.00 g, 12.42 mmol) in $Et_2O$ (45 mL). After 20 min at –78 °C, an excess of dry ice was added, and the mixture was warmed slowly to room temp. over 2 h. The reaction was quenched with 0.2 M aq. $Na_2CO_3$ (ca 100 mL), the aqueous layer was washed with diethyl ether (3 × 50 mL), and then acidified with concd. HCl under ice cooling. The resulting mixture was extracted with diethyl ether (3 × 50 mL), and then with pentane (2 × 30 mL); the combined organic phases were dried with anhydrous $Na_2SO_4$ and concentrated to give the acid **10d** as colorless crystals (1.40 g, 11.10 mmol, 89%), m.p. 51–52 °C. IR (KBr): $\tilde{\nu}$ = 3085 (cPr-H), 1688 (C=O) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.05–0.00 (m, 2 H, cPr-H), 0.40–0.47 (m, 2 H, cPr-H), 0.57–0.61 (m, 2 H, cPr-H), 1.10–1.14 (m, 2 H, cPr-H), 1.40–1.49 (m, 1 H, cPr-H), 12.18 (br. s, 1 H, COOH) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 2.5 (–, cPr-C), 10.8 (–, cPr-C), 13.6 (–, cPr-C), 24.4 ($C_q$, cPr-C), 183.2 (+, C=O) ppm.

**1-Cyclopropylcyclopropanecarbaldehyde (10e):** A solution of *t*BuLi (1.7 M in pentane, 3.7 mL, 6.3 mmol) was added dropwise at –78 °C within 15 min to a solution of 1-bromobicyclopropyl (**1**) (996 mg, 6 mmol) in $Et_2O$ (20 mL). After 45 min at –78 °C, *N*,*N*-dimethylformamide (512 mg, 7 mmol) was added from a syringe (5 min), and the mixture was allowed to slowly warm to room temp. over 1 h. The reaction was quenched by addition of diluted HCl ($H_2O$/concd. HCl, 50:1; 51 mL), the aqueous layer was extracted with diethyl ether (3 × 60 mL), then with pentane (2 × 20 mL); the combined organic phases were washed with aq. $NaHCO_3$ solution, brine, dried with anhydrous $Na_2SO_4$ and concentrated in a rotary evaporator at 0 °C/115 Torr to give the aldehyde **10e** as a mixture with diethyl ether (ca. 1:1), corresponding to approximately 610 mg (5.54 mmol, 92%) of **10e**. IR (film): $\tilde{\nu}$ = 3084 (cPr-H), 1716, 1687 (C=O) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.03–0.04 (m, 2 H, cPr-H), 0.45–0.53 (m, 2 H, cPr-H), 0.73–0.78 (m, 2 H, cPr-H), 0.99–1.03 (m, 2 H, cPr-H), 1.34–1.43 (m, 1 H, cPr-H), 8.97 (s, 1 H, CHO) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 1.9 (–, cPr-C), 8.9 (–, cPr-C), 11.5 (–, cPr-C), 33.4 ($C_q$, cPr-C), 202.9 (+, C=O) ppm. The NMR spectra of **8e** were identical with those of the aldehyde obtained in 73% yield by Dess–Martin oxidation of (1-cyclopropylcyclopropyl)methanol (**10f**).[26]

