Supporting Information

(***Organic Letters***)

Asymmetric Wolff Rearrangement Reactions With *alpha*-Alkylated-*alpha*-Diazoketones: Stereoselective Synthesis of *alpha*-Substituted-*beta*-Amino Acid Derivatives

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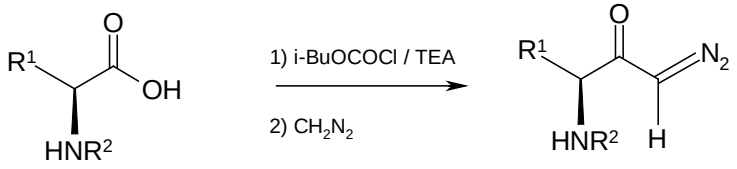
Experimental Part

All chemicals were purchased (Aldrich, Fluka, Sigma, Bachem) at the highest purity available and used without further purification unless otherwise stated. Hexamethylphosphoramide, THF, and methyl iodide were distilled prior to use. All reactions were performed under a nitrogen atmosphere. TLCs were run on Merck silica gel 60 F254 and visualized under UV light. Column chromatography was performed using EM separations technology silica gel with particle size 0.063-0.200 (70-230 mesh ASTM). ^{1}HNMR spectra were recorded on a Varian 400MHz using $CDCl_3$ as solvent. Chemical shifts were measured using TMS as a reference. IR spectra were obtained on a Perkin Elmer FTIR spectrometer Paragon 1000 using NaCl disks. Analytical HPLC were performed on 1050 Hewlett Packard System and LC-MS were run by the quattro-LC (micromass) system.

General procedure **A** for preparation of the *alpha*-diazoketones

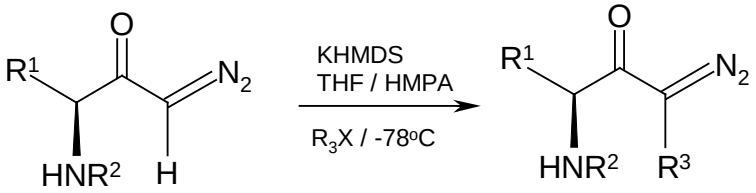


1 **2**

Ethanol was added to a solution of KOH (27eq.) and water and warmed to 55°C. Diazald (7eq.) in ether was added at a rate that the diazomethane along with diethyl ether was distilled out at the same rate. The acid **1** (1eq.) was dissolved in THF at -10^{o}C and iso-butylchloroformate (1.5eq.) and TEA (1.5eq.) were added dropwise, respectively. This mixture stirred for 30 minutes at -10^{o}C followed by filtration through celite to remove the white precipitate. The freshly

distilled diazomethane ethereal solution was added dropwise to the above mixture. The reaction proceeded until the TLC showed the reaction to be complete. The reaction was quenched with water, and the aqueous layer extracted 3X with ethyl acetate. The combined organic layers were washed with water, $NaHCO_3$ aqueous solution, brine and dried over magnesium sulphate. Flash column chromatography gave the desired product.

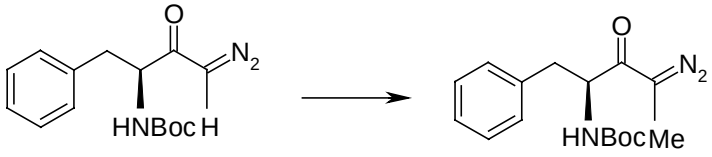
General procedure **B** for *alpha*-alkylation of the *alpha*-diazoketones



2 **3**

A solution of KHMDS (2 eq.), HMPA (33%v/v), alkyl halide (10 eq.) in THF was prepared and cooled to -78°C. A solution of **2** in THF at -78°C was then transferred dropwise to the above solution. The reaction was stirred for 30 minutes and then a second portion of KHMDS (2 eq.) was added. The reaction proceeded for another half an hour and then it was quenched with NH_4Cl (satd. aq.). The aqueous layer was extracted 3x with ethyl acetate and the combined organic layers were washed with water 2x, brine 1x and dried with magnesium sulphate, and evaporated to dryness. The resulting mixture was purified using column chromatography (20% ethyl acetate: 80% heptane).

1. (1-Benzyl-3-diazo-2-oxo-butyl)-carbamic acid tert-butyl ester (**4**).

