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Retro iminonitroso Diels-Alder reactions: interconversion of nitroso cycloadducts

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Abstract

Retro iminonitroso Diels-Alder reactions were investigated in both solution and solid phase. In thermal or Cu(I)-mediated reactions, interconversion of various nitroso cycloadducts occurred in the presence of separate dienes. Up to 99% of conversion was observed. Use of chiral ligands in the Cu (I)-medicated reactions gave new cycloadducts enantioselectively.

Since its discovery in 1947, the nitroso Diels-Alder reaction (NDA) has become a powerful synthetic tool for the formation of 1-amino-4-hydroxy-2-ene derivatives in one step.[1] Many groups have continued to develop and apply nitroso Diels-Alder reactions in organic syntheses. 2 We successfully used nitroso Diels-Alder reactions to obtain cycloadducts as versatile building blocks for a variety of synthetic applications, including preparation of carbocyclic nucleoside analogs and novel natural product scaffolds.3

The retro Diels-Alder reaction (retro DA) has been known since the discovery of the forward DA itself and has been used to generate a wide variety of reactive species in a synthetically useful manner.[4] The retro DA strategy has been of considerable utility in promoting acylnitroso cycloaddition reactions. For example, it has been used to store *in situ* generated transient and unisolable acylnitroso agents **1** by cycloaddition with dimethylanthracene (DMA).[5] To avoid the direct use of oxidant, the resultant cycloadducts can be thermolized at relatively low temperature to release the free acylnitroso species **1** (Scheme 1). However, very few examples have been reported regarding retro nitroso Diels-Alder reactions (retro NDA) related to aryl or heteroaryl nitroso agents.[6] Studies of retro NDA reactions would benefit understanding of reaction mechanisms and extend their synthetic use. We envisioned that the dissociation of nitroso cycloadducts might occur under thermal or Lewis acid-mediated conditions to generate new nitroso cycloadduct scaffolds in the presence of added dienes. Herein we describe the preliminary results of this study in both solution and solid phase.

Three structurally differentiated nitroso cycloadducts **6a–c** were obtained from NDA reactions between 6-methyl-2-nitrosopyridine **2a** and colchicine **3**, 1,3-cyclopentadiene **4** and ergosterol **5**, respectively (Scheme 2).[3e] We chose those cycloadducts for initial investigations of the retro NDA reactions since, in our early report, we noticed that cycloaddition with colchicine was a reversible process.[3e] The experiments were conducted by treating cycloadducts **6a–c** with 5.0 equivalents of 1,3-cyclohexadiene **7** at both 25 °C and 50 °C.[7] As shown in Table 1, dissociations of colchicine adduct **6a** and ergosterol adduct **6c** at 25 °C were observed and *in*

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situ trapping of the released nitroso species **2a** with **7** gave adduct **8** in 43% and 20% yield, respectively (entries 1 and 5). Not surprisingly, at elevated temperature (50 °C), complete retro NDA reactions of **6a** and **6c** occurred within several hours, affording adduct **8** in good yields (entries 2 and 6). In the presence of a large excess of **7,** the net reaction of **6c** was accelerated and compound **8** was obtained in 54% yield at 25 °C (entry 7). In contrast, no retro NDA reaction was detected for adduct **6b** at 25 °C or even at high temperature (entries 3 and 4). These observations clearly indicated that structure and configuration played important roles in the related retro NDA reactions. Compared to their parent natural products or adduct **6b**, NDA adducts **6a** and **6c** are more sterically congested.

Heating **6a** and **6b** in the presence of **7** at 50 °C produced only 89% and 86% of adduct **8** even though no starting compounds (**6a** and **6c**) were recovered (entries 2 and 6, Table 1). This encouraged further study and revealed that a small portion of released nitroso **2a** underwent reaction to form azo-oxy compound **9**.[8] To the best of our knowledge, the formation of **9** directly from a pyridinylnitroso precursor has not been reported. Further analyses of solutions of 6-methyl-2-nitrosopyridine, **2a**, showed that while **2a** existed in equilibrium with the corresponding azodioxy dimer,[9] azo-oxy compound **9** slowly formed upon standing in pure organic solvent[10] (Figure 1).