**(1-Cyclopropylcyclopropyl)diphenylphosphane–Borane Complex (10l):** A solution of *t*BuLi (1.6 M in pentane, 4.08 mL, 6.52 mmol) was added dropwise at –78 °C within 15 min to a solution of 1-bromobicyclopropyl (**1**) (1.00 g, 6.21 mmol) in $Et_2O$ (30 mL). After 20 min at –78 °C, a solution of $Ph_2PCl$ (1.038 g, 6.21 mmol) in $Et_2O$ (4 mL) was added from a syringe (15 min), and the mixture was warmed slowly to room temp. over 2 h. Borane–THF complex (1 M, 8 mL, 8 mmol) was added at 0 °C, and the mixture was stirred for an additional 1 h. The reaction was then quenched by addition of MeOH (3 mL) and water (20 mL). The aqueous layer was extracted with diethyl ether (3 × 60 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$) and concentrated in a rotary evaporator to give 2.04 g of a colorless oil, which crystallized slowly. Recrystallization from methanol afforded **10l** as a colorless solid (1.12 g, 4.00 mmol, 64%), m.p. 98–99 °C. IR (KBr): $\tilde{\nu}$ = 3075 (cPr-H) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.19 to –0.13 (m, 2 H, cPr-H), 0.15–0.22 (m, 2 H, cPr-H), 0.48–0.59 (m, 2 H, cPr-H), 0.98–1.07 (m, 2 H, cPr-H), 1.21–1.31 (m, 1 H, cPr-H), 7.39–7.49 (m, 6 H, Ph-H), 7.71–7.78 (m, 4 H, Ph-H) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 3.1 (–, d, $J_{CP}$ = 3 Hz, cPr-CHP), 7.7 (–,d, $J_{CP}$ = 1.2 Hz, cPr-C), 12.2 (+, d, $J_{CP}$ = 4.2 Hz cPr-C), 13.9 ($C_q$, d, $J_{CP}$ = 54.8 Hz, cPr-C), 128.3–133.4 (Ph-C) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = 34.7 (q, $^1J_{BP}$ = 71 Hz) ppm. $^{11}B$ NMR (96 MHz, $CDCl_3$): $\delta$ = –39.4 (q, $^1J$ = 55 Hz) ppm. EI-MS: *m*/*z* = 279, 277 $[M]^+$, 265, 266, 267, 251, 183, 108. $C_{18}H_{22}BP$ (280.15): calcd. C 77.2, H 7.9; found C 76.9, H 7.8.

**2-(1-Cyclopropylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10m):** 2-Isopropyloxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared according to a puplished procedure.[27] From a solution of triisopropyl borate (31.0 g, 0.164 mol) and pinacol (19.4, 0.164 mol) in hexane (230 mL), a 2-propanol/hexane azeotrope was slowly distilled off at 55–60 °C. The residue was distilled to give 25.0 g (0.134 mol, 82%) of the product, b.p. 52 °C/12 mbar. A solution of *t*BuLi (1.5 M in pentane, 17.5 mL, 26.3 mmol) was added dropwise at –78 °C within 30 min to a solution of the bromide **1** (3.62 g, 22.5 mmol) in $Et_2O$ (80 mL). After 30 min at –78 °C, isopropyloxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was added dropwise within 10 min, and the mixture was warmed slowly to room temp. over 6 h. The reaction was quenched with satd. $NH_4Cl$ solution (ca. 20 mL). The resulting mixture was extracted with diethyl ether (3 × 60 mL), then with pentane (2 × 20 mL); the combined extracts were dried ($Na_2SO_4$), concentrated, and the residue was purified by flash chromatography (200 mL of silica gel, ether/pentane, 1:100 → 1:50) to give compound **10m** as a colorless oil (3.34 g, 16.1 mmol, 71%), which solidified upon standing in the refrigerator. IR (film): $\tilde{\nu}$ = 3078 (cPr-H) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.09 to –0.02 (m, 2 H, cPr-H), 0.19–0.29 (m, 4 H, cPr-H), 0.49–0.52 (m, 2 H, cPr-H), 0.97–1.08 (m, 1 H, cPr-H), 1.20 (s, 12 H, Me) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 1.8 (–, cPr-C), 8.7 (–, cPr-C), 12.9 (+, cPr-C), 24.6 (+, Me), 82.8 ($C_q$, OC) ppm. EI-MS: *m*/*z* = 208 $[M^+]$, 193, 180, 165, 151, 107, 101, 84. $C_{12}H_{21}BO_2$ (208.10): calcd. C 69.3, H 10.2; found C 69.4, H 10.4.

**General Procedure for Palladium-Catalyzed Cross-Coupling Reactions of 2-(1-Cyclopropylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10m) (GP2):** A 25 mL two-necked flask was charged with the borolane **10k** (1.00 mmol), $Pd(PPh_2)_4$ (0.10 mmol, 10 mol-%), the respective (het)aryl halide (1.00 mmol) and DME (10–12 mL), and flushed with dry nitrogen. Then degassed KO*t*Bu (1 M in *t*BuOH, 3.30 mmol) was added, and the mixture was heated in the sealed flask under nitrogen at 85 °C (bath temperature) for 20–25 h. After cooling to room temp., the DME was removed in vacuo in a rotary evaporator, the residue was diluted with diethyl ether/pentane (5:1, 50 mL) and the solution filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by column chromatography.

