Enantioselective Synthesis and Photoreactivity of a Diazirinyl-substituted (*R*)-β-Phenylalanine

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Dedicated to Professor Hubert Schmidbaur on the occasion of his 80th birthday

The first enantioselective synthesis of a photoreactive (*R*)-β-phenylalanine is described. In the key step, *m*-diazirinyl-substituted benzaldehyde is converted to a chiral sulfinimine in a $Ti(OEt)_4$-mediated reaction, followed by diastereoselective enolate addition. The absolute configuration of photo (*R*)-β-phenylalanine was confirmed by Mosher analysis. The photo amino acid proved to be thermally stable under standard laboratory conditions. Irradiation in toluene afforded cycloheptatriene/norcaradiene valence tautomers, together with carbene benzylation. Quantum-chemical calculations indicate a small triplet-singlet gap.

Key words: Amino Acids, Diazirines, Photochemistry, Carbenes, DFT Calculation

Introduction

Photoaffinity labeling (PAL) is important for the identification of biological targets of natural products [1 – 5]. A photoreactive moiety is installed at a given compound, and the conjugate is irradiated after incubation in the cell. This leads to covalent binding at the target, to be followed by isolation and analysis of the adduct. Diazirines are particularly suitable, because they are small, and the resulting carbenes are reactive [6 – 9]. Ideally, there would be a set of photoreactive analogs of frequently occurring building blocks. Currently known diazirine-functionalized amino acids include photophenylalanine [10 – 12], L-phototryptophan [13, 14], L-photoleucine, *rac*-photoisoleucine/*rac*-photo-*allo*-isoleucine, L-photomethionine [15], L-photolysine [16], and L-photoproline [17, 18].

In this paper, we describe the first synthesis of a diazirine-substituted (*R*)-β-phenylalanine (**1**), which is not proteinogenic, but functions as partial structure of biologically active natural products. These include the cytotoxic astines (**2**: astine C) from the aster *Aster tataricus* [19, 20], the peptide-polyketide antibiotic andrimid (**3**) from the bacterium *Pantoea agglomerans* (Fig. 1) [21, 22], and the anticancer drug paclitaxel containing an *N*-benzoylated α-hydroxy-β-phenylalanine side chain. β-Phenylalanine has been employed as structural motif in medicinal chemistry [23]. Photo compound **1** might also become interesting for photoaffinity labeling experiments with the F-actin binders of the jasplakinolide class, which contain a β-tyrosine moiety [24, 25].

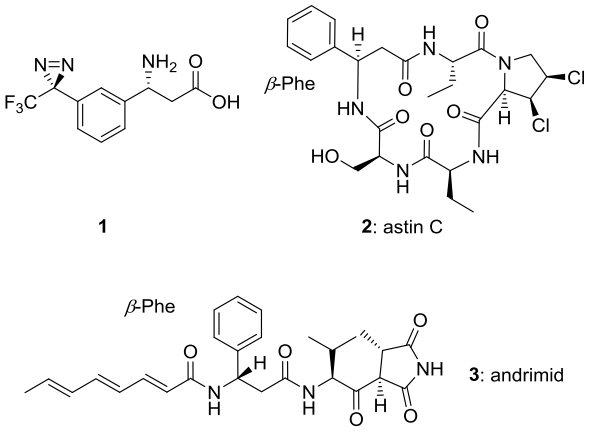
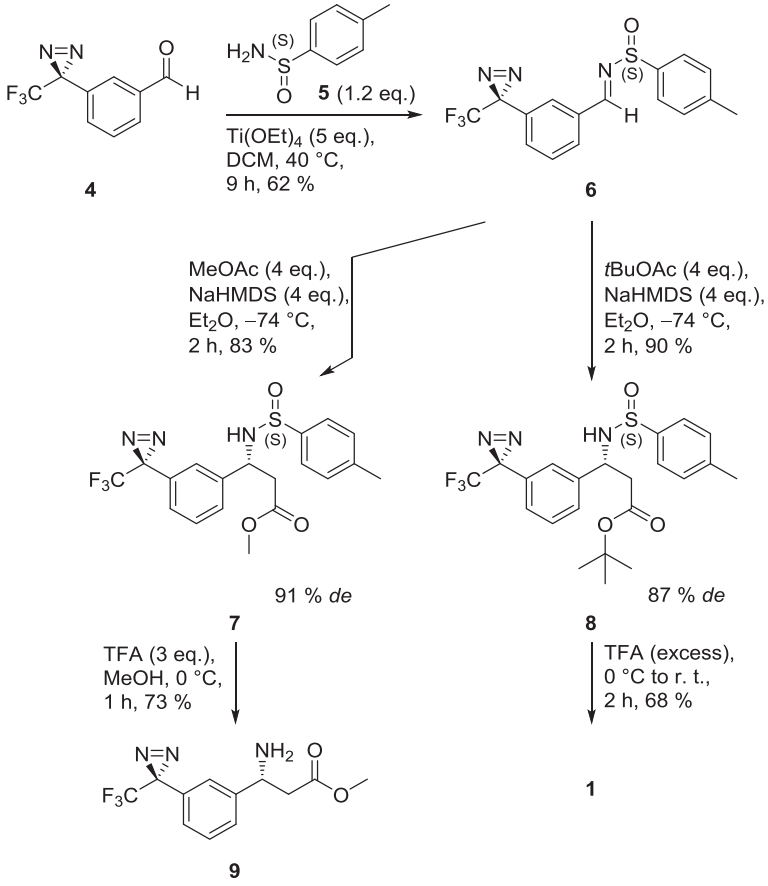


Fig. 1. Photo (*R*)-β-phenylalanine **1** and biologically active natural products containing a β-phenylalanine partial structure.