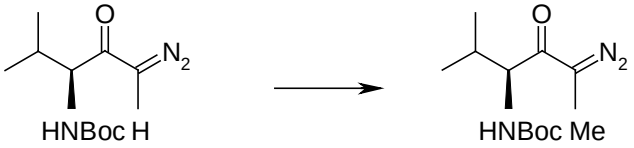


3 **4**

Following the general procedure **B.** The chemicals and solvent used in reaction were as following: the *alpha*-diazoketone **3** (0.3 g, 1.04 mmol), KHMDS (5.25 ml, 2.4 mmol, 0.5M in toluene), THF (10 ml), HMPA (4.8

ml, 27.6 ml), MeI (0.65 ml, 10.4 mmol). The desired title compound **4** was obtained (0.189 g, 60%); $[\alpha]_D$ +40.5^o (c 0.28, $CHCl_3$); IR 3344 (N-H), 2968 (N_2), 1690 (C=O), 1627 (C=O) cm^{-1}; ^{1}HNMR δ 1.44 (s, 9H, OCH_3), 1.86 (s, 3H, Me), 2.95 (m, 2H, CH_2), 4.73 (m, 1H, CH), 5.27 (s, 1H, NH), 7.20 (m, 5H, Phenyl); m/e: 303.36. HRMS for $C_{16}H_{21}O_3N_3$+H, obsd. 304.1653; calcd: 304.1661.

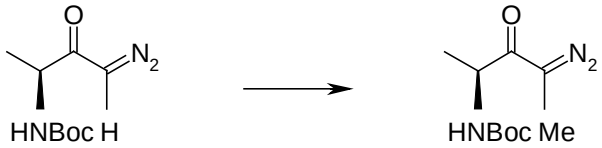
2. (3-Diazo-1-isopropyl-2-oxo-butyl)-carbamic acid tert-butyl ester (**6**).



5 **6**

Following the general procedure **B.** The chemicals and solvent used in reaction were as following: **5** (0.5 g, 2.07 mmol), KHMDS (16.6 ml, 8.3 mmol, 0.5 M in toluene), THF (17 ml), HMPA (9.6 ml, 55 mmol), MeI (1.3 ml, 20.7 mmol). The desired title compound **6** was obtained (0.182 g, 35%); $[\alpha]_D$ +33.6^o (c 0.53, $CHCl_3$); IR 3334 (NH), 2070 (N_2), 1714 (C=O), 1621 (C=O) cm^{-1}; ^{1}HNMR δ 0.85 (d, 3H, J= 6.71Hz , CHMe), 0.95 (d, 3H, J= 6.72Hz, CHMe), 1.44 (s, 9H, $OCMe_3$), 1.95 (s, 3H, Me), 2.13 (m, 1H, CH), 4.35 (m, 1H, CH), 5.19 (b, 1H, NH); m/e:255.32. HRMS for $C_{12}H_{21}O_3N_3$+H, obsd: 256.1669, calcd: 256.1661.

3. (3-Diazo-1-methyl-2-oxo-butyl)-carbamic acid tert-butyl ester (**8**).

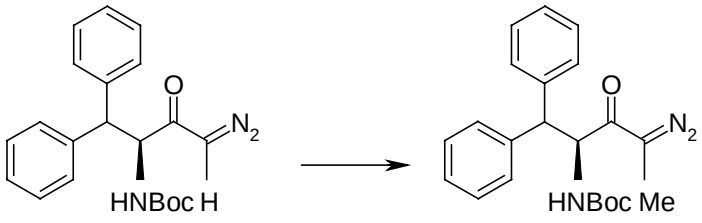


7 **8**

Following the general procedure **B.** The chemicals and solvent used in reaction were as following: **7** (0.6 g, 2.82 mmol), KHMDS (22.6 ml, 11.3 mmol, 0.5 M in toluene), THF (28 ml), HMPA (13 ml, 74.8 mmol), MeI (1.7

ml, 28.1 mmol). The desired title compound **8** was obtained (0.27 g, 45%); $[\alpha]_D$ +21.5^o (c 0.53, $CHCl_3$); IR 3335 (N-N), 2065 (N_2), 1685 (C=O), 1634 (C=O) cm^{-1}; ^{1}HNMR δ 1.25 (d, 3H, J= 7.32Hz, CHMe), 1.40 (s, 9H, $OCMe_3$), 1.95 (s, 3H, Me), 4.51 (m, 1H, CH), 5.28 (b, 1H, NH); m/e: 227.27. HRMS for $C_{10}H_{17}O_3N_3$+H, obsd: 228.1341, calcd: 228.1348.

