Water-compatible one-pot organocatalytic asymmetric synthesis of cyclic nitrones with application in intramolecular 1,3-dipolar cycloadditions

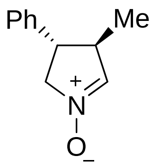
David Sádaba,[a] Ignacio Delso,[a,b] Tomás Tejero,[a] and Pedro Merino [a]*

[a] *Laboratorio de Síntesis Asimétrica, Departamento de Química Orgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Universidad de Zaragoza, CSIC, E-50009, Zaragoza, Aragon, Spain*

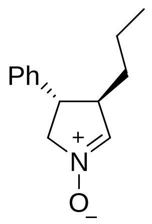
[b] *NMR Service, CEQMA, Institute of Chemical Synthesis and Homogeneous Catalysis (ISQCH), University of Zaragoza, CSIC, E-50009 Zaragoza, Aragón, Spain, Spain*

Supporting Information

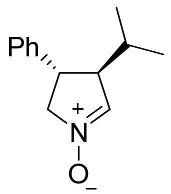
Characterization of compounds



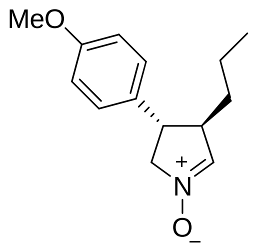
Compound 5a: oil; $[\alpha]_D^{25}$ +42 (c 0.42, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.25 (d, J = 6.9 Hz, 3H, CH_3), 3.08-3.21 (m, 1H, H_4), 3.27 (td, J = 9.1, 7.3 Hz, 1H, H_3), 4.15 (ddt, J = 14.0, 8.9, 2.1 Hz, 1H, H_2), 4.33 (dddd J = 13.8, 9.4, 2.1, 1.3 Hz, 1H, H_2'), 6.91-6.96 (m, 1H, H_5), 7.22-7.42 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 17.3 (CH$_3$), 45.5 (C_4), 48.7 (C_3), 68.8 (C_2), 127.2 (Ar), 127.7 (Ar), 129.2 (Ar), 139.6 (C_5) 139.7 (Ar). HRMS Calculated for $C_{11}H_{13}NO$: 175.0997. Found: 175.1085 Anal Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found C, 75.59; H, 7.29; N, 7.60.



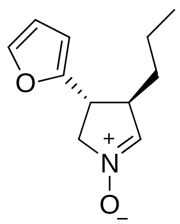
Compound 5b: oil; $[\alpha]_D^{25}$ + (c 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90 (t, J = 7.2 Hz, 3H, $CH_2CH_2C\mathit{H}_3$), 1.29-1.45 (m, 2H, $CH_2C\mathit{H}_2CH_3$), 1.53-1.63 (m, 2H, $C\mathit{H}_2CH_2CH_3$), 3.01-3.12 (m, 1H, H_4), 3.34 (ddd, J = 9.6, 7.9, 6.4 Hz, 1H, H_3), 4.09 (ddt, J = 14.2, 7.9, 1.9 Hz, 1H, H_2), 4.36 (dddd J = 13.9, 9.5, 2.2, 1.6 Hz, 1H, H_2'), 6.96-7.01 (m, 1H, H_5), 7.23-7.42 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 13.9 ($CH_2CH_2\mathit{C}H_3$), 20.5 ($CH_2\mathit{C}H_2CH_3$), 35.1 ($\mathit{C}H_2CH_2CH_3$), 46.4 (C_3), 50.8 (C_4), 68.9 (C_5), 127.1 (Ar), 127.5 (Ar), 129.1 (Ar), 138.2 (C_2) 141.0 (Ar). HRMS Calculated for $C_{13}H_{17}NO$: 203.1310. Found: 203.1393. Anal Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found C, 76.93; H, 8.54; N, 6.69.