Scheme 1. Synthesis of photo (*R*)-β-phenylalanine **1** and its methyl ester **9** *via* the chiral sulfinimine **6**.

Results and Discussion

Synthesis

Our route was to start from *m*-diazirinyl-substituted benzaldehyde **4** which has served as building block for the synthesis of the first photo derivative of the marine natural product psammaplin A [26]. For the assembly of the amino acid head, we adopted an auxiliary-based protocol developed for the synthesis of (*R*)-(+)-β-phenylalanine by Davis *et al.* [27, 28], which has also been applied by Ghosh *et al.* for the synthesis of jasplakinolide and derivatives [29, 30].

Diazirinyl-substituted benzaldehyde **4** [26] and commercially available (*S*)-sulfinamide **5** afforded sulfinimine **6** (62 %) in a $Ti(OEt)_4$-mediated condensation (Scheme 1). Beforehand, it was not clear whether the diazirinyl unit of **4** would survive treatment with $Ti(OEt)_4$, since $[TiCp_2(CO)_2]$ had cleaved the N=N bond of dialkyldiazirines [31]. We were pleased to observe that no significant decomposition of **4** had occurred, as judged by TLC. An excess of $Ti(OEt)_4$ (5.0 eq.) was employed, because it activates the aldehyde carbonyl group and has a dehydrating effect [27].

Diazirine **6** also proved to be compatible with enolate addition at low temperature, as it could be expected [32]. When using MeOAc (4 eq.) as enolate precursor and NaHMDS in Et_2O for deprotonation, we obtained the best yield (90 %) and *de* (91 %, determined by integration of the ^{19}F NMR signals). Use of LiHMDS was inferior (yield 16 %, *de* 20 %). For his case, Davis had reported a yield of 74 % and a *de* of 80 % when using LDA in THF. When employing *tert*-butyl acetate-LiHMDS in Et_2O, our yield (55 %)

and *de* (33 %) were better, but again not as good as when using sodium as counterion (*tert*-butyl acetate-NaHMDS, 83 % yield, 87 % *de*). It should be noted that after prolonged standing (72 h) in the NMR tube ($CDCl_3$) esters **7** and **8** underwent significant epimerization, most likely at the stereogenic sulfur atom. Treatment of methyl ester **7** with TFA (3.0 eq.) in MeOH at 0 °C afforded β-phenylalanine methyl ester **9** (73 %), whereas free photo (*R*)-β-phenylalanine **1** was obtained from *tert*-butyl ester **8** in pure TFA (68 %).

Stereochemical analysis

For an independent confirmation of the absolute configuration of methyl ester **9**, we prepared the diastereomeric Mosher amides **10** and **11** (Supporting Information available online; see note at the end of the paper for availability), which showed signals at $\delta_F = -69.30$ and -69.27 ppm in the ^{19}F NMR spectrum ($CDCl_3$, 376 MHz). The *de* was determined as 91 %. The signals of the diazirine trifluoromethyl groups at about $\delta_F = -65.6$ ppm were not resolved (Fig. 2).

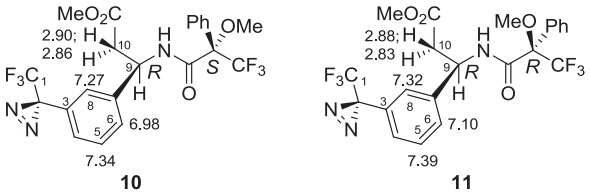


Fig. 2. Mosher amides **10** and **11** and ^1H NMR chemical shifts (ppm) in $CDCl_3$.

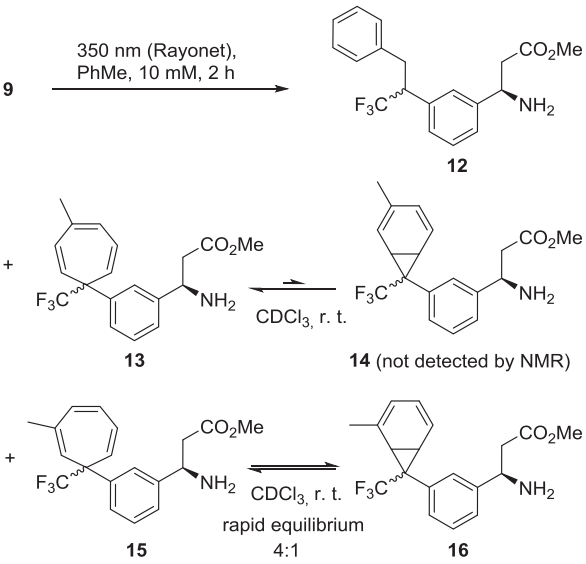
Comparison of the decisive ^1H NMR chemical shifts of the diastereomeric Mosher amides (5-*H*, 6-*H*, 8-*H* and 10-*H*) allowed to assign the absolute configuration of C-9 as *R* [33–35]. As shown in Fig. 2, 5-*H*, 6-*H* and 8-*H* of (*R*,*R*)-amide **11** are less shielded (downfield shift) than the corresponding hydrogens of the (*R*,*S*)-amide **10**, whereas the ^1H NMR chemical shifts of both diastereotopic methylene hydrogens at C-10 behave in the opposite manner. In the idealized preferred conformation of Mosher amides, the CF_3 carbon atom, the methine hydrogen and the carbonyl group are coplanar and *syn*-oriented [34].

