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Continuous Flow of Nitroso Diels-Alder Reaction

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General Methods and Materials

All reactions were carried out using anhydrous solvent unless otherwise noted. Anhydrous CH₂Cl₂ and THF were dried using an M BRAUN solvent system (A2 alumina). N-Boc-hydroxylamine, dienes (1,3-cyclohexadiene, 1,3-cycloheptadiene, *cis,cis*-1,3-Cyclooctadiene, 2,3-dimethyl-1,3-butadiene, isoprene, 9,10-dimethylantracene and *trans,trans*-1,4-Diphenyl-1,3-butadiene), CuCl, pyridine and Celite were purchased from Sigma-Aldrich Company and used without further purification. MnO₂ was received form Wako Company.

All reactions were monitored by thin layer chromatography (TLC) on Whatman Partisil ® K6F TLC plates (silica gel 60 Å, 0.25 mm thickness) and yields were calculated by NMR spectra of crude products. Flash chromatography was performed on silica gel E. Merck 9385 or silica gel 60 extra pure. ¹H- NMR spectra were recorded on Bruker DMX Model 500 spectrometer at ambient temperature in CDCl₃ at 500 and 126 MHz. The chemical shifts are given in ppm relative to tetramethylsilane [¹H: δ (SiMe₄) = 0.00 ppm] as an internal standard or relative to the resonance of the solvent [¹H: δ (CDCl₃) = 7.26 ppm, ¹³C: δ (CDCl₃) = 77.16 ppm]. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). The NMR yields were calculated in the case of volatile dienes based on BocNHOH and in the case of non-volatile dienes based on dienes.

General Procedure

- I. Flask reaction
- 1) CuCl



CuCl (0.1 mmol, 0.2 equiv.) and pyridine (0.025 mmol, 0.05 equiv.) were added to a mixture of *N*-Bochydroxylamine (0.5mmol, 1.0 equiv.) and diene (0.6 mmol, 1.2 equiv.) in THF (5.3mL). The resulting mixture was stirred for 3 h at RT in flask.

2) MnO₂



 MnO_2 (1.5 mmol, 3 equiv.) and diene (1.2 equiv.) were added to test tube equipped with a magnetic stir under the protection of nitrogen in CH₂Cl₂ (3.3 mL). A solution of N-Boc-hydroxylamine (0.5mmol, 1.0 equiv.) in CH₂Cl₂ (2 ml) was added slowly via syringe pump during a period of 10 h.

II. Flow reaction

1) CuCl



We examined this flow reactions with different ratios of BocNHOH to dienes; 2:1, 1:1, 1:1.2, 1:2. According to the general procedure, injection loop A was loaded with the reactant solution of CuCl (0.1 mmol, 0.2 equiv.), pyridine (0.1 mmol, 0.2 equiv.), N-Boc-hydroxylamine (0.5mmol, 1.0 equiv. or 1.0mmol, 2.0 equiv.) and diene (0.5mmol, 1.0 equiv. or 0.6 mmol, 1.2 equiv. or 1.0mmol, 2.0 equiv.) in THF (0.075M). The solutions from loop A (flow rate: 0.03 mL/min) and air from loop B (flow rate: 0.21 mL/min) were simultaneously injected into a T-shaped tube connector (T-type reactor by YMC Co., Ltd., 1.0 mm i.d.) followed by a tube (PEFT, 1/16 inch.). The crude product solution was collected in a flask.

2) MnO₂



We examined this flow reactions with different ratios of BocNHOH to dienes; 2:1, 1:1, 1:1.2, 1:2 in all cases using 3 equiv. or 5 equiv. of MnO₂. *N*-Boc-hydroxylamine (0.5mmol, 1.0 equiv. or 1.0mmol, 2.0 equiv.) and diene (0.5mmol, 1.0 equiv. or 0.6 mmol, 1.2 equiv. or 1.0mmol, 2.0 equiv.) in CH₂Cl₂ (0.075M) was pumped

through a column reactor (Empty Column by YMC Co., Ltd, 4.6mm i.d. \times 30.0 mm length) packed with manganese dioxide (1.5 mmol, 3 equiv. or 2.5 mmol, 5 equiv.) at room temperature and the end of the column reactor was packed with Celite. The optimised condition of flow rate was 0.03 mL/min.