**1-(1-Cyclopropylcyclopropyl)benzene (11n):** From **10m** (208 mg, 1.00 mmol) and iodobenzene (204 mg, 1.00 mmol) according to GP2, the product **11n** was obtained as a colorless oil (79 mg, 0.50 mmol, 50%). IR (film): $\tilde{\nu}$ = 3079 (cPr-H) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 0.15–0.18 (m, 2 H, cPr-H), 0.41–0.46 (m, 2 H, cPr-H), 0.63–0.68 (m, 2 H, cPr-H), 0.72–0.77 (m, 2 H, cPr-H), 1.25–1.36 (m, 1 H, cPr-H), 7.17–7.40 (m, 5 H, Ph) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 2.8 (–, cPr-C), 11.6 (–, cPr-C), 17.1 (+, cPr-C), 25.0 ($C_q$, cPr-C), 125.6 (+, Ph-C), 127.7 (+, Ph-C), 128.1 (+, Ph-C), 146.8 ($C_q$, Ph-C) ppm. EI-MS: *m*/*z* = 158 $[M^+]$, 143, 129, 115, 102, 91. $C_{12}H_{14}$ (158.24): calcd. C 91.1, H 8.9; found C 91.3, H 8.8.

**5-(1-Cyclopropylcyclopropyl)imidazolidine-2,4-dione (15):** A suspension of 1-cyclopropylcyclopropanecarbaldehyde (**10e**) (ca. 495 mg, 4.5 mmol), NaCN (700 mg, 14.3 mmol), $(NH_4)_2CO_3$ (4.0 g, 41.6 mmol) in 50% aq. EtOH (16 mL) was heated at 50 °C with stirring for 4.5 h and then left overnight. Water (15 mL) was added, and the reaction mixture then concentrated in a rotary evaporator under reduced pressure (10 Torr) to half of the original volume. The residue was acidified with concd. HCl to pH ≈ 1 under cooling (0 °C), the precipitate was filtered off, washed with ice/water and dried under reduced pressure (0.01 Torr) to give the hydantoin (250 mg, 1.39 mmol, 31%; m.p. 173 °C), which was used for the next step without further purification. IR (KBr): $\tilde{\nu}$ = 3175 (br., NH), 3083 (cPr-H), 1779, 1731 (C=O) $cm^{-1}$. $^1H$ NMR (250 MHz, [D$_6$]DMSO): $\delta$ = –0.06–0.16 (m, 2 H, cPr-H), 0.17–0.32 (m, 2 H, cPr-H), 0.46–0.50 (m, 2 H, cPr-H), 1.02–1.12 (m, 2 H, cPr-H), 3.52 (s, 1 H, CH), 7.98 (s, 1 H, NH), 10.55 (s, 1 H, NH) ppm. $^{13}C$ NMR (62.9 MHz, [D$_6$]DMSO, additional DEPT): $\delta$ = 1.0 (–, cPr-C), 1.6 (–, cPr-C), 6.2 (–, cPr-C), 6.8 (–, cPr-C), 10.2 (+, cPr-C), 21.7 ($C_q$, cPr-C), 65.2 (+, CH), 157.5 ($C_q$, C=O), 174.9 ($C_q$, C=O) ppm. HRMS: calcd. for $C_9H_{13}N_2O_2^+$ [M + H$^+$] 181.09715; found 181.09713.