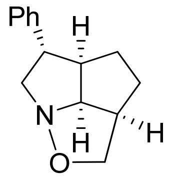
Compound 5c: oil; $[\alpha]_D^{25}$ +41 (c 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.89 (d, J = 6.8 Hz, 3H, $CH(C\mathit{H}_3)_2$), 0.91 (d, J = 6.8 Hz, 3H, $CH(C\mathit{H}_3)_2$), 1.82 (oct, J = 6.7 Hz, 1H, $C\mathit{H}(CH_3)_2$), 2.82-2.88 (m, 1H, H_4), 3.35 (ddd, J = 9.6, 6.4, 5.5 Hz, 1H, H_3), 3.95 (ddt, J = 14.4, 6.6, 6.0 Hz, 1H, H_2), 4.31 (dddd J = 14.1, 9.6, 2.4, 1.8 Hz, 1H, H_2'), 6.23-6.95 (m, 1H, H_5), 7.14-7.32 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 ($CH(\mathit{C}H_3)_2$), 20.6 ($CH(\mathit{C}H_3)_2$), 31.5 ($\mathit{C}H(CH_3)_2$), 43.3 (C_3), 58.0 (C_4), 69.5 (C_2), 127.0 (Ar), 127.4 (Ar), 129.2 (Ar), 137.6 (C_5), 142.6 (Ar). HRMS Calculated for $C_{13}H_{17}NO$: 203.1310. Found: 203.1379. Anal Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found C, 76.94; H, 8.59; N, 6.60.



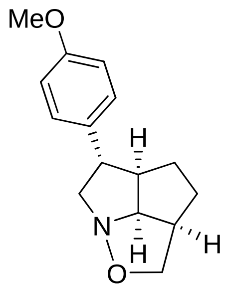
Compound 5d: oil; $[\alpha]_D^{25}$ +36 (c 0.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.87 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.28-1.38 (m, 2H, $CH_2CH_2CH_3$), 1.49-1.57 (m, 2H, $CH_2CH_2CH_3$), 2.95-3.03 (m, 1H, H_4), 3.26 (ddd, J = 9.4, 8.2, 6.5 Hz, 1H, H_3), 3.79 (s, 3H, OCH_3), 4.02 (ddt, J = 14.2, 8.2, 2.0 Hz, 1H, H_2), 4.29 (dddd J = 14.2, 9.5, 2.3, 1.5 Hz, 1H, $H_2{}^{'}$), 6.86-6.89 (m, 2H, Ar_{para}), 6.93-6.65 (m, 1H, H_5), 7.13-7.4218 (m, 2H, Ar_{para}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.0 ($CH_2CH_2CH_3$), 20.6 ($CH_2CH_2CH_3$), 35.1 ($CH_2CH_2CH_3$), 45.9 (C_3), 50.9 (C_4), 55.3 (OCH_3) 69.1 (C_2), 114.5 (Ar), 128.2(Ar), 132.9 (Ar), 138.3 (C_5) 158.9 (Ar). HRMS Calculated for $C_{14}H_{19}NO_2$: 233.1416. Found: 233.1485. Anal Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found C, 72.15; H, 8.02; N, 6.27.



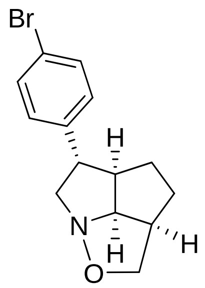
Compound 5e: oil; $[\alpha]_D^{25}$ +49 (c 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.86 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.26-1.39 (m, 2H, $CH_2CH_2CH_3$), 1.44-1.61 (m, 2H, $CH_2CH_2CH_3$), 3.05-3.13 (m, 1H, H_4), 3.39 (ddd, J = 9.1, 8.2, 6.6 Hz, 1H, H_3), 4.08 (ddt, J = 14.0, 8.1, 2.0 Hz, 1H, H_2), 4.17 (dddd J = 13.8, 9.5, 2.2, 1.5 Hz, 1H, $H_2{}^{'}$), 6.09 (dt, J = 3.2, 0.7 Hz, 1H, *Ar*), 6.26 (dd, J = 3.2, 1.9 Hz, 1H, *Ar*), 6.83-6.85 (m, 1H, H_5), 7.30 (dd, J = 1.9, 0.8 Hz, 1H, *Ar*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 13.7 ($CH_2CH_2CH_3$), 20.3 ($CH_2CH_2CH_3$), 34.9 ($CH_2CH_2CH_3$), 39.3 (C_4), 47.3 (C_3), 65.5 (C_2), 106.0 (Ar), 110.2 (Ar), 137.5 (C_2) 142.1 (Ar), 151.7 (Ar). HRMS Calculated for $C_{11}H_{15}NO_2$: 193.1103. Found: 193.1182. Anal Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found C, 68.26; H, 7.66; N, 7.43.