The retro iminonitroso Diels-Alder reaction was also observed when we subjected racemic spirocyclic adduct **11b**[3d] to the catalytic asymmetric iminonitroso Diels-Alder reaction conditions. Trapping of nitroso agent **2b** generated from the degradation of **11b** with 1,3-cyclohexadiene **7** in the presence of $Cu(I)PF_6(MeCN)_4$ and (*S*)-BINAP produced cycloadduct **12** with moderate enantioselectivity (19% yield, 52% *ee*, Scheme 3).[11] The absolute stereochemistry was proposed based on the literature-based mechanistic model.[12]

To minimize the competing non-catalytic asymmetric iminonitroso Diels-Alder reaction process, work-up temperature was modified from room temperature to −20 °C. By doing this, cycloadduct **11b** was obtained in 74% yield and with an improved *ee* value (entries 1 and 2, Table 2). Under these optimized conditions, an extended study was performed using different iminonitroso reagents **2a**–**c** and chiral phosphine ligands.[13] Use of chiral ligand (*S*)-DifluoroPhos and 6-methyl-2-nitrosopyridine, **2a**, provided spirocyclic adduct **11a** with the highest *ee* value (96% *ee*, entry 5). A dramatically decreased *ee* value was observed when 5-methyl-3-nitrosoisoxazole, **2c**, was used (28% *ee*, entry 6).

Retro Diels-Alder reactions were also attempted in solid phase using NDA adducts attached to resin. The adduct resins **13a** and **13b**,[14] derived from α-terpinene, were exposed to various dienes in a microwave cavity for 5 min, then products **15** were cleaved from the resin with TBAF and analyzed by LC/MS.[15] The results are summarized in Table 3. While the nitrophenyl NDA adduct **13a** provided quantitative retro-NDA adducts with all tested dienes, the pyridyl derivative **13b** was less reactive under the same conditions (entries 1–6, Table 3). Reactions with unsymmetric dienes such as 2,4-hexadien-1-ol, **7b**, and 1-methoxy-1,3-cyclohexadiene, **7c**, gave cycloadducts as mixtures of two regioisomers in good to excellent yields (entries 4–6).

In summary, we found that various iminonitroso cycloadducts can undergo retro nitroso Diels-Alder reactions in both solution and solid phase under thermal or Cu(I)-mediated conditions. By trapping the released nitroso dienophiles with separate dienes, new adduct scaffolds were generated in an efficient fashion. Use of chiral ligands in the Cu(I)-medicated reactions gave new cycloadducts enantioselectively. We hope that the chemistry we describe here can help expand the use of retro iminonitroso Diels-Alder reactions in organic syntheses.

Acknowledgments

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References and notes

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7. General procedures: To a solution of cycloadduct **6** (0.05 mmol) in $CHCl_3$ (2 mL) was added 1,3-cyclohexadiene **7** (24 uL, 0.25 mmol). The reaction mixture was stirred at room temperature for 24 h, or heated at 50 °C and monitored by TLC until **6** was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (hexanes:EtOAc = 5:1) to yield compound **8** as a yellowish solid.
8. Spectral data of **9** (yellowish solid): mp: 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 1 H), 8.17 (d, J = 8.2 Hz, 1 H), 7.80 (m, 1 H), 7.76 (m, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 2.70 (s, 3 H), 2.63 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 158.7, 157.1, 155.8, 139.2, 138.2, 127.0, 123.8, 115.6, 114.9, 24.6, 24.5; (FAB) MS: 229 $[M+1]^+$.
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11. Cu(I)-mediated retro NDA reaction with spirocyclic adduct **11b**: To an oven dried round-bottomed flask was added anhydrous CH_2Cl_2 (5 mL), $Cu(I)PF_6(CH_3CN)_4$ (9 mg, 0.025 mmol,) and (*S*)-BINAP (16 mg, 0.025 mmol) in order. After stirring for 0.5 h under Ar, the reaction mixture was cooled to −78 °C, racemic compound **11b** (94 mg, 0.25 mmol) and 1,3-cyclohexadiene (0.1 mL) were added. The solution was gradually warmed to room temperature over 2 h. The crude product was chromatographed on silica gel (hexanes:EtOAc = 5:1) to afford **11b** (70 mg, yield 75%, *ee* = 24%) as a white solid and **12** (9 mg, yield 19%, *ee* = 52%) as a colorless oil, respectively. Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (95:5 hexanes:2-propanol), 1.0 mL/min, for **11b**, major enantiomer t_r = 19.6 min, minor enantiomer t_r = 18.0 min; for **12**, major enantiomer t_r = 14.8 min, minor enantiomer t_r = 10.9 min.
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13. General procedures: To a oven-dried round-bottomed flask was added anhydrous CH_2Cl_2 (4 mL), $Cu(I)PF_6(CH_3CN)_4$ (9 mg, 0.025 mmol,), and chiral phosphine ligand (0.025 mmol) in order under