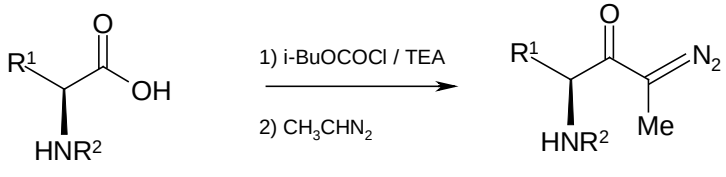
4. (1-Benzhydryl-3-diazo-2-oxo-butyl) carbamic acid tert-butyl ester (**10**)



9 **10**

Following the general procedure **B.** The chemicals and solvent used in reaction were as following: **9** (0.16g, 0.453mmol), KHMDS(3.6ml, 1.81mmol, 0.5M in toluene), THF (4.5ml), HMPA (2.1ml, 12.0mmol), MeI (0.28ml, 4.5mmol). The desired title compound **10** was obtained (0.09 g, 54%); $[\alpha]_D$ +103.0^o (c 0.17, $CHCl_3$); IR 3354 (N-H), 2980 (C-H), 2067 (N_2), 1686 (C=O), 1625 (C=O) cm^{-1}; ^{1}HNMR δ 1.28 (s, 9H, $OCMe_3$), 1.65 (s, 3H, Me), 4.21 (d, 1H, J=10.32Hz , NCH), 4.96 (d, 1H, J= 7.32Hz, CH), 5.20 (b, 1H, NH), 7.08-7.31 (m, 10H, Phenyl); m/e: 379.50. HRMS for $C_{22}H_{25}N_3O_3$+H, obsd. 380.1987, calcd. 380.1974.

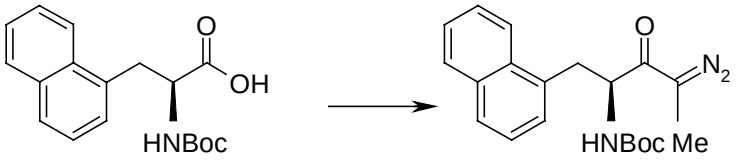
General procedure **C** for preparation of *alpha*-methyl-*alpha*-diazoketone derivatives from diazoethane and amino acids



11 **12**

To a solution of the amino acid **11** (1 eq.) in THF at -10^{o}C was added i-BuOCOCl (1.2 eq.), and TEA (3 eq.), respectively. This solution stirred for 2 hours and then filtered through celite. Diazoethane in ether was freshly prepared by adding N-nitroso N-ethyl urea (5.4 eq.) in two portions to a precooled solution of ether and 40% KOH (0^{o}C), the ether layer was then dried over pellet KOH, and then added to the mixed anhydride generated from the amino acid. The solution was stirred for approx.16 hrs. The mixture was quenched with water and the aqueous layer extracted with EtOAc (3x). The combined organic layers were washed with water (1x), $NaHCO_3$ (saturated solution 1x) and brine (1x) and then dried over magnesium sulfate. Evaporation and column chromatography (2:8 ethyl acetate: heptane on silica gel) gave the desired product.

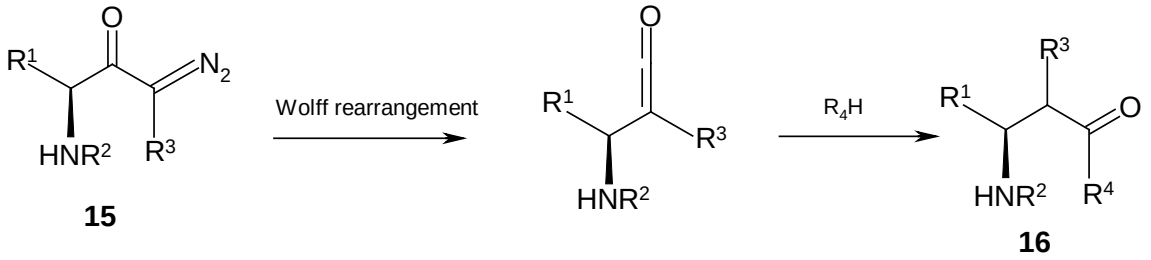
5. (3-Diazo-1-naphthalen-1-yl-2-oxo-butyl) carbamic acid tert-butyl ester (**14**)