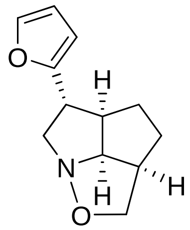
Compound 9a: yellow oil; $[\alpha]_D^{25}$ -25 (c 0.14, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.49-1.77 (m, 3H, H_3, H_4, $H_{4'}$), 1.88-2.00 (m, 1H, $H_{3'}$), 2.64 (tdd, J = 8.7, 6.1, 2.4 Hz, 1H, H_{4a}), 2.87-3.05 (m, 2H, H_{2a}, H_6), 3.18 (ddd, , J = 11.3, 9.1, 6.0 Hz, 1H, H_5), 3.61-3.73 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 4.17 (t, J = 8.3 Hz, 1H, H_{2a}), 7.10-7.32 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.1 (C_4), 31.5 (C_3), 49.0 (C_5), 50.0 (C_{2a}), 53.7 (C_{4a}), 64.5 (C_6), 71.9 (C_2), 77.5 (C_{2a}), 125.5 (Ar), 128.6 (Ar), 128.6 (Ar), 144.7 (Ar). HRMS Calculated for $C_{14}H_{17}NO$: 215.1310. Found [M+H]: 216.1375. Anal Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found C, 78,47; H, 8.32; N, 6.35.



Compound 9b: transparent oil; $[\alpha]_D^{25}$ -9 (c 0.12, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.57-1.84 (m, 3H, H_3, H_4, $H_{4'}$), 1.99-2.09 (m, 1H, $H_{3'}$), 2.69 (tdd, J = 8.6, 6.4, 1.9 Hz, 1H, H_{4a}), 2.84-3.10 (m, 3H, H_{2a}, H_5, H_6), 3.51-3.73 (m, 6H, H_2, $H_{2'}$, $H_{6'}$, CH_3O), 4.19 (t, J = 8.1 Hz, 1H, H_{2a}), 6.69-6.76 (m, 2H, Ar), 6.99-7.05 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.0 (C_4), 31.3 (C_3), 47.8 (C_5), 49.8 (C_{2a}), 53.5 (C_{4a}), 55.3 (CH_3O), 64.1 (C_6), 72.5 (C_2), 77.2 (C_{2a}), 114.1 (Ar), 128.5 (Ar), 132.8 (Ar), 158.4 (Ar). HRMS Calculated for $C_{15}H_{19}NO_2$: 245.1416. Found [M+H]: 246.1478. Anal Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found C, 73.32; H, 7.98; N, 5.49.



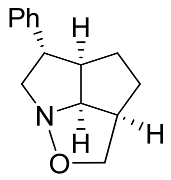
Compound 9c: yellow oil; $[\alpha]_D^{25}$ -9.9 (c 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.59-1.81 (m, 3H, H_3, H_4, $H_{4'}$), 2.01-2.09 (m, 1H, $H_{3'}$), 2.69 (ddd, J = 9.3, 8.9, 2.2 Hz, 1H, H_{4a}), 3.00-3.08 (m, 2H, H_{2a}, H_6), 3.23 (ddd, J = 11.4, 9.2, 6.2 Hz, 1H, H_5), 3.70-3.80 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 4.27 (t, J = 8.3 Hz, 1H, H_{2a}), 7.13-7.17 (m, 2H, Ar), 7.44-7.48 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.0 (C_4), 31.4 (C_3), 48.5 (C_5), 49.9 (C_{2a}), 53.7 (C_{4a}), 64.5 (C_6), 71.9 (C_2), 77.4 (C_{2a}), 129.3 (Ar), 131.7 (Ar), 140.7 (Ar). HRMS Calculated for $C_{14}H_{16}BrNO$: 293.0415. Found [M+H]: 294.0502; 296.0483. Anal Calcd. for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48; Br, 27.16; N, 4.76. Found C, 57.36; H, 5.29; Br, 28.21; N, 4.94.