Stability

The diazirinyl-substituted analog **1** of β-phenylalanine is a colorless solid, which shows a weak absorption maximum at 348 nm ($\lg\varepsilon = 2.29$) in the UV/Vis spectrum (MeOH). Differential scanning calorimetry (DSC) of product **1** shows an exothermic reaction between 125 and 175 °C, meaning that photo (*R*)-β-phenylalanine **1** is thermally stable enough to be handled under standard laboratory conditions.

Photoreactivity

To test its photoreactivity, methyl ester **9** was irradiated in toluene (10 mM, $\lambda_{max} = 350$ nm, Rayonet, 2 h, Scheme 2). The ^{19}F NMR spectrum of the crude mixture indicated formation of four fluorinated products, of which three were present as a 1 : 1 mixture of diastereomers ($\delta_F = -69.57/-69.58$, $-72.76/-72.81$ and $-74.49/-74.50$ ppm) in the ratio of 5 : 3 : 2. Chromatography led to the disappearance of the ^{19}F NMR signal at $\delta_F = -57$ ppm, which was probably caused by the diazo isomer of **9** [36]. However, we were not able to separate the remaining mixture by normal-phase column chromatography or reversed-phase HPLC. GC/MS analysis revealed the presence of toluene adducts, and the ^1H NMR spectrum of the mixture ($CDCl_3$) showed three sets of signals, which were sufficiently resolved for structure elucidation. All products shared the β-amino acid head of the starting material **9**. We were able to identify the



Scheme 2. Irradiation of photo (*R*)-β-phenylalanine methyl ester **9** in toluene affording a mixture of three 1 : 1 pairs of diastereomers in the ratio of 5 : 2 : 3 (**12**, **13**, **15**/**16**).

major product **12** (Scheme 2) as being benzylated at the former diazirine carbon. The newly formed C–C bond was confirmed by COSY and HMBC correlations of the neighboring methylene ($\delta_H = 3.06$ and 3.37, $\delta_C = 35.7$ ppm) and methine groups ($\delta_H = 3.52$, $\delta_C = 52.3$ ppm). About 20 % of the mixture could be assigned to cycloheptatriene **13**, which exhibited characteristic signals of five olefinic hydrogens between $\delta_H = 6.33$ and 5.55 ppm. The position of the methyl group was established by the COSY spectrum. Decisive HMBC correlations were detected between the olefinic hydrogens at $\delta_H = 5.55$ and $\delta_H = 5.57$ ppm of the triene system and the former diazirine carbon ($\delta_C = 51.9$ ppm). The remaining component (30 %, **15**/**16**) exhibited methine signals at $\delta_H = 4.57/\delta_C = 87.9$ and $\delta_H = 4.81/\delta_C = 89.2$ ppm with $J_{HH} = 4.1$ Hz. The olefinic section integrates for three vicinal hydrogens.

It has long been known that the valence tautomerism between cycloheptatriene and norcaradiene systems results in NMR chemical shifts between those expected for the pure components [37–41]. In a cycloheptatriene, 1-H and 6-H appear at about $\delta_H = 5.5/\delta_C = 113$ ppm, whereas the corresponding hydrogens in a norcaradiene are expected at $\delta_H = 2.3/\delta_C = 31$ ppm. A linear relationship between NMR shifts and ratio allows to estimate the position of the equilibrium [42], which in our case would be 4 : 1 in favor of cycloheptatriene **15** over norcaradiene **16**. It is in agreement with the literature [37] that 3-methylated cycloheptatriene **13** is preferred to a greater extent over the norcaradiene valence tautomer **14** than in the case of 2-methylation. In fact, we did not observe 3-methylnorcaradiene **14**, differing from the case of 2-methylnorcaradiene **16**.

Norcaradiene-cycloheptatriene products **13**, **15** and **16** were formed by cyclopropanation of the solvent toluene, probably *via* the singlet carbene formed from diazirine **9** [43]. Benzyl adduct **12**, however, could be formed *via* the singlet or triplet carbene [44]. We did not observe any homodimer of carbene **17**, which should be expected in the case of triplet multiplicity [45]. Thus, it could be the singlet carbene which caused the formation of all products **12**, **13** and **15**/**16**. If the energy gap between the two spin states is small enough, it can occur that the energetically less favored spin state is responsible for the observed reactions [43]. Therefore, we performed a quantum-chemical calculation of the singlet-triplet energy gap expected for carbene **17**.

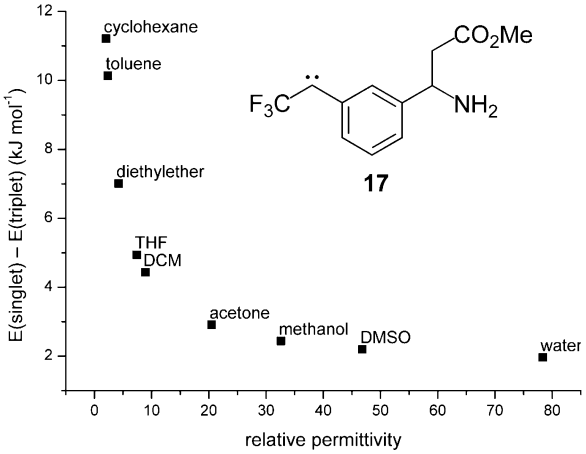


Fig. 3. Results of the quantum-chemical calculations of the preferred spin state of carbene **17** derived from diazirine **9** in different solvents (energetically most favored conformation, B3LYP/6-311G (2d, 2p)).