13 **14**

Following the general procedure **C.** The chemicals and solvent used in reaction were as following: **13** (0.5 g, 1.59 mmol), i-BuOCOCl (0.2 ml, 1.9 mmol), TEA (0.66 ml, 4.76 mmol) in THF (10 ml). Diazoethane was prepared from N-nitroso N-ethyl urea (1.0 g, 8.54 mmol), ether (20 ml), 40% KOH (10 ml). The desired title compound **14** was obtained (0.097 g, 17%); $[\alpha]_D$ +143.6^{o} (c 0.55, $CHCl_3$); IR 2975 (C-H), 2074 (N_2), 1698 (C=O), 1632 (C=O) cm^{-1}; ^{1}H NMR δ 1.40 (s, 9H, $OCMe_3$), 1.63 (s, 3H, Me), 3.40 (m, 2H, CH_2), 4.85 (m, 1H, CH), 5.45 (d, 1H, J= 7.32Hz, NH), 7.20-7.65 (m, 7H, naphthalene rings); m/e:353.42.

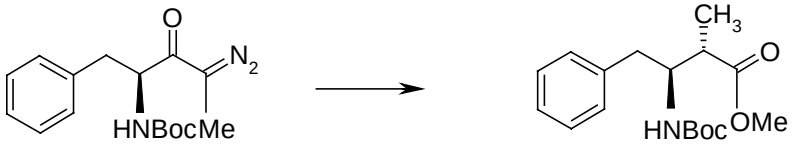
General procedure **D** for the Wolff rearrangement of *alpha*-alkyl-*alpha*-diazoketones



15 **16**

Compound **15** (1 eq.) was dissolved in a 1:1 (V/V) solution of dichloromethane and methanol. This solution was placed in the UV apparatus and cooled to the specified temperature. The nitrogen flow was essential as it stirred the solution. The reaction mixture was irradiated with UV light for 4 hours. The reaction mixture was concentrated and purified to give the desired product **16** using column chromatography with eluent of 20% ethyl acetate in heptane silica gel.

6. 3-tert-Butoxycarbonylamino-2-methyl-4-phenyl-butyric acid methyl ester (**17**)

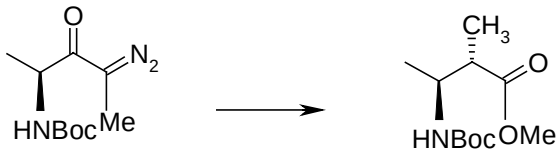


4 **17**

Following the general procedure D. Compound **4** (0.030g, 0.099mmol) in CH_2Cl_2 (6ml) and MeOH (6ml) was irradiated with UV light to yield the desired title compound **17** (5.2 mg, 17%, when the reaction was run at –78^oC; 8 mg, 26%, at 0^oC).

$[\alpha]_D$ -6.6^o (c 0.21, $CHCl_3$); IR 3386 (N-H), 1732 (C=O), 1602 (C=O) cm^{-1}; ^1H NMR δ 1.15 (d, 3H, J=6.71Hz, Me), 1.37 (s, 9H, $OCMe_3$), 2.53-2.72 (m, 2H, CH_2), 2.83 (m, 1H, CH), 3.68 (s, 3H, OMe), 3.91 (m, 1H, NCH), 5.35 (d, 1H, J=9.77Hz, NH), 7.12-7.8 (m, 5H, Phenyl); m/e:307.40. HRMS for $C_{17}H_{26}O_4N$+H, obsd: 308.1875, calcd: 308.1862.

7. 3-tert-Butoxycarbonylamino-2-methyl butyric acid methyl ester (**18**)

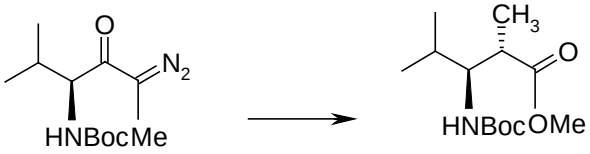


8 **18**

Following the general procedure D. Compound **8** (0.030 g, 0.132 mmol) in CH_2Cl_2 (6 ml) and MeOH (6 ml) was irradiated with UV light to yield the desired title compound **18** (7.7 mg, 25%, when the reaction was run at –78^{o}C; 11 mg, 34 %, at –20oC; 8 mg, 26%, at 0^{o}C).

