

Highly Regio- and Stereoselective Intramolecular 1,3-Dipolar Cycloadditions of Norbornadiene-Tethered Nitrile Oxides

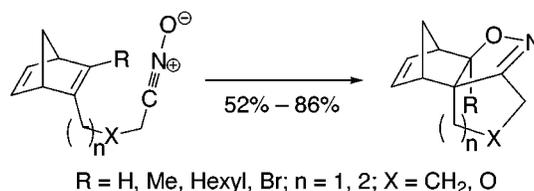
Carol Yip, Sean Handerson, Robert Jordan, and William Tam*

Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry,
Department of Chemistry and Biochemistry, University of Guelph,
Guelph, Ontario, Canada N1G 2W1

tam@chembio.uoguelph.ca

Received June 25, 1999

ABSTRACT

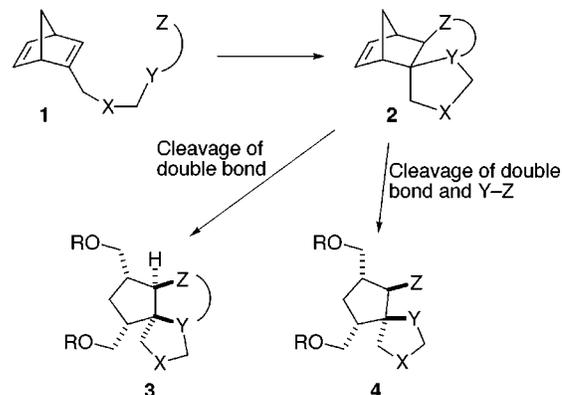


Intramolecular cycloadditions with high regio- and stereocontrol are important methods for the efficient assembly of complex molecular structures. Efficient routes to the synthesis of norbornadiene-tethered nitrile oxides have been developed, and their intramolecular 1,3-dipolar cycloadditions were studied. The cycloadditions occurred in good yields for a variety of substrates and were found to be highly regio- and stereoselective.

Cycloaddition reactions are among the most powerful methods for the construction of rings.¹ In particular, intramolecular cycloadditions with high regio- and stereocontrol are important tools for the efficient assembly of complex molecular structures. We have recently initiated a program on the study of various types of intramolecular cycloadditions of substituted norbornadienes. Our long-term goal is to develop an efficient route for the construction of angularly fused tricyclic frameworks and spirocyclic frameworks with high regio- and stereocontrol (Scheme 1).

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety of complex five-membered heterocycles.² 1,3-Dipolar cycloadditions of nitrile oxides are well-documented and provide efficient entries to the synthesis of 2-isoxazolines which are valuable intermedi-

Scheme 1. General Outline for Construction of Tricyclic and Spirocyclic Frameworks via Intramolecular Cycloadditions of Norbornadienes and Subsequent Cleavage of the Cycloadducts



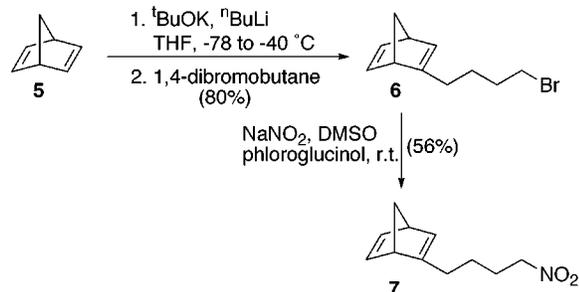
ates in organic synthesis.³ In this paper, we report our initial result on the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrile oxides.