Quantum-chemical calculation of the preferred carbene spin ground state

For carbene **17** the five conformers with the lowest energy were determined employing the MMFF force field. They were selected for subsequent DFT calculation. Fig. 3 shows the calculated energy gap between singlet and triplet multiplicities for the energetically most favored conformer in solvents of different polarity, calculated on the B3LYP/6-311G (2d, 2p) level of theory (GAUSSIAN 09 [46]). The solvent influence was taken into account by applying the polarizable continuum model (PCM) [47].

Carbene **17** was calculated to exhibit a triplet ground state in every solvent, which is favored over the singlet state by about 11 kJ mol^{-1} in cyclohexane, 10 kJ mol^{-1} in toluene, and only 2 kJ mol^{-1} in methanol and water. The singlet-triplet gap is indeed small, which is in agreement with the possibility that the singlet carbene causes formation of all toluene adducts. There are also metal-catalyzed singlet carbene reactions with the solvent toluene, which had afforded product mixtures very similar to ours [48, 49].

In summary, we have achieved the first enantioselective synthesis of a photoreactive (*R*)-β-phenylalanine (**1**). The diazirine unit survived the use of Ti(OEt)$_4$. The (*R*) configuration of **1** was confirmed by Mosher analysis. Photo (*R*)-β-phenylalanine (**1**) proved to be thermally stable enough for biological studies un-

der standard laboratory conditions. Irradiation of **9** in toluene afforded the benzyl adduct **12** and the two regioisomeric cycloheptatriene/norcaradiene adducts **13** and **15**. Quantum-chemical calculations confirm the expected small energy gap between triplet and singlet carbenes. Photoreactive (*R*)-β-phenylalanine (**1**) is now ready to be incorporated into biologically active natural products such as astin or andrimid derivatives for photoaffinity labeling.

Experimental Section

General methods

NMR spectra were taken with a Bruker DPX-200 (200.1 MHz for ^{1}H), a Bruker AV II-300 (300.1 MHz for ^{1}H; 75.5 MHz for ^{13}C), a Bruker DRX-400 (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C), and a Bruker AV II-600 instrument (600.1 MHz for ^{1}H, 150.9 MHz for ^{13}C, referenced to solvent signal or TMS). Mass spectra were obtained with a ThermoFinnigan MAT95XL or a ThermoFisher Scientific (LTQ-Orbitrap Velos) spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer. UV/Vis spectra were measured with a Varian Cary 100 Bio UV/Vis spectrometer. Optical rotations were measured on a Dr. Kernchen Propol Automatic Polarimeter. Chemicals were purchased from commercial suppliers and used without further purification. Silica gel 60 (40 – 63 μm, Merck), and silica gel LiChroprep RP-18 (50 – 63 μm, Merck) were used for column chromatography.

*(+)-N-(3-(3-(Trifluoromethyl)-3H-diazirin-3-yl) benzylidene) 4-methylbenzene-(S)-sulfinimine (**6**)*

At 0 °C, Ti(OEt)$_4$ (2.18 mL, 10.31 mmol) and (*S*)-*p*-toluene sulfonamide (**5**, 380 mg, 2.47 mmol, synthesized from *p*-toluene sulfinate [50]) were added to a solution of aldehyde **4** (441 mg, 2.062 mmol) in dichloromethane (DCM, 7 mL). The reaction mixture was stirred for 9 h at 40 °C until the aldehyde **4** had been consumed, as judged by TLC. The reaction mixture was cooled to 0 °C, and water (15 mL) was added. A solid precipitated which was removed by filtration with celite 545. The organic layer was diluted with DCM (15 mL) and washed with water (10 mL). The aqueous layer was extracted with DCM (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in a vacuum. Purification by column chromatography (petroleum ether-EtOAc, 9 : 1) afforded imine **6** (450 mg, 1.28 mmol, 62%) as a slightly yellow solid. R_f (petroleum ether-EtOAc, 9 : 1) = 0.50; m. p.: 70 °C; $[\alpha]_D^{23} = +53$ (c = 1.0, $CDCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (m, 1H, C*H*(N)), 7.87 (dt, J = 1.3, 7.7 Hz, 1H, C*H*$_{phenyl}$), 7.65 – 7.64 (m, 1H, C*H*$_{phenyl}$), 7.64 – 7.62 (m, 2H, *m*-C*H*$_{tosyl}$), 7.51 (dd, J = 7.8, 7.8 Hz, C*H*$_{phenyl}$), 7.38 – 7.37 (m, 1H, C*H*$_{phenyl}$), 7.34 – 7.32 (m, 2H, *o*-C*H*$_{tosyl}$), 2.41 (s, 3H, C*H*$_3$) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (1C, *C*H(N)), 142.0 (1C, S*C*$_q$), 141.2 (1C, *C*$_{q,phenyl}$), 134.5 (1C, *C*$_{q,phenyl}$), 130.8 (1C, *C*H$_{phenyl}$), 130.2 (1C, *C*H$_{phenyl}$), 130.1 (1C, *C*$_q$CH$_3$), 129.9 (2C, *m*-*C*H$_{tosyl}$), 129.5 (1C, *C*H$_{phenyl}$), 127.2 (1C, *C*H$_{phenyl}$), 124.7 (2C, *o*-*C*H$_{tosyl}$), 121.9 (1C, q, J_{C-F} = 274.8 Hz, *C*$_q$F$_3$), 28.24 (1C, q, J_{C-F} = 40.7 Hz, *C*$_q$CF$_3$), 21.4 (1C, *C*H$_3$) ppm. – ^{19}F NMR (376 MHz, $CDCl_3$): δ = −65.6 (s, 3F, C*F*$_3$) ppm. – IR (ATR): ν = 3061 (w), 2963 (w), 2928 (w), 2872 (w), 1611 (m), 1597(m), 1579 (m), 1488 (m), 1446 (w), 1398 (w), 1356 (m), 1338 (m), 1299 (w), 1246 (m), 1197 (m),1171 (s), 1143 (s), 1096 (s), 1070 (m), 1013 (m), 975 (m), 864 (m), 803 (s), 745 (m), 689 (m), 653 (m), 610 (m), 573 (m), 531 (m) cm^{-1}. – UV/Vis (MeOH): λ_{max} (lg ε) = 202 (3.50), 214 (3.52), 257 (3.24) nm. – MS ((+)-ESI): m/z (%) = 1076.19 (24) [3M+Na]$^+$, 725.12 (100) [2M+Na]$^+$, 374.05 (41) [M+Na]$^+$. – HRMS ((+)-ESI): m/z = 374.05463 (0.24 ppm) (calcd. 374.05454 for $C_{16}H_{12}F_3N_3OS$, [M+Na]$^+$).