Ar. After stirring for 1 h, the reaction mixture was cooled to −78 °C, nitroso compound **2** (0.30 mmol) was added. The resulting dark blue mixture was stirred for 10 min, then spriocyclic diene **10** (0.10 g, 0.36 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. The solution was gradually warmed to −20 °C over 2 h and chromatographed immediately on silica gel to afford nitroso-Diels-Alder adduct **11**. Compound **11a** (colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 6 H), 6.64 (d, *J* = 6.9 Hz, 1 H), 6.58 (d, *J* = 7.2 Hz, 1 H), 5.14 (s, 3 H), 4.74 (s, 1 H), 3.59 (m, 4 H), 2.43 (s, 3 H), 2.03 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 134.3, 130.2, 128.5, 128.0, 127.9, 116.4, 108.7, 86.2, 70.4, 67.0, 60.1, 42.2, 41.7, 29.2; HPLC: Chiralcel AD-H column (95:5 hexanes:2-propanol), 1.0 mL/min, major enantiomer t_r = 14.6 min, minor enantiomer t_r = 15.6 min; Compound **11b** (white solid, mp: 123–124 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 3.9, 4.8, 1 H), 7.49 (m, 1 H), 7.36 (m, 6 H), 6.78 (d, *J* = 12 Hz, 1 H), 6.21 (m, 1 H), 6.04 (m, 1 H), 5.14 (s, 3 H), 4.74 (s, 1 H), 3.52 (m, 4 H), 2.04 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 146.8, 139.2, 137.3, 134.1, 130.3, 128.3, 127.8, 127.6, 125.5, 118.5, 116.8, 111.7, 86.2, 69.9, 66.8, 60.0, 42.0, 41.4; Compound **11c** (colorless oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 6.33 (m, 1 H), 6.22 (m, 1 H), 5.65 (s, 1 H), 5.13 (s, 2 H), 4.69 (s, 1 H), 4.64 (s, 1 H), 3.44 (m, 4 H), 2.30 (s, 3 H), 1.97 (m, 1 H), 1.90 (m, 1 H), 1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.0, 136.7, 134.2, 131.7, 128.5, 128.0, 95.6, 85.7, 67.1, 61.4, 42.2, 41.5; HPLC: Chiralcel AD-H column (88:12 hexanes:2-propanol), 1.0 mL/min, major enantiomer t_r = 26.1 min, minor enantiomer t_r = 31.0 min.

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15. Gerneral procedures: Resin-bounded α-terpinene HDA adduct **13** (~ 50 mg) was washed three times with THF, then 2 mL of a 0.25 M solution of diene in DMF was added. The resin slurry was transfered to a vial and exposed to 100 °C in a microwave cavity for 5 min. The resultant resin was washed five times with THF and the product was released by treatment with 0.1 M TBAF in 1 mL of THF for 30 min. The obtained product was analyzed by LC/MS. For analytical data of compound **15**, sec ref. [14].