Characterization



tert-Butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (2a) was isolated by flash chromatography on silica gel (hexane : EtOAc= 4:1). ¹H NMR (500 MHz, CDCl₃): δ = 6.41-6.39 (m, 2H), 5.20-5.19 (m, 1H) ,4.97 (s, 1H), 1.99-1.96 (m, 1H), 1.71 (d, *J*= 8.5 Hz, 1H), 1.45 (s, 9H) ppm. Boc ¹³C NMR (126 MHz, CDCl3): δ =158.7, 134.2, 133.1, 83.6, 82.2, 65.1, 48.2, 28.3 (3C).

tert-Butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (2b) was isolated by flash chromatography on silica gel (hexane : EtOAc= 4:1). ¹H NMR (500 MHz, CDCl₃): δ = 6.53-6.50 (m, 2H), 4.71-4.69(m, 2H), 2.16-2.07 (m, 2H), 1.46-1.30 (m, 4H), 1.44 (s,9H) ppm. ¹³C NMR (126 MHz, CDCl3): δ =157.7, 131.8, 131.6, 81.6, 70.7 50.1, 28.3 (3C), 23.7, 20.6.

tert-Butyl 6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (2c) was isolated by flash chromatography on silica gel (hexane : EtOAc= 4:1). ¹H NMR (500 MHz, CDCl₃): δ = 6.35-6.31 Boc (m, 1H), 6.15-6.11(m, 1H), 4.74-4.72(m, 2H), 1.85-1.74 (m, 4H), 1.51-1.50(m, 1H), 1.44(s, 9H)

1.43-1.35(m, 1H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ =156.4, 129.6, 127.7, 81.2, 75.1, 54.4 30.7, 28.4 (3C), 27.7, 18.6.



tert-Butyl 8-oxa-7-aza-bicyclo[4.2.2]dec-9-ene-7-carboxylate (2d) was isolated by flash chromatography on silica gel (hexane : EtOAc= 6:1). ¹H NMR (500 MHz, CDCl₃): δ = 6.38-6.35 (m, 1H), 5.78-5.75 (m, 1H), 4.92-4.87 (brs, 1H), 4.60-4.53 (brs, 1H), 2.15-2.00 (m, 3H), 1.79-1.49 (m,

5H), 1.46 (s, 9H) ppm. ¹³C NMR (126 MHz, CDCl3): δ =158.3, 132.3, 126.6, 81.5, 75.6, 54.4, 34.4, 31.8, 28.4 (3C), 26.0, 22.5.

tert-Butyl 4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (2e) was isolated by Me flash chromatography on silica gel (hexane : EtOAc= 6:1). ¹H NMR (500 MHz, CDCl₃): δ = 4.22 (s, 2H), 3.91 (s, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.52 (s, 9H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ =155.1, 123.3, 122.2, 81.5, 71.4, 48.7, 28.5 (3C), 15.4, 13.9.

 $Me + O_{N_{BOC}} Kert-Butyl 5-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (2f) and tert-butyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (2f') were isolated by flash chromatography on silica gel (hexane : EtOAc= 6:1). ¹H NMR (500 MHz, CDCl₃, mixture of two isomers) : <math>\delta = 5.51-5.55$ (m, 2H), 4.35-4.33 (m, 2H), 4.23 (s, 2H), 4.02-4.00 (m, 2H), 3.92 (s, 2H), 1.71 (s, 3H), 1.64 (s, 3H), 1.45 (m, 18H); TM_c (CDCl₃, 100MHz, mixture of two isomers) δ : 155.7, 153.7 131.7, 130.5, 118.2, 116.7, 81.6, 71.3, 68.2, 48.7, 44.9, 28.4 (3C), 28.1 (3C), 19.9, 18.4.

Boc, N O Me *tert*-Butyl 1,8-dimethyl-15-oxa-16-azatetracyclo[6.6.2.0.^{2,7}0^{9,14}]hexadeca-2,4,6,9,11,13hexaene-16-carboxylate (2g) was isolated by flash chromatography on silica gel (hexane : EtOAc= 5:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.45-7.43 (m, 2H), 7.37-7.36 (m, 2H), 7.25-7.22 (m, 4H), 2.56 (s, 3H), 2.23 (s, 3H), 1.21 (s, 9H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ

=159.5, 142.2, 140.7, 127.1, 127.0, 121.5, 120.6, 81.8, 78.7, 64.2, 27.9 (3C), 16.8, 15.1.



tert-Butyl 3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (2h) was isolated by flash chromatography on silica gel (hexane : EtOAc= 5:1). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.39-7.25$ (m, 10 H), 6.16–6.07 (m, 2 H), 5.61-5.53 (m, 2 H), 1.49 (s, 9 H) ppm. ¹³C NMR (126 MHz, CDCl₃): $\delta = 154.4$, 139.4, 137.4, 129.1, 128.8, 128.7, 128.3, 127.9, 127.8, 127.8, 126.6, 81.8, 79.2, 57.3, 28.5

(3C).

NMR spectra for calculating NMR yields of flask reaction using CuCl/air (Method 1)

















NMR spectra for calculating NMR yields of flow reaction using CuCl/air (Method 3)

































NMR spectra for calculating NMR yields of flow reaction using MnO₂ (Method 4a)

































NMR spectra for calculating NMR yields of flow reaction using MnO₂ (Method 4b)