Enolate addition to the sulfinimine

At −74 °C, a solution of NaHMDS in THF (1.5 M, 1.65 mL, 2.47 mmol) was added dropwise to a solution of the respective ester (2.47 mmol) in dry Et_2O (5 mL), and the resulting solution was stirred for 50 min at −74 °C. A solution of imine **6** (217 mg, 0.618 mmol) in dry Et_2O (5 mL) was added dropwise at the same temperature. After stirring for another 80 min at −74 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (15 mL) at −74 °C, and the reaction mixture was allowed to warm to room temperature over night. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether-EtOAc, 1 : 1) affording esters **7** and **8**, respectively, as colorless oils.

*Methyl (3R)-(+)-3-(4-methylphenylsulfinamido)-3-(3-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoate (**7**)*

Yield: 83%. R_f (petroleum ether-EtOAc, 1 : 1) = 0.26. $[\alpha]_D^{23} = +55$ (c = 1.0, $CDCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 – 7.56 (m, 2H, *o*-C*H*$_{tosyl}$), 7.50 – 7.47 (m, 1H, C*H*$_{phenyl}$), 7.45 – 7.40 (m, 1H, C*H*$_{phenyl}$), 7.33 – 7.31 (m, 2H, *m*-C*H*$_{tosyl}$), 7.24 – 7.23 (m, 1H, C*H*$_{phenyl}$), 7.17 – 7.13 (m, 1H, C*H*$_{phenyl}$), 5.06 (d, J = 5.6 Hz, 1H, N*H*), 4.88 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H, C*H*CH$_2$), 3.61 (s, 3H, OCH$_3$), 2.83 (d, J = 6.3 Hz, 2H, CH$_2$), 2.43 (s, 3H, CC*H*$_3$) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9 (1C, *C*$_q$(O)OCH$_3$), 141.9 (1C, S*C*$_q$), 141.7 (2C, *C*-7, *C*$_q$CH$_3$), 129.7 (2C, *m*-*C*H$_{tosyl}$), 129.7 (1C, *C*$_{q,phenyl}$), 129.3 (1C, *C*H$_{phenyl}$), 128.6

(1C, CH_{phenyl}), 126.1 (1C, CH_{phenyl}), 125.3 (2C, *o*-CH_{tosyl}), 125.1 (1C, CH_{phenyl}), 122.1 (1C, q, $J_{C-F} = 274.7$ Hz, C_qF_3), 54.5 (1C, $CHCH_2$), 51.9 (1C, OCH_3), 41.8 (1C, CH_2), 28.4 (1C, q, $J_{C-F} = 40.4$ Hz, C_qCF_3), 21.4 (1C, CCH_3) ppm. – ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -65.5$ (s, 3F, CF_3) ppm. – IR (ATR): $\nu = 3191$ (w), 3052 (w), 2955 (w), 1736 (s), 1608 (m), 1493 (m), 1438 (m), 1343 (m), 1243 (m), 1151 (s), 1089 (m), 1050 (s), 1016 (m), 905 (w), 808 (m), 701 (m), 653 (m), 565 (m), 537 (m) cm^{-1}. – UV/Vis (MeOH): λ_{max} (lg ε) = 203 (4.49), 235 (4.04), 355 (2.32) nm. – MS ((+)-ESI): m/z(%) = 873.2 (100) [2M+Na]$^+$, 448.1 (37) [M+Na]$^+$, 420.1 (23) [M-N_2+Na]$^+$. – HRMS ((+)-ESI): m/z = 448.09165 (0.74 ppm) (calcd. 448.09132 for $C_{19}H_{18}F_3N_3O_3S$, [M+Na]$^+$).