**2-Amino-2-(1-cyclopropylcyclopropyl)acetic Acid (16):** A suspension of the hydantoin **15** (214 mg, 1.19 mmol) and LiOH (279 mg, 11.66 mmol) in water (5 mL) was heated under reflux for 25 h. The reaction mixture was cooled, concentrated in a rotary evaporator under reduced pressure (10 Torr), the residue was acidified with concd. HCl to pH ≈ 1, and the mixture was filtered. The pH of the filtrate was adjusted with aq. LiOH to 5.5, and the solution was concentrated to dryness in a rotary evaporator (10 Torr). The residue was stirred with MeOH (4 mL) for 1 h, the precipitate was filtered off, washed with cold MeOH and dried under reduced pressure (0.01 Torr) to give the amino acid **16** [125 mg, 0.81 mmol, 68%; m.p. (decomp.) > 260 °C] as a colorless solid. IR (KBr): $\tilde{\nu}$ = 3100–2600 (br., $NH_3^+$), 1654 ($NH_3^+$), 1590 ($CO_2^-$) $cm^{-1}$. $^1H$ NMR (300 MHz, $D_2O$): $\delta$ = 0.00–0.17 (m, 2 H, cPr-H), 0.35–0.55 (m, 4 H, cPr-H), 0.59–0.66 (m, 1 H, cPr-H), 0.80–0.87 (m, 1 H, cPr-H), 1.05–1.14 (m, 1 H, cPr-H), 3.26 (s, 1 H, CH), 4.73 (s, 3 H, $NH_3$) ppm. $^{13}C$ NMR (75.6 MHz, $D_2O$, additional APT): $\delta$ = 0.5 (–, cPr-C), 1.9 (–, cPr-C), 7.7 (–, cPr-C), 10.0 (+, cPr-C), 10.2 (–, cPr-C), 21.8 (–, cPr-C), 63.8 (+, CH), 173.6 (+, C=O) ppm. HRMS: calcd. for $C_8H_{14}NO_2^+$ [M + H$^+$] 156.10191; found 156.10196. $C_8H_{13}NO_2$ (155.19): calcd. C 61.9, H 8.4, N 9.0; found C 61.8, H 8.5, N 8.9.

**Ethyl (*E*)-3-(1-Cyclopropylcyclopropyl)acrylate (17):** A solution of diethyl (diethoxyphosphoryl)acetate (13.5 g, 60.2 mmol) in THF (45 mL) was added dropwise at room temp. within 30 min to a stirred suspension of sodium hydride (60% suspension, 2.41 g, 60.2 mmol) in THF (45 mL), and the mixture was stirred at room temp. for 1 h. A solution of the aldehyde **10e** (ca. 5 g, ca. 46 mmol) in THF (25 mL) was added in one portion. The mixture was heated under reflux for 30 min, then stirred at room temp. overnight, before satd. aq. $NH_4Cl$ solution (10 mL) was added. The THF was evaporated in vacuo, and the residue was then partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (150 mL of silica gel, ether/pentane, 1:200 → 1:50) to give the acrylate **17** as a colorless oil (5.05 g, 28.02 mmol, 61%). IR (film): $\tilde{\nu}$ = 3083 (cPr-H), 1714 (C=O), 1641 (C=C) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.01–0.05 (m, 2 H, cPr-H), 0.42–0.50 (m, 2 H, cPr-H), 0.66–0.70 (m, 4 H, cPr-H), 1.14–1.25 (m, 1 H, cPr-H), 1.29 (t, $J$ = 7.2 Hz, 3 H, Me), 4.18 (q, $J$ = 7.2 Hz, 2 H, $CH_2$), 6.08 (d, $J$ = 5.6 Hz, 1 H, =CH), 6.56 (d, $J$ = 5.6 Hz, 1 H, =CH) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 2.2 (–, cPr-C), 12.2 (+, cPr-C), 13.1 (–, cPr-C), 14.3 (+, Me), 23.7 ($C_q$, cPr-C), 60.0 (–, $CH_2$), 117.1 (+, =CH), 157.5 (+, =CH), 167.2 ($C_q$, C=O) ppm. EI-MS: $m/z$ = 180 [M$^+$], 152, 124, 107, 91, 79. $C_{11}H_{16}O_2$ (180.24): calcd. C 73.3, H 9.0; found C 73.1, H 8.8.

**Ethyl (3*RS*,4*SR*,5*SR*)- and (3*RS*,4*RS*,5*RS*)-5-(1-Cyclopropylcyclopropyl)-2,3-diphenylisoxazolidine-4-carboxylate (*trans*,*trans*- and *cis*,*trans*-18):** A mixture of diphenyl nitrone (197 mg, 1 mmol) and the acrylate **17** (360 mg, 2 mmol) was heated in a sealed vial at 85 °C for 65 h. The excess of **17** was removed in vacuo in a Kugelrohr apparatus (80 °C/0.05 mbar), and the residue was purified by column chromatography (60 mL of silica gel, ether/pentane, 1:50 → 1:25) to give *trans*,*trans*-**18** as a colorless solid (291 mg, 0.77 mmol, 77%), m.p. 60–61 °C and *cis*,*trans*-**18** as a colorless solid (39 mg, 0.10 mmol, 10%), m.p. 75–76 °C.