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapters 1–9. (b) *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1994; Vols. 1–3. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vols. 1 and 2. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

An efficient route to the synthesis of norbornadiene-tethered nitro compound **7** was developed, and **7** served as a precursor of the required nitrile oxide for the cycloaddition (Scheme 2). Deprotonation of norbornadiene **5** with Schlo-

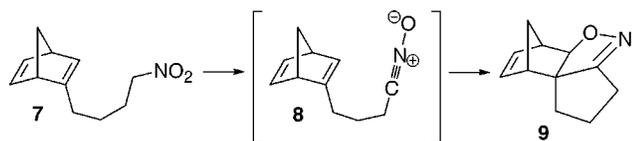
Scheme 2. Synthesis of Norbornadiene-Tethered Nitro Compound **7**



sser's base ($t\text{BuOK}/n\text{BuLi}$) in THF at $-78\text{ }^\circ\text{C}$,⁴ followed by addition of the resulting norbornadienyl anion to an excess of 1,4-dibromobutane, provided the norbornadiene-tethered bromide **6**.⁵ Displacement of the bromide with NaNO_2 in the presence of phloroglucinol in DMSO⁶ afforded the required nitro compound **7**. In the absence of phloroglucinol, a significant amount of the corresponding nitrite was obtained and the yield of nitro compound **7** was very low.

Three different methods (the Mukaiyama aromatic isocyanate method,⁷ the Shimizu ethyl chloroformate method,⁸ and the Hassner $(\text{BOC})_2/\text{DMAP}$ method⁹) were employed to generate the corresponding nitrile oxide in situ from **7** (Table 1). The use of $(\text{BOC})_2\text{O}$ and DMAP in toluene at $90\text{ }^\circ\text{C}$ was found to be the best method in our system, giving the highest yield in the cycloaddition.

Table 1. Three Different Methods To Generate Nitrile Oxide **8** and Cycloadduct **9**



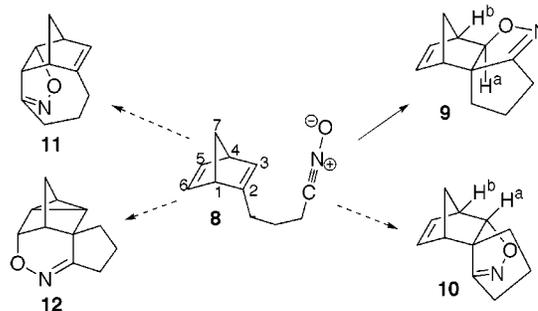
method	solvent ^a	temperature	yield ^b
$(\text{BOC})_2\text{O}$ DMAP	toluene	$90\text{ }^\circ\text{C}$	86 %
	CHCl_3	$60\text{ }^\circ\text{C}$	61 % ^c
PhNCO Et_3N	toluene	$90\text{ }^\circ\text{C}$	54 % ^c
	CHCl_3	$60\text{ }^\circ\text{C}$	76 %
EtOCOCI Et_3N , DMAP	toluene	$90\text{ }^\circ\text{C}$	25 % ^c
	CHCl_3	$60\text{ }^\circ\text{C}$	72 %

^aLower yields were obtained with other solvents such as THF, DME, 1,2-dichloroethane and Et_2O at reflux temperature. ^bIsolated yields after column chromatography.

^c33–65% of starting materials were recovered

Four different cycloadducts are theoretically possible in the cycloaddition (Scheme 3). Cycloaddition of the tethered

Scheme 3. Possible Cycloadducts



nitrile oxide on the $\text{C}_2\text{--C}_3$ double bond from the *exo* and *endo* faces would provide the *exo* and *endo* cycloadducts **9** and **10**. Formation of the cycloadducts **11** (with the distal $\text{C}_5\text{--C}_6$ double bond) and **12** (with both of the double bonds in the norbornadiene) are not very likely due to the high strain in these resulting molecules. The intramolecular cycloaddition of the norbornadiene-tethered nitrile oxide **8** was found to be highly regio- and stereoselective, giving the *exo* cycloadduct **9** as a single regio- and stereoisomer. It is noteworthy to mention here that the intermolecular 1,3-dipolar cycloaddition of norbornadiene with benzonitrile oxide is known to produce a 4:1 *exo/endo* cycloadducts.¹⁰