*tert-Butyl (3R)-(+)-3-(4-methylphenylsulfinamido)-3-(3-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoate (**8**)*

Yield: 90%. R_f (petroleum ether-EtOAc, 9 : 1) = 0.33; m. p.: 70 °C; $[\alpha]_D^{23} = +61$ (c = 1.0, $CDCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 – 7.57 (m, 2H, *o*-CH_{tosyl}), 7.51 – 7.49 (m, 1H, CH_{phenyl}), 7.46 – 7.40 (m, 1H, CH_{phenyl}), 7.33 – 7.31 (m, 2H, *m*-CH_{tosyl}), 7.24 – 7.23 (m, 1H, CH_{phenyl}), 7.17 – 7.14 (m, 1H, CH_{phenyl}), 5.09 (d, J = 5.2 Hz, N*H*), 4.84 (ddd, J = 5.5, 5.8, 6.2 Hz, 1H, $CHCH_2$), 2.73 (d, J = 6.6 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.32 (s, 9H, $C(CH_3)_3$) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (1C, C_q(O)OCH_3), 142.1 (1C, SC_q), 141.8 (1C, $C_{q,phenyl}$), 141.6 (1C, C_qCH_3), 129.7 (2C, *m*-CH_{tosyl}), 129.6 (1C, $C_{q,phenyl}$), 129.2 (1C, CH_{phenyl}), 128.9 (1C, CH_{phenyl}), 126.1 (1C,CH_{phenyl}), 125.2 (3C, CH_{phenyl}, *o*-CH_{tosyl}), 122.1 (1C, q, J_{C-F} = 274.8 Hz, C_qF_3), 81.8 (1C, $OC_q(CH_3)_3$), 54.7 (1C, $CHCH_2$), 43.1 (1C, CH_2), 28.4 (1C, q, J_{C-F} = 40.4 Hz, C_qCF_3), 27.9 (3C, $(CH_3)_3$), 21.4 (1C, CH_3) ppm. – ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -65.5$ (s, 3F, CF_3) ppm. – IR (ATR): ν = 3174 (m), 2981 (w), 1728 (m), 1608 (w), 1493 (m), 1458 (w), 1394 (w), 1367 (m), 1345 (m), 1298 (w), 1242 (m), 1194 (m), 1147 (s), 1091 (m), 1037 (m), 990 (m), 955 (m), 905 (m), 885 (m), 845 (m), 805 (m), 761 (m), 731 (m), 700 (m), 654 (m), 621 (m), 576 (m), 542 (m) cm^{-1}. – UV/Vis (MeOH): λ_{max} (lg ε) = 203 nm (4.54), 235 (4.06), 355 (2.42) nm. – MS ((+)-ESI): m/z(%) = 957.3 (100) [2M+Na]$^+$, 490.1 (20) [M+Na]$^+$. – HRMS ((+)-ESI): m/z = 490.13816 (0.22 ppm) (calcd. 490.13827 for $C_{22}H_{24}F_3N_3O_3S$, [M+Na]$^+$).

*Methyl (R)-(+)-3-amino-3-(3-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)propanoate (**9**)*

At 0 °C, TFA (97 μL, 1.269 mmol) was added to a stirred solution of sulfonamide **7** (180 mg, 0.420 mmol) in MeOH (5 mL). The solution was stirred for 3 h, poured into saturated aqueous $NaHCO_3$ (15 mL) and the pH adjusted to 8 – 9 with 1 M HCl (1.5 mL). The aqueous layer was extracted with DCM (3 × 15 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. After purification by column chromatography (petroleum ether-EtOAc, 3 : 1), amine **9** (89 mg, 0.31 mmol, 73%) was obtained as colorless oil. R_f (petroleum ether-EtOAc, 1 : 1) = 0.28; $[\alpha]_D^{23} = +13$ (c = 1.0, $CDCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.43 (m, 1H, CH_{phenyl}), 7.39 – 7.36 (m, 1H, CH_{phenyl}), 7.16 – 7.14 (m, 2H, CH_{phenyl}), 4.44 (dd, J = 6.8, 6.8 Hz, 1H, $CHCH_2$), 3.69 (s, 3H, OCH_3), 2.63 (d, J = 6.8 Hz, 2H, CH_2), 1.84 (s_b, 2H, NH_2) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 (1C, C_qOOCH_3), 145.5 (1C, $C_{q,phenyl}$), 129.5 (1C, $C_{q,phenyl}$), 129.2 (1C, CH_{phenyl}), 127.6 (1C, d, J_{C-F} = 0.9 Hz, CH_{phenyl}), 125.7 (1C, CH_{phenyl}), 124.3 (1C, d, J_{C-F} = 0.9 Hz, CH_{phenyl}), 122.1 (1C, q, J_{C-F} = 274.7 Hz, C_qF_3), 52.4 (1C, $CHCH_2$), 51.7 (1C, OCH_3), 43.8 (1C, CH_2), 28.4 (1C, q, J_{C-F} = 40.4 Hz, C_qCF_3) ppm. – ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -65.6$ (s, 3F, CF_3) ppm. – IR (ATR): ν = 3383 (w), 2955 (w), 1733 (m), 1608 (m), 1492 (w), 1439 (m), 1342 (m), 1241 (m), 1192 (m), 1152 (s), 996 (m), 894 (w), 796 (m), 701 (m), 654 (m), 591 (w) cm^{-1}. – UV/Vis (MeOH): λ_{max} (lg ε) = 202 (3.47), 215 (3.26), 255 (2.24), 355 (1.73) nm. – MS ((+)-ESI): m/z(%) = 310.1 (7) [M+Na]$^+$, 288.1 (100) [M+H]$^+$, 260.1 (22) [M–N_2+H]$^+$. – HRMS ((+)-ESI): m/z = 288.09536 (0.28 ppm) (calcd. 288.09544 for $C_{12}H_{12}F_3N_3O_2$, [M+H]$^+$).