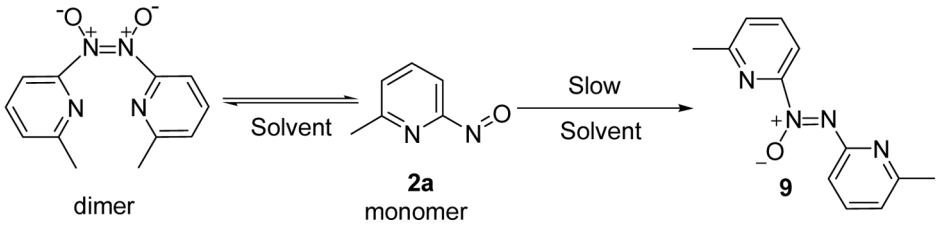
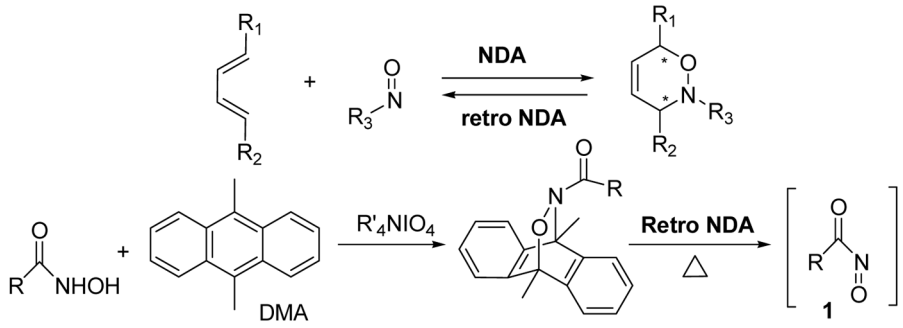
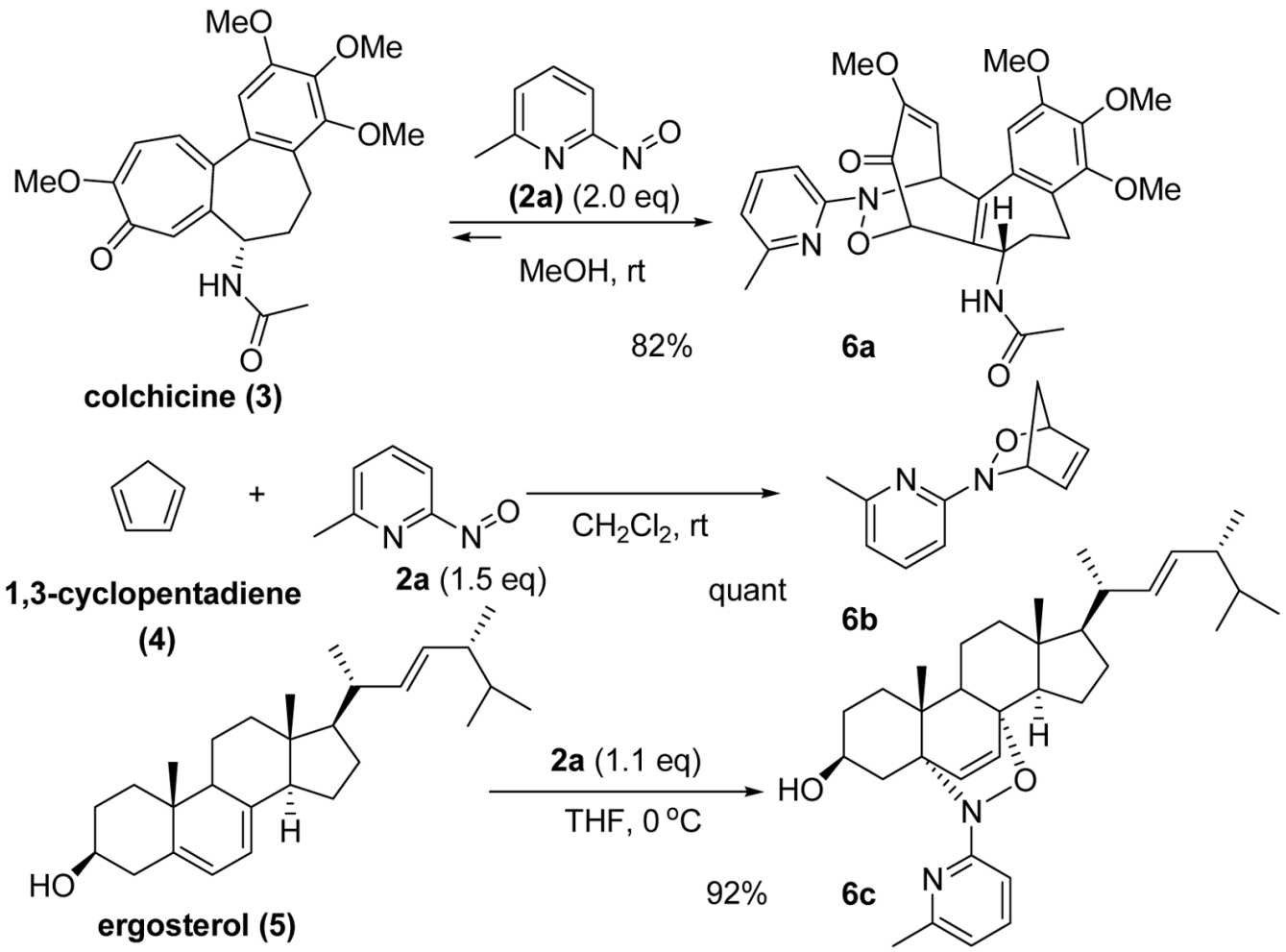