The regio- and stereochemistries of the cycloadduct **9** were proven by NMR techniques. The presence of two olefinic protons in the ^1H NMR spectrum eliminated the possibilities of cycloadducts **11** and **12**. The *exo* and *endo* stereochemistry of the cycloadduct can easily be distinguished by the coupling constant of H^a and H^b in the ^1H NMR.¹¹ As the dihedral angle between H^a and H^b in the *exo* cycloadduct **9** is close to 90° , the coupling constant between H^a and H^b would be very small ($J \sim 0\text{--}2\text{ Hz}$). In the *endo* cycloadduct **10**, the dihedral angle between H^a and H^b is approximately 42° and would give a doublet with $J \sim 5\text{ Hz}$.¹² NOESY experiments also provided an additional confirmation of the *exo* stereochemistry of the cycloadduct.

To study the generality of the cycloaddition, a variety of norbornadiene-tethered nitro compounds were synthesized

(3) (a) Curran, D. P. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1988; Vol. 1, pp 129–189. (b) *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Torssell, K. B. G., Ed.; VCH: New York, 1988. (c) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719.

(4) Brandsma, L.; Verkuruijse, H. D. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 66.

(5) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8.

(6) *Organic Functional Group Preparation*; Sandler S. R., Karo, W., Eds.; Academic Press: New York, 1968; Vol. 1, pp 425–429.

(7) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

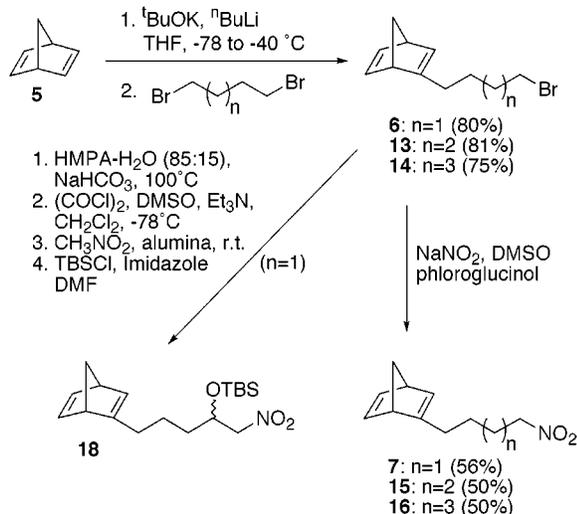
(8) Shimizu, T.; Hayashi, T.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2827.

(9) Basel, Y.; Hassner, A. *Synthesis* **1997**, 309.

(10) De Micheli, C.; Gandolfi, R.; Oberti, R. *J. Org. Chem.* **1980**, *45*, 1209.

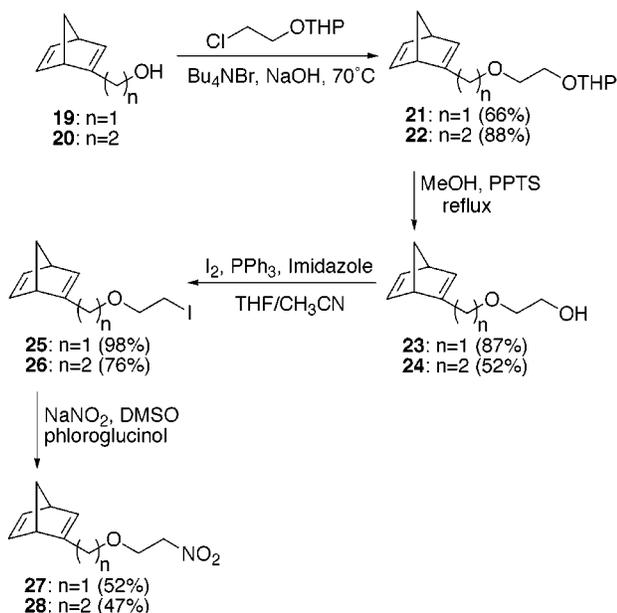
(11) (a) Flaute, T. J.; Erman, W. F. *J. Am. Chem. Soc.* **1963**, *85*, 3212.