Compound 9d: yellow oil; $[\alpha]_D^{25}$ -12 (c 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.43-1.81 (m, 3H, H_3, H_4, $H_{4'}$), 1.89-2.00 (m, 1H, $H_{3'}$), 2.69 (td, J = 8.7, 1.9 Hz, 1H, H_{4a}), 2.91 (tdd, , J = 8.4, 4.5, 1.1 Hz, 1H, H_{2a}), 3.02 (ddd, J = 13.4, 11.3, 0.8 Hz, 1H, H_6), 3.25 (ddd, , J = 11.2, 9.2, 6.0 Hz, 1H, H_5), 3.57-3.71 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 4.12 (t, J = 8.2 Hz, 1H, H_{2a}), 5.98 (dt, J = 3.1, 0.7 Hz, 1H, Ar), 6.22 (dt, J = 3.1, 1.9 Hz, 1H, Ar), 7.26 (dd, J = 1.8, 0.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.1 (C_4), 31.4 (C_3), 42.6 (C_5), 49.8 (C_{4a}), 50.9 (C_{2a}), 62.0 (C_6), 71.9 (C_2), 77.1 (C_{2a}), 104.9 (Ar), 110.1 (Ar), 141.4 (Ar), 155.3 (Ar). HRMS Calculated for $C_{12}H_{15}NO_2$: 205.1103. Found [M+H]: 207.1186. Anal Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found C, 70.46; H, 7.509; N, 6.73.

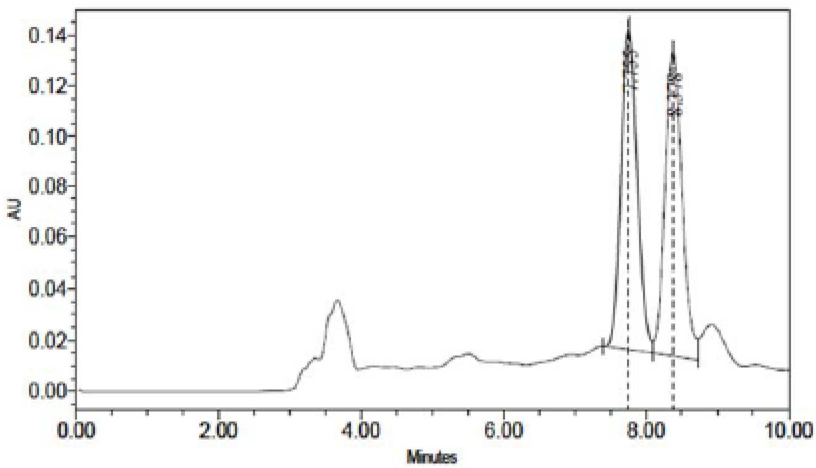
HPLC of compounds 9a-d

The racemic derivatives were prepared by using pyrrolidine, instead of **3**, as a catalyst.

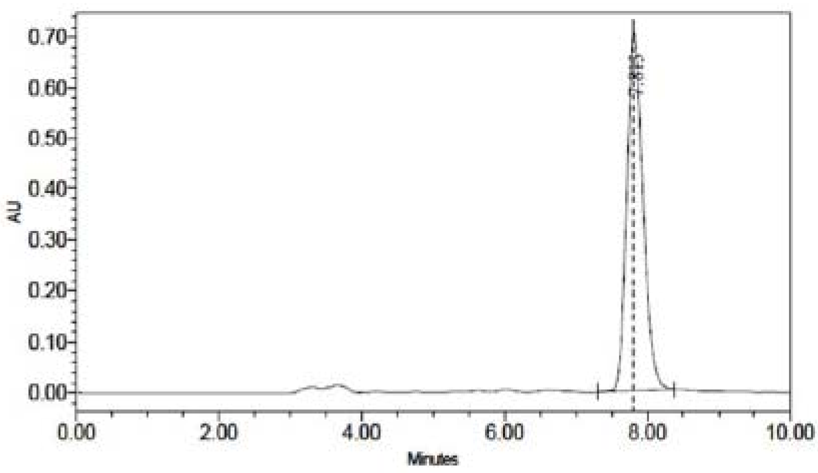


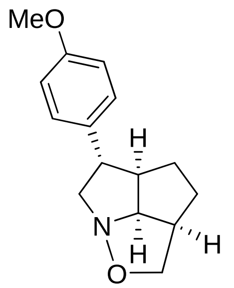
Compound **9a**: (Chiralpak IC, hexane/iPrOH, 9:1, 1 mL/min)

Racemic:



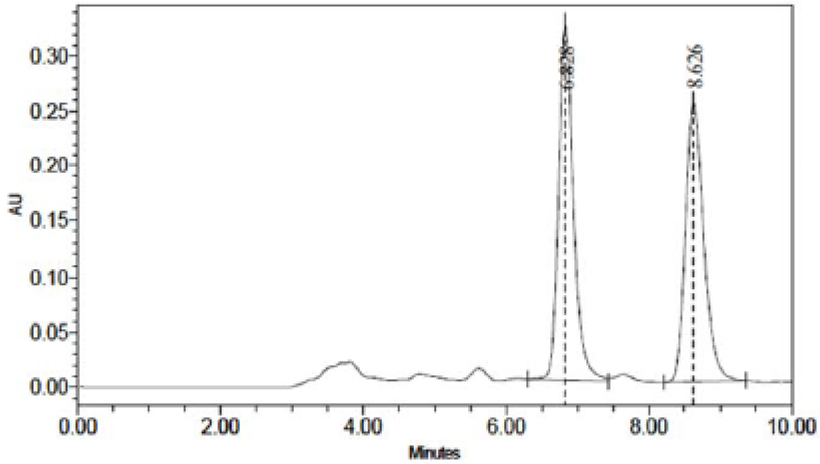
Optically active:





Compound **9b**: (Chiralpak IC, hexane/iPrOH, 9:1, 1 mL/min)

Racemic:



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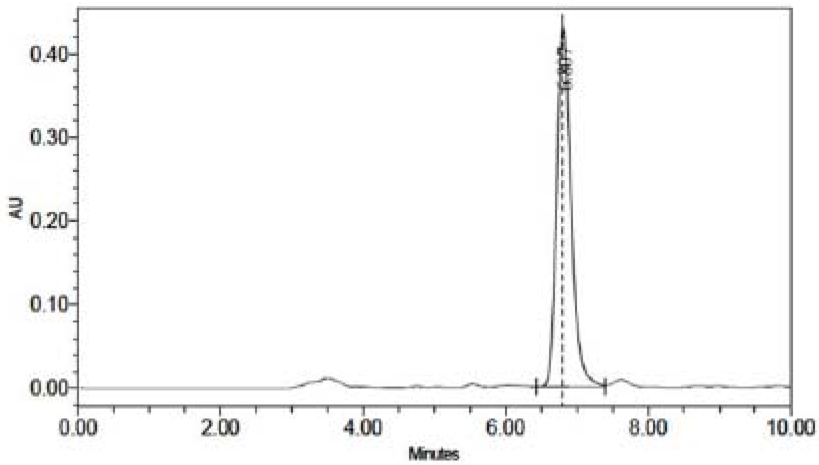
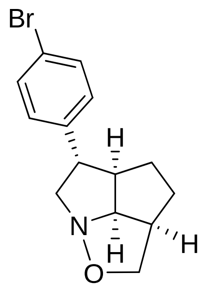
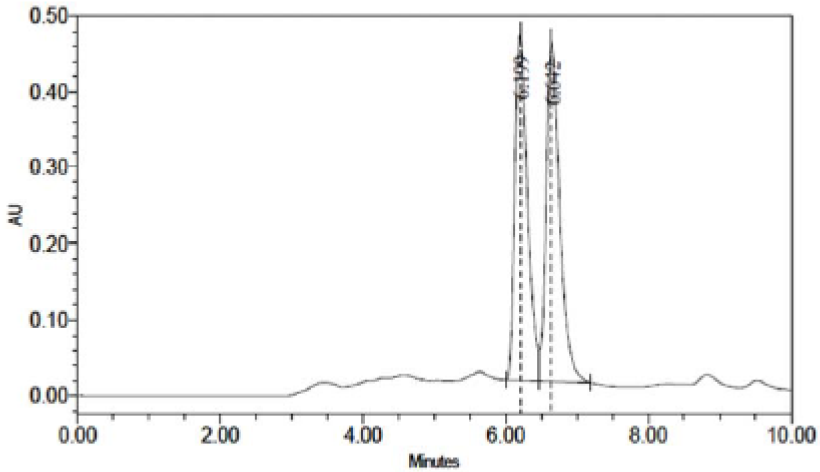




Compound **9c:** (Chiralpak IC, hexane/iPrOH, 4:1, 1 mL/min)

Racemic:



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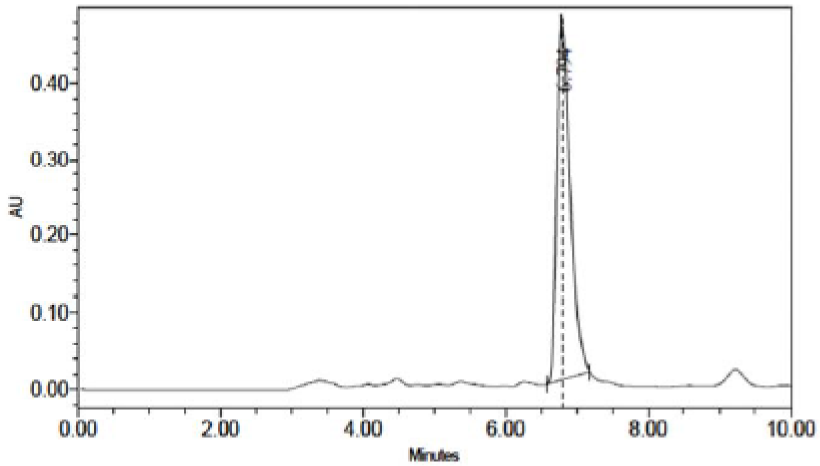
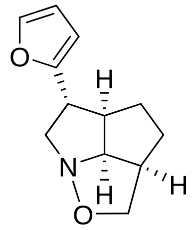
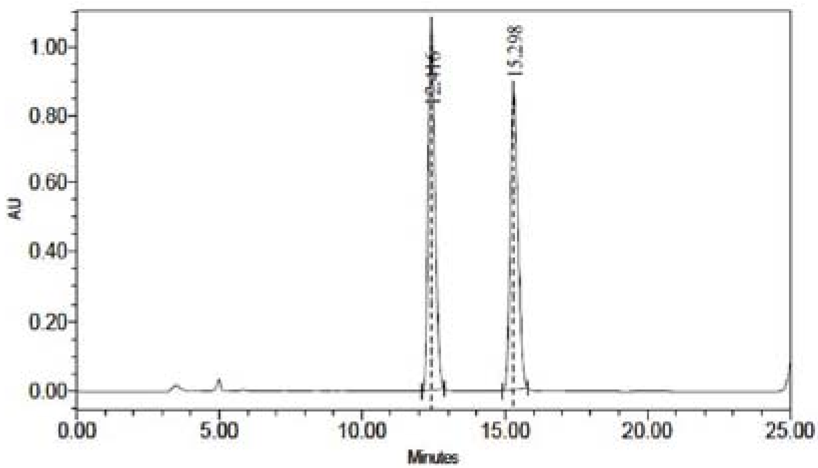




Compound **9d**. (Chiralpak IC, hexane/iPrOH, 9:1, 1 mL/min)

Racemic:



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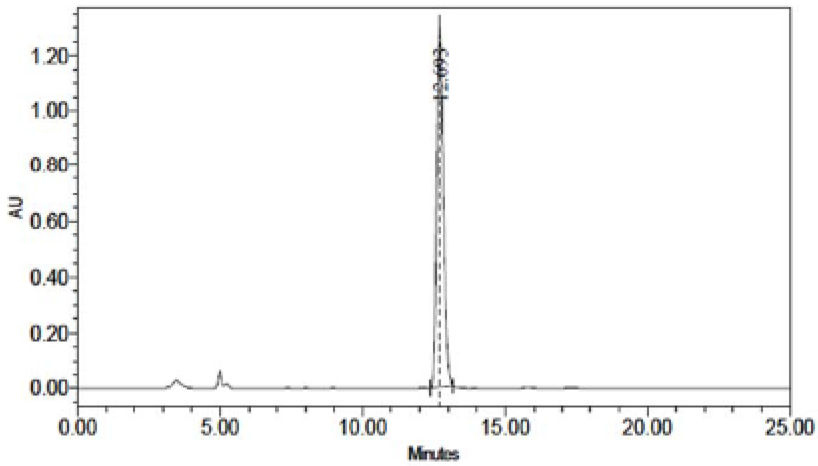

Details on Theoretical Calculations

All calculations were performed with the GAUSSIAN 03 package.[1] The hybrid density functional theory B3LYP[2] with the 6-31G* basis set[35] were employed. Geometry optimizations and vibrational analyses were performed without any constraint and the transition structure was characterized by analysis of the normal mode corresponding to its unique imaginary frequency.