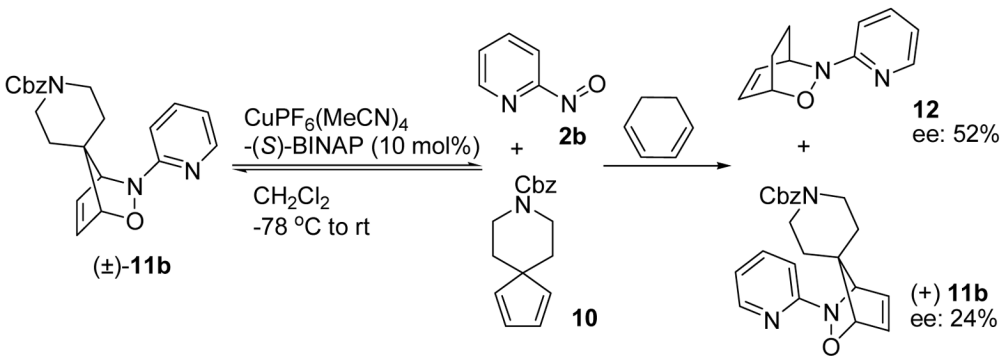
Figure 1.
Solution state equilibrium of 6-methyl-2-nitrosopyridine **2a** and generation of **9**.



Scheme 1.
Nitroso Diels-Alder and retro acylnitroso Diels-Alder reaction.



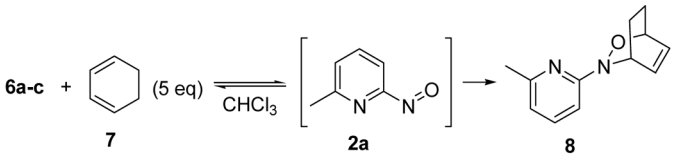
Scheme 2.
Nitroso Diels-Alder reaction with various dienes.



Scheme 3.
Retro NDA reaction of spirocyclic adduct **11b**.

Table 1

Retro NDA reaction of iminonitroso cycloadducts **6a–c**



Entry	Adduct	Temp. (°C)	Time (h)	8 (%)[a]
1	**6a**	25	24	43
2	**6a**	50	5	89
3	**6b**	25	24	0
4[b]	**6b**	>50	-	0
5	**6c**	25	24	20
6	**6c**	50	2	86
7[c]	**6c**	25	24	54

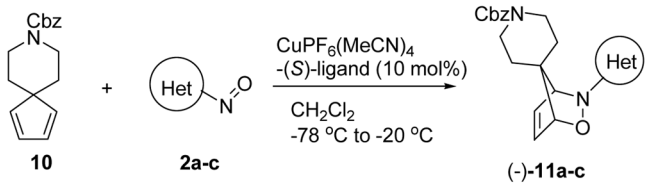
[a] Isolated yields reported.

[b] Temperature was increased from 50 °C to 70 °C (reflux).

[c] $CHCl_3$/1,3-cyclohexadiene **7** (10% v:v) as solvent.