***trans*,*trans*-18:** IR (KBr): $\tilde{\nu}$ = 3070 (cPr-H), 1730 (C=O) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.09–0.00 (m, 1 H, cPr-H), 0.07–0.24 (m, 2 H, cPr-H), 0.26–0.41 (m, 3 H, cPr-H), 0.46–0.54 (m, 1 H, cPr-H), 0.58–0.66 (m, 1 H, cPr-H), 1.21 (t, $J$ = 7 Hz, 3 H, Me), 1.24–1.34 (m, 1 H, cPr-H), 3.83 (dd, $J$ = 6.7, 9.1 Hz, 1 H, 4-H), 3.98 (d, $J$ = 9.1 Hz, 1 H, 3-H), 4.12 (q, $J$ = 7 Hz, 2 H, $OCH_2$), 5.15 (d, $J$ = 6.7 Hz, 1 H, 5-H), 6.90–7.01 (m, 3 H, Ph-H), 7.21–7.40 (m, 5 H, Ph-H), 7.54–7.58 (m, 2 H, Ph-H) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 0.4 (–, cPr-C), 3.2 (–, cPr-C), 5.6 (–, cPr-C), 9.3 (–, cPr-C), 10.4 (+, cPr-C), 14.1 (+, Me), 20.0 ($C_q$, cPr-C), 60.7 (+, C-4), 61.1 (–, $OCH_2$), 74.3 (+, C-3), 88.5 (+, C-5), 113.9 (+, Ph-C), 121.5 (+, Ph-C), 126.3 (+, Ph-C), 127.5 (+, Ph-C), 128.8 (+, Ph-C), 128.9 (+, Ph-C), 141.8 ($C_q$, Ph-C), 151.8 ($C_q$, Ph-C), 171.1 ($C_q$, C=O) ppm. EI-MS: $m/z$ = 377 [M$^+$], 262, 198, 181, 91. $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.4, N 3.7, H 7.2; found C 76.6, N 3.7, H 7.4. The relative configuration of this product was confirmed by a 2D NOESY $^1H$ NMR spectrum that disclosed interactions 3-H/$CH_2O$, 3-H/5-H, 4-H/*o*-H(3-Ph), 4-H/cPr-H.

***cis*,*trans*-18:** IR (KBr): $\tilde{\nu}$ = 3075 (cPr-H), 1734 (C=O) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = –0.07–0.10 (m, 2 H, cPr-H), 0.13–0.20 (m, 1 H, cPr-H), 0.24–0.34 (m, 1 H, cPr-H), 0.38–0.54 (m, 3 H, cPr-H), 0.62–0.70 (m, 1 H, cPr-H), 0.90 (t, $J$ = 7 Hz, 3 H, Me), 1.23–1.34 (m, 1 H, cPr-H), 3.55–3.78 (m, 2 H, $OCH_2$), 3.97 (dd, $J$ = 9.4, 10.5 Hz, 1 H, 4-H), 4.45 (d, $J$ = 9.4 Hz, 1 H, 3-H), 4.79 (d, $J$ = 10.5 Hz, 1 H, 5-H) 6.90–6.98 (m, 3 H, Ph-H), 7.15–7.33 (m, 5 H, Ph-H), 7.45–7.49 (m, 2 H, Ph-H) ppm. $^{13}C$ NMR (62.9 MHz, $CDCl_3$, additional DEPT): $\delta$ = 0.8 (–, cPr-C), 3.0 (–, cPr-C), 5.6 (–, cPr-C), 8.6 (–, cPr-C), 10.9 (+, cPr-C), 13.7 (+, Me), 20.5 ($C_q$, cPr-C), 55.7 (+, C-4), 60.5 (–, $OCH_2$), 72.3 (+, C-3), 84.5 (+, C-5), 116.3 (+, Ph-C), 122.2 (+, Ph-C), 128.0 (+, Ph-C), 128.2 (+, Ph-C), 128.3 (+, Ph-C), 128.5 (+, Ph-C), 137.9 ($C_q$, Ph-C), 149.7 ($C_q$, Ph-C), 169.5 ($C_q$, C=O) ppm. EI-MS: $m/z$ = 377 [M$^+$], 269, 198, 181, 91. $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.4, N 3.7, H 7.2; found C 76.5, N 3.9, H 7.1.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures for all new compounds as well as $^1H$ and $^{13}C$ NMR spectra for compounds **4**–**6**, **10g**.

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