1 Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

2 (a) Becke, A. D: *J. Chem. Phys* **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785-789. (c) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200-205.

3 (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys* **1971**, *54*, 724-728. (b) Hehre, W.. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys* **1972**, *56*, 2257-2261. (c) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209-214. (d) Gordon, M. S: *Chem. Phys. Lett.* **1980**, *76*, 163-168. (e) Franci, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; DeFrees, D. J.; Pople, J. A.; Gordon, M. S. *J. Chem. Phys* **1982**, *77*, 3654-3655. (f) Rassolow, V. A.; Pople, J. A:; Ratner, M. A:; Windus, T. L. *J. Chem. Phys* **1998**, *109*, 1223-1229.

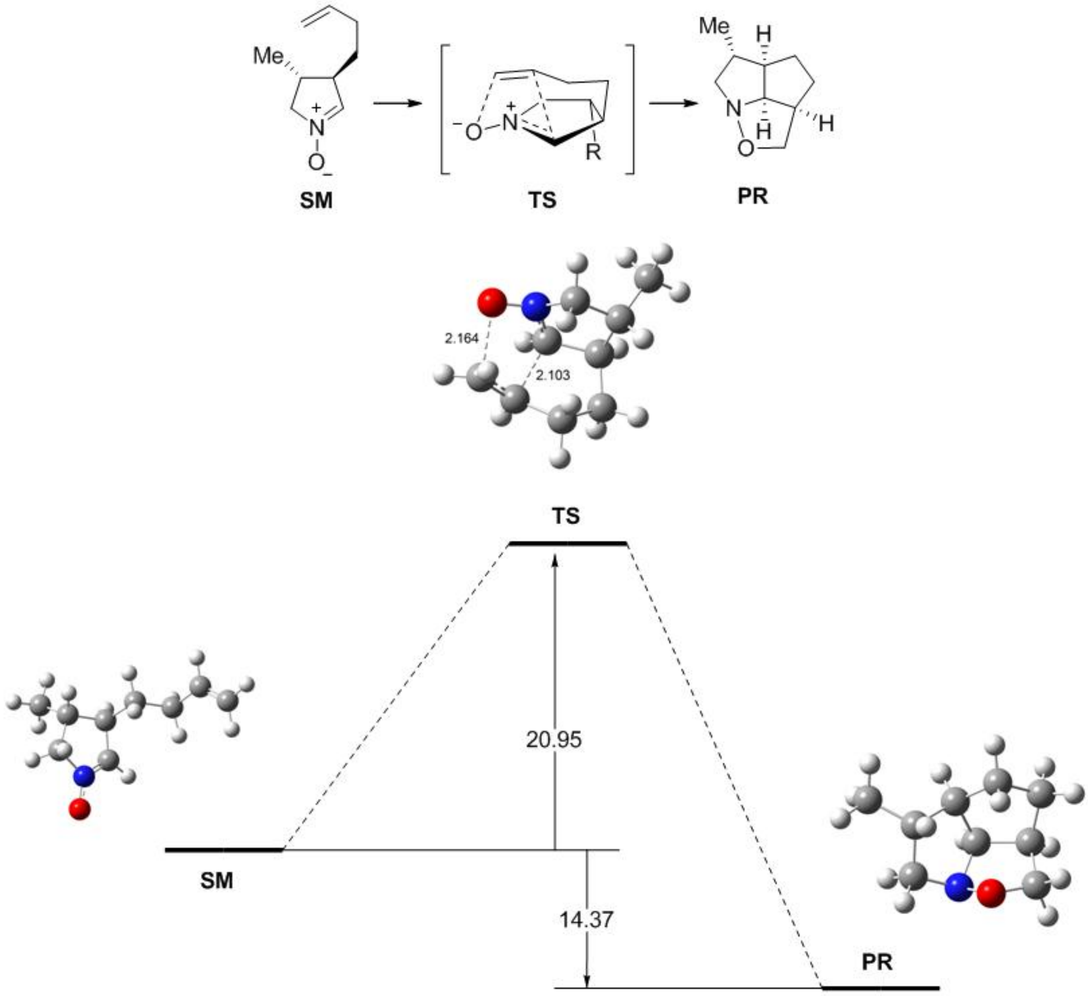

Figure S1. Reaction paths for the intramolecular cycloaddition of nitrones **8a-d**. The R substituent has been approached by a methyl group.