$[\alpha]_D$ -3.3^o(c 0.54, $CHCl_3$); IR 3367 (N-H), 1714 (C=O) cm^{-1}; ^{1}H NMR δ 1.18 (d, 3H, J=6.71Hz, Me), 1.23 (d, 3H, J=6.72Hz, Me), 1.41 (s, 9H, $OCMe_3$), 2.58 (m, 1H, CH), 3.64 (s, 3H, OMe), 3.82 (m, 1H, NCH), 5.03 (b, 1H, NH); m/e:231.30. HRMS for $C_{11}H_{21}O_4N$+H, obsd: 232.1542, calcd: 232.1549.

8. 3-tert-Butoxycarbonylamino-2,4 dimethyl-pentanoic acid methyl ester (**19**)

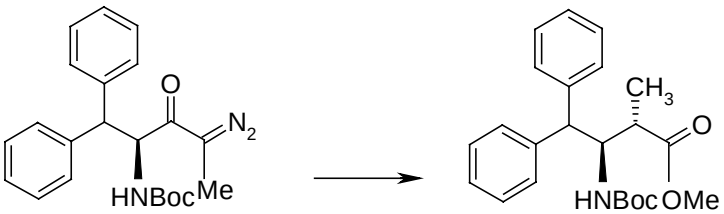


6 **19**

Following the general procedure D. Compound **6** (0.030 g, 0.117 mmol) in CH_2Cl_2 (6 ml) and MeOH (6 ml) was irradiated with UV light to yield the desired title compound **19** (12 mg, 40%, when the reaction was run at –78^{o}C; 19 mg, 67%, at 0^{o}C).

$[\alpha]_D$ -10.9^o (c 0.55, $CHCl_3$); IR 3435 (N-H), 1715 (C=O) cm^{-1}; ^{1}H NMR δ 0.85 (d, 3H, J=6.41Hz, MeCH), 0.89 (d, 3H, J=6.41Hz, MeCH), 1.18 (d, 3H, J=7.33Hz, Me), 1.41 (s, 9H, $OCMe_3$), 2.75 (m, 1H, CH), 3.37 (m, 1H, NCH), 3.64 (s, 3H, OMe), 5.19 (b, 1H, NH); m/e: 259.30. HRMS for $C_{13}H_{25}NO_4$+H, obsd: 260.1869, calcd: 260.1862.

9. 3-tert-Butoxycarbonylamino-2-methyl-4,4-diphenyl butyric acid methyl ester (**20**)

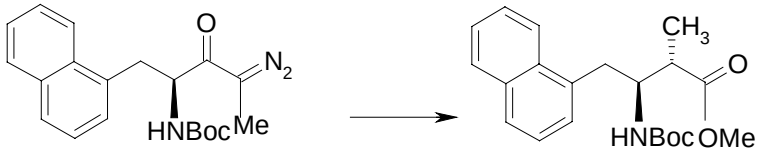


10 **20**

Following the general procedure D. Compound **10** (0.030g, 0.079mmol) in CH_2Cl_2 (6ml) and MeOH (6ml) was irradiated with UV light to yield the desired title compound **20** (13 mg, 45%, when the reaction was run at –78^oC; 7.3 mg, 24%, at -20^oC; 15 mg, 49%, at 0^oC).

$[\alpha]_D$ +10.8^o (c 1.1, $CHCl_3$); IR 3439 (N-H), 2977 (C-H), 1715 (C=O) cm^{-1}. ^1H NMR δ 1.20 (s, 9H, $OCMe_3$), 2.51 (m, 1H, CH), 3.65 (s, 3H, OMe), 4.05 (m, 1H, CH), 4.55 (m, 1H, CH), 5.23 (d, 1H, J=11Hz, NH), 7.05-7.37 (m, 10H, Phenyl); m/e: .383.50. HRMS for $C_{23}H_{29}O_4N$+H, obsd: 384.2185, calcd: 384.2175.

10. 3-tert-Butoxycarbonylamino-2-methyl-4-naphthalen-1-yl butyric acid methyl ester (**21**).