*Photo (R)-β-phenylalanine **1***

tert-Butyl ester **8** (145 mg, 0.310 mmol) was added to stirring TFA (2.5 mL) at 0 °C. The solution was allowed to warm up to room temperature and was stirred for another 2 h. The reaction mixture was concentrated under reduced pressure, and the residue dissolved in DCM (10 mL) and 1 M HCl (5 mL). The organic layer was extracted with 1 M HCl (3 × 7 mL), and the combined aqueous layers were concentrated in a vacuum. Purification of the crude product by reversed-phase column chromatography (MeOH-H_2O, 2 : 1 to 1 : 0) afforded the free amino acid (**1**, 58 mg, 0.212 mmol, 68%). R_f (MeOH-H_2O, 2 : 1) = 0.44; m. p.: 146 °C (decomp.); $[\alpha]_D^{23} = +5.4$ (c = 1.0, MeOH). – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.65 (s_b, 0.4H, COO*H*), 8.68 (s_b, 2H, NH_2), 7.75 – 7.73 (m, 1H, CH_{phenyl}), 7.60 – 7.56 (m, 1H, CH_{phenyl}), 7.49 – 7.11 (m, 2H, CH_{phenyl}), 4.63 (dd, J = 6.0, 8.5 Hz, 1H, $CHCH_2$), 3.11 (dd, J = 5.9, 16.6 Hz, 1H, CH_2), 2.92 (dd, J = 8.6, 16.6 Hz, 1H, CH_2) ppm. – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 170.5 (1C, C_qOOH), 138.4 (1C, $C_{q,phenyl}$), 129.8 (1C, CH_{phenyl}), 129.7 (1C, CH_{phenyl}), 127.9 (1C, $C_{q,phenyl}$), 126.9 (1C, CH_{phenyl}), 126.0 (1C, CH_{phenyl}), 121.8 (1C, q, J_{C-F} = 273.5 Hz, C_qF_3), 50.5 (1C, $CHCH_2$), 38.3 (1C, CH_2), 28.0 (1C, q, J_{C-F} = 40.1 Hz, C_qCF_3) ppm. – ^{19}F NMR (376 MHz, [D_6]DMSO): $\delta = -64.1$ (s, 3F, CF_3) ppm. – IR (ATR): ν = 2969 (bm),

2920 (bm), 1709 (m), 1609 (m), 1496 (m), 1413 (m), 1343 (m), 1275 (m), 1241 (m), 1170 (s), 1147 (s), 1072 (m), 1035 (m), 1001 (m), 956 (m), 902 (w), 879 (m), 794 (m), 737 (m), 700 (m), 648 (m), 574 (m) cm^{-1}. – UV/Vis (MeOH): λ_{max} ($\lg\varepsilon$) = 348 (2.29), 218 (3.96), 201 (4.11) nm. – MS ((+)-ESI): m/z(%) = 547.2 (6) $[2M–H]^+$, 274.1 (100) $[M+H]^+$, 246.1 (28) $[M–N_2+H]^+$. – HRMS ((+)-ESI): m/z = 274.07997 (0.66 ppm) (calcd. 274.07979 for $C_{11}H_{10}F_3N_3O_2$, $[M+H]^+$).