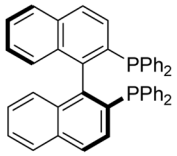
Table 2

NDA Reaction with various iminonitroso agents and chiral phosphine ligands

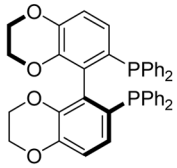


10 **2a-c** **(-)-11a-c**

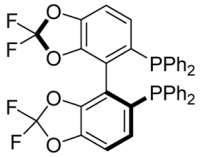
Ligand :



(*S*)-BINAP

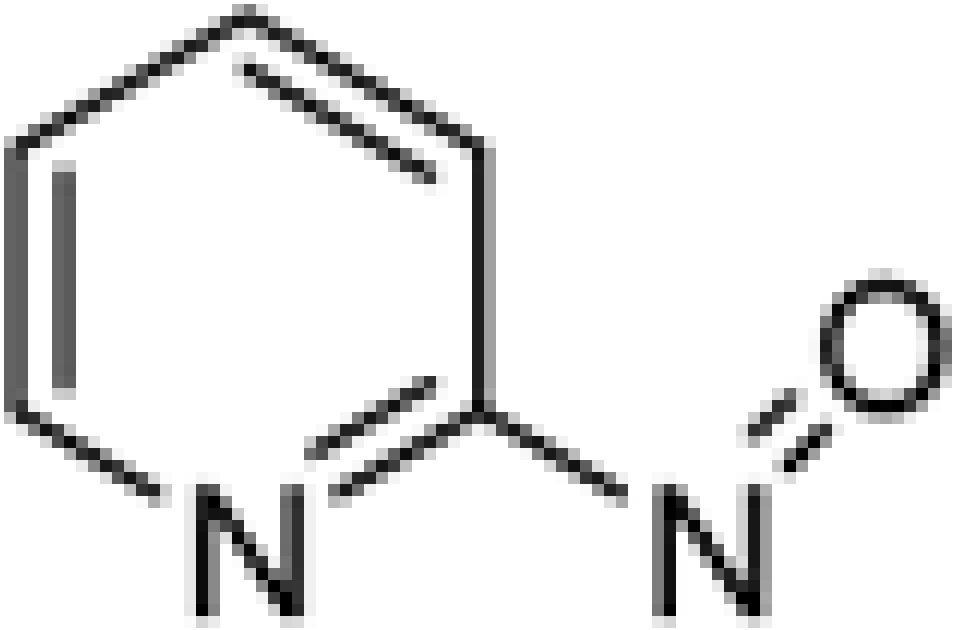


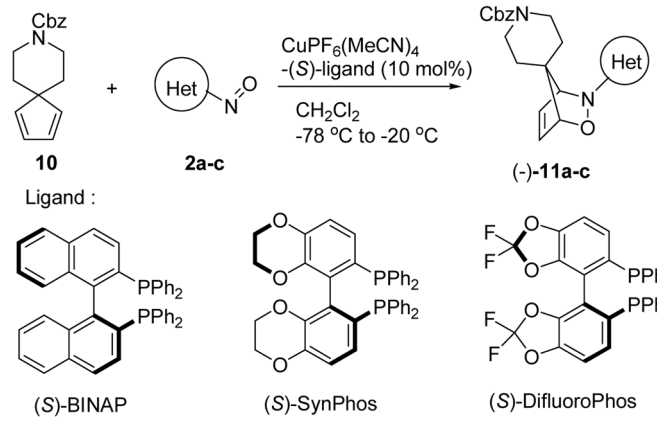
(*S*)-SynPhos