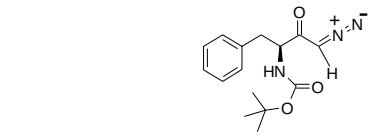


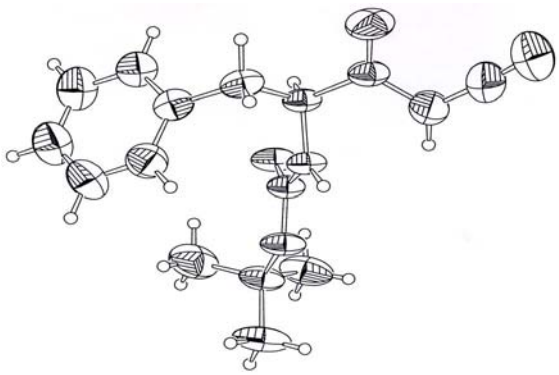
14 **21**

Following the general procedure D. Compound **14** (0.030 g, 0.085 mmol) in CH_2Cl_2 (6 ml) and MeOH (6 ml) was irradiated with UV light to yield the desired title compound **21** (23 mg, 77%, when the reaction was run at –78^oC; 6.1 mg, 20%, at 0^oC).

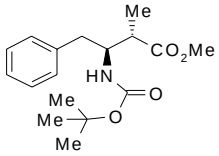
$[\alpha]_D$ -1.43^o (c 0.4, $CHCl_3$); IR 3404 (N-H), 1710 (C=O) cm^{-1}; ^1H NMR δ 1.12 (d, 3H, J=7.33Hz, Me), 1.37 (s, 9H, $OCMe_3$), 3.0-3.48 (m, 2H, CH_2), 3.71 (s, 3H, OMe), 4.13 (m, 1H, CH), 5.58 (d, 1H, J=7.93Hz , NH), 7.2-8.2 (m, 7H, naphthalene rings); m/e: 357.50. HRMS for $C_{21}H_{27}O_4N$+H, obsd: 358.2012, calcd: 358.2018.

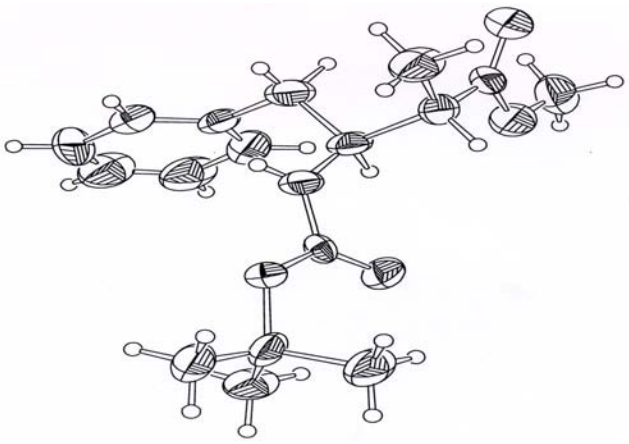
Geometry Requirement for Wolff Rearrangement Reactions



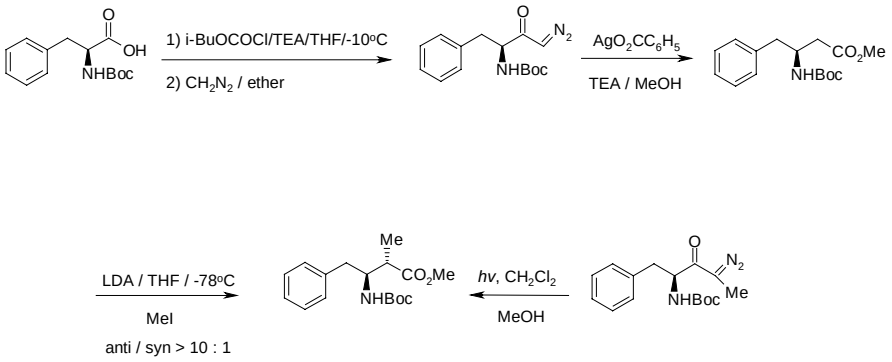


Stereochemistry Confirmation by X-ray Structure Analysis

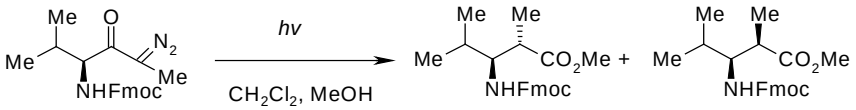




Stereochemistry Correlation



Temperature Effects on Asymmetric Wolff Rearrangement Reactions



Temp.(°C)	Ratio (anti/syn)	Yield
-78	6 : 1	33%
-20	4 : 1	66%
0	2 : 1	74%