Irradiation experiment

A solution of diazirine **9** (85 mg, 0.296 mmol) in dry toluene (29.6 mL) under argon was irradiated in a Rayonet apparatus (λ_{max} = 350 nm) for 2 h. To prevent high pressure during the irradiation, the flask was closed by a septum pierced by a hollow needle. After irradiation, 1 mL of the reaction mixture was taken for ^{19}F NMR analysis, the remaining solution was concentrated in a vacuum and purified by reversed-phase HPLC and column chromatography affording a mixture of three 1 : 1 pairs of diastereomers in the ratio of 5 : 2 : 3 (**12**, **13**, **15**/**16**), which could not be separated further. – GC/MS (EI, 70 eV): **12**: t = 22.18 min (m/z(%) = 351.15 (12) $[M]^+$, 278.15 (100), 187.06 (33), 91.06 (55)); 22.21 min (m/z(%) = 351.14 (10) $[M]^+$, 278.12 (100), 187.06 (20), 91.06 (77)). **13**, **15**/**16**: t = 21.67 min (m/z(%) = 351.15 (3) $[M]^+$, 334.12 (11), 302.10 (100), 277.11 (65), 260.08 (70), 165.07 (46)); 21.71 min (m/z(%) = 351.16 (1) $[M]^+$, 334.12 (7), 302.10 (100), 277.11 (76), 260.08 (89), 165.07 (42)). – Benzyl adduct **12** (two diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.28 (m, 1H, CH_{phenyl}), 7.07 – 7.20 (m, 6H, CH_{phenyl}, CH_{tol}), 6.93 – 6.96 (m, 2H, CH_{tol}), 4.32 – 4.38 (m, 1H, CHCH$_2$), 3.67 (s, 3H, OCH_3), 3.46 – 3.56 (m, 1H, CHCF$_3$), 3.37 (dd, J = 4.1, 13.8 Hz, 1H, CH_2CHCF$_3$), 3.04 – 3.11 (m, 1H, CH_2CHCF$_3$), 2.55 – 2.59 (m, 2H, CH_2), 1.88 (s, 2H, NH$_2$) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (1C, C_qOOCH$_3$), 144.7 (1C, $C_{q,phenyl}$), 137.5 (1C, $C_{q,tol}$), 134.6 (1C, $C_{q,phenyl}$), 128.9 (2C, CH$_{tol}$), 128.1 (2C, CH$_{tol}$), 128.0 (1C, CH$_{phenyl}$), 127.3 (1C, CH$_{phenyl}$), 127.1 (1C, CH$_{phenyl}$), 126.5 (1C, CH$_{Tol}$), 125.9 (1C, CH$_{phenyl}$), 122.5 (1C, C_qF$_3$), 52.4 (1C, CHCH$_2$), 52.1 (1C, CHCF$_3$), 51.6 (1C, OCH_3), 43.9 (1C, CH$_2$), 35.7 (1C, CH$_2$CHCF$_3$) ppm. – ^{19}F NMR (376 MHz): δ = −69.57, −69.58 ppm. – Cycloheptatriene **13** (two diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.28 (m, 2H, CH_{phenyl}), 7.07 – 7.20 (m, 2H, CH_{phenyl}), 6.28 – 6.33 (m, 1H, CH_{triene}), 6.23 – 6.24 (m, 1H, CH_{triene}), 6.02 – 6.03 (m, 1H, CH_{triene}), 5.56 (dd, J = 9.6, 9.6 Hz, 1H, CH_{triene}), 5.55 (dd, J = 7.9 Hz, 1H, CH_{triene}), 4.32 – 4.38 (m, 1H, CHCH$_2$), 3.65 (s, 3H, OCH_3), 2.55 – 2.59 (m, 2H, CH_2), 1.88 (s, 2H, NH$_2$), 1.75 (s, 3H, C$_q$CH_3) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (1C, COOCH$_3$), 142.8 (1C, $C_{q,phenyl}$), 139.5 (1C, C_qCH$_3$), 128.8 (1C, CH$_{triene}$), 128.4 (1C, CH$_{phenyl}$), 127.8 (1C, CH$_{triene}$), 127.5 (1C, CH$_{phenyl}$), 127.2 (1C, CH$_{phenyl}$), 126.5 (1C, CH$_{triene}$), 125.9 (1C, CH$_{phenyl}$), 113.5 (1C, CH$_{triene}$), 112.7 (1C, CH$_{triene}$), 52.4 (1C, CHCH$_2$), 51.9 (1C, C_qCF$_3$), 51.6 (1C, OCH$_3$), 43.9 (1C, CH$_2$), 23.3 (1C, C$_q$CH$_3$) ppm. – ^{19}F NMR (376 MHz): δ = −74.49, −74.50 ppm. – Cycloheptatriene/norcaradiene equilibrium (**15**/**16**, two diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.28 (m, 2H, CH_{phenyl}), 7.07 – 7.20 (m, 2H, CH_{phenyl}), 6.20 (dd, J = 7.7, 7.7 Hz, 1H, C$H_{triene/norc}$), 5.97 – 5.99 (m, 1H, C$H_{triene/norc}$), 5.94 – 5.91 (m, 1H, C$H_{triene/norc}$), 4.81 (ddd, J = 4.1, 8.4, 8.4 Hz, 1H, C$H_{triene/norc}$), 4.57 (dd, J = 4.1, 8.1 Hz, 1H, C$H_{triene/norc}$), 4.32 – 4.38 (m, 1H, CHCH$_2$), 3.66 (s, 3H, OCH_3), 2.55 – 2.59 (m, 2H, CH_2), 1.88 (s, 2H, NH$_2$), 2.07 (s, 3H, C$_q$CH_3) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (1C, COOCH$_3$), 142.7 (1C, $C_{q,phenyl}$), 134.0 (1C, C_qCH$_3$), 129.1 (1C, CH$_{phenyl}$), 129.0 (1C, CH$_{triene/norc}$), 128.4 (1C, CH$_{phenyl}$), 128.0 (1C, CH$_{triene/norc}$), 127.6 (1C, CH$_{phenyl}$), 126.9 (1C, CH$_{phenyl}$), 125.8 (1C, $C_{q,phenyl}$), 123.9 (1C, CH$_{triene/norc}$), 123.1 (1C, C_qF$_3$), 89.2 (1C, CH$_{triene/norc}$), 87.9 (1C, CH$_{triene/norc}$), 52.4 (1C, CHCH$_2$), 51.6 (1C, OCH$_3$), 43.9 (1C, CH$_2$), 43.7 (1C, C_qCF$_3$), 23.1 (1C,C$_q$CH$_3$) ppm. – ^{19}F NMR (376 MHz): δ = −72.76, −72.81 ppm.

Supporting information

Details of the synthesis and spectral characterization of the Mosher amides **10** and **11**, pictures of NMR spectra including 2D NMR data, GC/MS data, differential scanning calorimetry of **1**, as well as computational details on the carbene **17** (27 pages) are given as Supporting Information available online (DOI: 10.5560/ZNB.2014-4152).

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