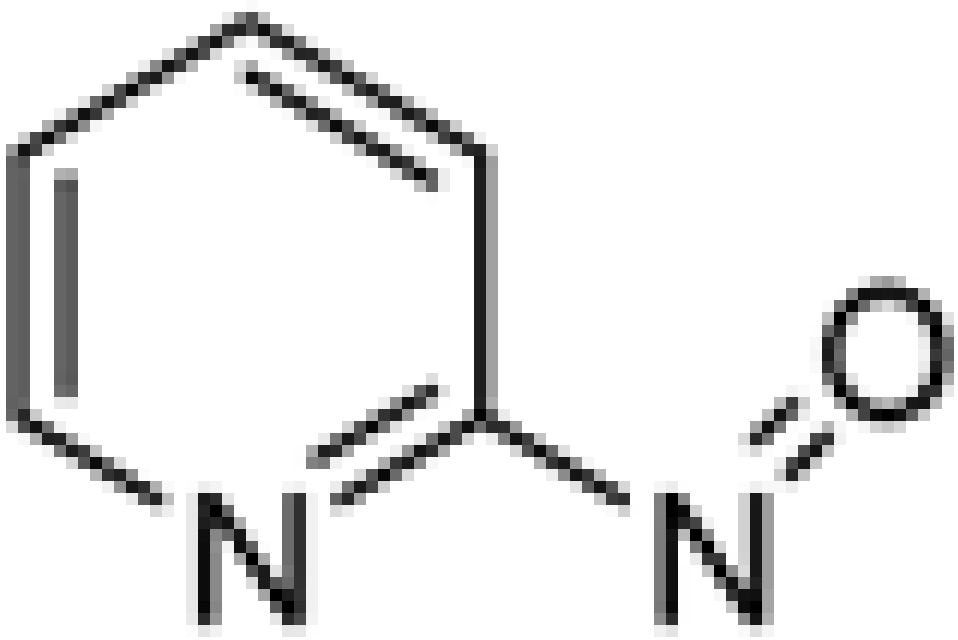
(*S*)-DifluoroPhos

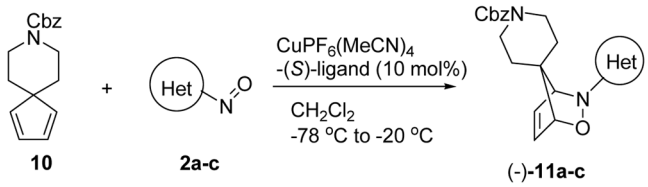
Entry	Nitroso	Ligand
1[a]	**2b**	(*S*)-BINAP





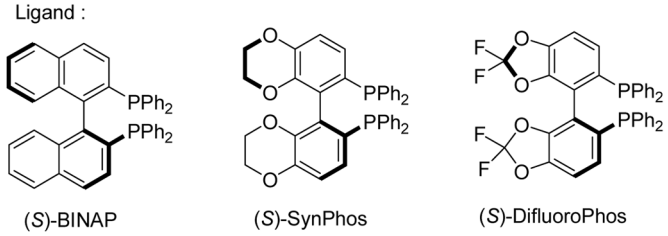
Entry	Nitroso	Ligand
2[b]	**2b**	(*S*)-BINAP





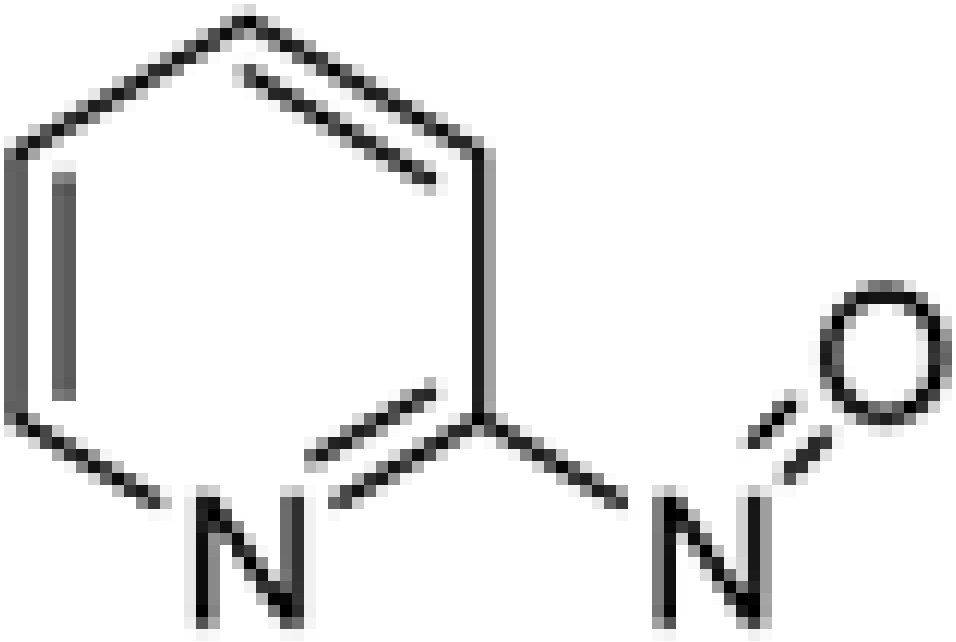
10 **2a-c** **(-)-11a-c**

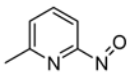
Ligand :