Coordinates of stationery points (B3LYP/6-31G(d))

SM

C	2.17594600	0.18546800	0.92860200
C	0.73498300	0.80414500	-0.78076800
C	0.29782700	-0.58803300	-0.43728100
C	1.47332800	-1.10155900	0.46455100
H	3.26728700	0.15303500	0.88299600
H	1.88212000	0.53160900	1.92400800
H	0.31288700	1.47354400	-1.51871300
H	0.23176600	-1.20654200	-1.34546400
H	1.06836500	-1.64331900	1.32669400
N	1.73153500	1.23285600	-0.04430400

O	2.30648600	2.35715700	-0.04896900
C	2.42286100	-2.02783800	-0.30456700
H	3.26033300	-2.34927700	0.32547900
H	1.89956000	-2.92566600	-0.65261700
H	2.83824600	-1.51798500	-1.18234300
C	-1.07688000	-0.65582500	0.26804000
H	-1.26409500	-1.70072200	0.55509000
H	-1.04037200	-0.07569000	1.19974700
C	-2.24746700	-0.15151000	-0.59650400
H	-2.10068300	0.90708700	-0.84441200
H	-2.24292200	-0.70400700	-1.54954300
C	-3.58112500	-0.32941600	0.07784800
H	-3.85864900	-1.35830600	0.31557500
C	-4.41360400	0.65833200	0.40827100
H	-4.17921500	1.69936900	0.19390000
H	-5.36246900	0.46703300	0.90233000

TS

C	0.81467400	-1.06854400	-0.86279800
C	-0.14476100	-0.15078600	1.05539900
C	0.85923300	0.88672000	0.61720700
C	1.69130200	0.13935700	-0.48175500
H	1.37781100	-1.98345000	-1.06980800
H	0.15171300	-0.87485100	-1.71647800
H	-0.54463700	-0.24382500	2.05788100
H	1.52056500	1.21014300	1.43111600
H	1.82916600	0.79159100	-1.35208700
C	-1.91462200	0.58168500	0.18631200
H	-2.33844200	0.96875800	1.11447000
C	0.06148100	2.11219800	0.09867200
H	-0.25466900	2.71103200	0.96411400
H	0.69360600	2.76348000	-0.51898200
C	-1.19374000	1.62711300	-0.65012000
H	-1.85034500	2.48225100	-0.86294800

H	-0.91972200	1.20154600	-1.62489600
C	-2.50193200	-0.56806300	-0.32890200
H	-3.27988200	-1.09038700	0.21459000
H	-2.41690200	-0.81700300	-1.38247400
N	-0.03584800	-1.28083100	0.32483700
O	-1.05297700	-2.07281300	0.23720200
C	3.06872100	-0.28846300	0.04066900
H	3.63149900	-0.83114100	-0.72777900
H	3.66422200	0.58089600	0.34250400
H	2.96863100	-0.94800900	0.91119400

PR

C	1.40198200	-1.34957000	0.08509000
C	-0.35078200	-0.12513300	1.02581100
C	0.56003600	0.93245800	0.31717500
C	1.68414300	0.10769200	-0.37323600
H	1.97347400	-1.58559100	0.99306000
H	1.63774100	-2.10823800	-0.66572700
H	-0.20113400	-0.16827700	2.10863300
H	0.98708000	1.61591400	1.06145700
H	1.54286300	0.16152600	-1.45861100
C	-1.81191400	0.15755400	0.59972200
H	-2.52706300	0.06888000	1.42329100
C	-0.38744900	1.71216500	-0.62665600
H	-0.08259700	2.75459700	-0.77371400
H	-0.39709700	1.23145100	-1.61169500
C	-1.77721000	1.58731900	0.02242300
H	-1.87595400	2.31013800	0.84348900
H	-2.59955900	1.78305400	-0.67639400
C	-2.03931600	-0.96997000	-0.43661400
H	-2.60299300	-1.79966600	0.01467200
H	-2.54975300	-0.63823600	-1.34627300
N	-0.01289300	-1.45275000	0.45577700
O	-0.74568000	-1.40621700	-0.82995900

C	3.10695700	0.56909300	-0.04492600
H	3.85541600	-0.07351900	-0.52495900
H	3.28476300	1.59511400	-0.38774800
H	3.29182600	0.54219000	1.03701100