(b) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482.

Scheme 4. Synthesis of Nitro Compounds **7**, **15**, **16**, and **18**

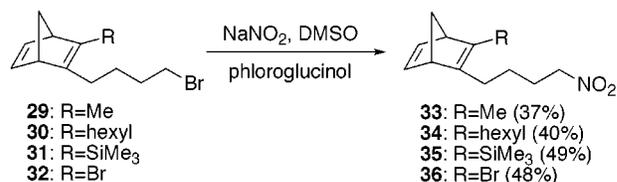
(Schemes 4–6) and subjected to the optimized cycloaddition conditions (Table 2).

Nitro compounds **15** and **16** were synthesized using the same protocol as nitro compound **7**. Nitro compound **18** with an α -silyl ether substituent was synthesized through the following sequence: hydration and Swern oxidation to the corresponding aldehyde;¹³ addition of nitromethane in the presence of alumina,¹⁴ followed by TBS protection. Nitro compounds with an oxygen within the tether were prepared as shown in Scheme 5. Norbornadiene-tethered allylic and homoallylic alcohols **19** and **20** were prepared according to literature procedures.⁴ Two-carbon homology to the alcohols **23** and **24** was achieved by a two-step sequence.¹⁵ Conversion of the alcohols **23** and **24** to the corresponding

Scheme 5. Synthesis of Nitro Compounds **27** and **28**

iodides **25** and **26** using I_2 , PPh_3 , and imidazole¹⁶ followed by displacement with sodium nitrite afforded the nitro compounds **27** and **28**.

To investigate the effect of a C_3 substituent on the cycloaddition, nitro compounds **33–36** were prepared as shown in Scheme 6, from bromides **29–32**.¹⁷

Scheme 6. Synthesis of Nitro Compounds **33–36**

The results of the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrile oxides are shown in Table 2. Similar to the three-carbon tethered nitrile oxide **8**, which provided cycloadduct **9** as the single cycloadduct (Table 1), cycloaddition of the four-carbon tethered nitrile oxide (generated in situ from nitro compound **15**) was also highly regio- and stereoselective, giving the *exo* cycloadduct **37** as the only cycloadduct in good yield. However, no cycloadduct was formed with the corresponding five-carbon tethered nitrile oxide.¹⁸ Formation of the five- and six-membered ring cycloadducts (**39** and **40**) with an oxygen within the tether was also found to be successful, giving a moderate yield of the cycloadducts. In the case of cycloaddition with the nitrile oxide generated from nitro compound **28**, other than the *exo* cycloadduct **40**, an unidentified product ($\sim 20\%$) was also detected. This is the only case in which we observed a product other than the *exo* cycloadducts in the cycloadditions. Nitrile oxide generated from nitro compound **18** with an α -silyl ether substituent also provided the corresponding *exo* cycloadduct **41** in good yield. With these five successful examples in hand, we investigated the effect of a C_3 substituent on the norbornadiene in the cycloaddition. We anticipated that a bulky C_3 substituent may retard the cycloaddition due to steric hindrance. But, in fact, cycloadditions of the nitrile oxides, generated from nitro compounds **33** (R = Me), **34** (R = hexyl), and **36** (R = Br), occurred smoothly, giving the corresponding *exo* cyclo-

(12) The *exo* and *endo* cycloadducts **9** and **10** were modeled for energy minimization at PM3 level (CS Chem 3D Pro Version 3.5.1) using MOPAC for the assessment of the dihedral angles between H^a and H^b . These dihedral angles were then compared to the Karplus curve for the determination of the theoretical coupling constants.

(13) Lautens M.; Edwards, L. G.; Tam, W.; Lough, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10276.

(14) Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014.

(15) Heinze, I.; Knoll, K.; Möller, R.; Eberbach, W. *Chem. Ber.* **1989**, *122*, 2147.

(16) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.

(17) We have recently developed a novel and efficient method for the preparation of unsymmetrical 2,3-disubstituted norbornadienes (e.g., compounds **29–32**). These results will be reported in due course.

(18) Only polymeric material was obtained. As the length of the tether increases, the rate of intramolecular cycloaddition decreases and side reactions such as rearrangement and dimerization of the nitrile oxide and polymerization could occur.

Table 2. Intramolecular 1,3-Dipolar Cycloaddition of Norbornadiene-Tethered Nitrile Oxides

nitroalkane	cycloadduct ^a	yield ^b
		n=1 86%
		n=2 75%
		n=3 0% ^c
		n=1 69%
		n=2 52% ^d
		78%
		R=Me 82%
		R=Hexyl 83%
		R=SiMe3 0% ^c
		69%

^a Typical Cycloaddition conditions: (BOC)₂O (2-3 equiv.) in toluene was added to the nitroalkane, DMAP (10 mol%) in toluene and the reaction mixture was stirred at 90°C for 24-96 h.

^b Isolated yields after column chromatograph.

^c No cycloadduct was obtained.

^d Accompanied with an unidentified product (~20%)

adducts as the only regio- and stereoisomers in moderate to good yields.¹⁹ However, with a very bulky group at C₃ of norbornadiene (**35**, R = SiMe₃), no cycloadduct was formed.

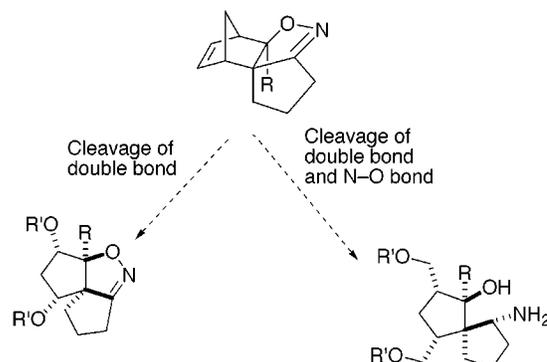
The regio- and stereochemistries of cycloadducts were confirmed by using NMR techniques as described earlier with

(19) In all the cycloadditions, in addition to the *exo*-cycloadducts some dark brown polymeric materials were obtained. But in all cases, no other isomeric cycloadduct was detected by TLC and by crude NMR.

cycloadduct **9**. The small coupling constant between H^a and H^b (Scheme 3) of cycloadducts **9** and **37–41** in ¹H NMR (normally *J* < 1.5 Hz) indicated the *exo* stereochemistry of the cycloadducts. With a substituent at C₃ (R ≠ H), this method is not useful. In these cases, NOESY experiments were used to confirm the *exo* stereochemistry of the cycloadducts. Furthermore, these assignments were also supported by X-ray crystallography.²⁰

In summary, we have demonstrated the first examples of the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrile oxides. These cycloadditions were found to be highly regio- and stereoselective, giving the *exo* cycloadducts in good yields. Further investigation on the electronic effect of a C₃ substituent (electron-withdrawing vs electron-donating) on the norbornadiene in the cycloaddition, as well as subsequent cleavage reactions of the cycloadducts (Scheme 7) for the construction of angular-fused tricyclic and spirocyclic frameworks, are ongoing in our laboratory.

Scheme 7. Cleavage Options



Acknowledgment. We thank the Natural Science and Engineering Research Council (NSERC) of Canada and the University of Guelph for the generous financial support of our program. Professor George Ferguson and Ms. Valerie Robinson from our department are thanked for X-ray structure determination and NMR experiments.

Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra of all new compounds). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL990765F

(20) Recrystallization of cycloadduct **42** (R = Me) in 20% EtOAc/hexanes provided suitable crystals for X-ray analysis. Details of the X-ray analysis will be submitted for publication in *Acta Crystallogr., Sect. C*.