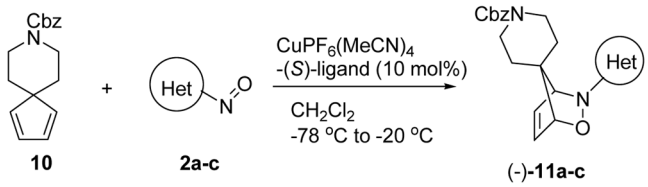


(*S*)-BINAP (*S*)-SynPhos (*S*)-DifluoroPhos

Entry	Nitroso	Ligand
3[b]	**2b**	(*S*)-DifluoroPhos
4[b]	**2a**	(*S*)-SynPhos

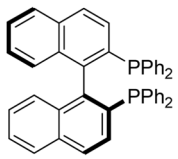




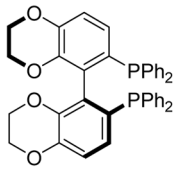


10 **2a-c** **(-)-11a-c**

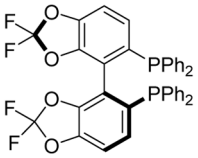
Ligand :



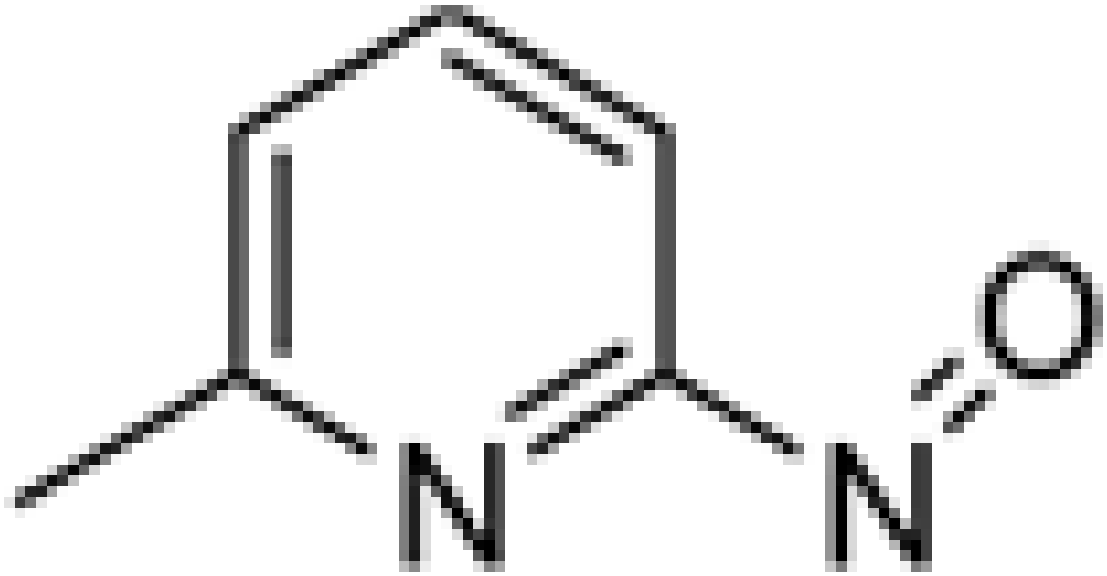
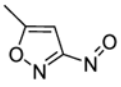
(*S*)-BINAP



(*S*)-SynPhos



(*S*)-DifluoroPhos

Entry	Nitroso	Ligand
5[b]	**2a** 	(*S*)-DifluoroPhos
6[b]	**2c** 	(*S*)-DifluoroPhos

[a] Reaction was worked up at room temperature.

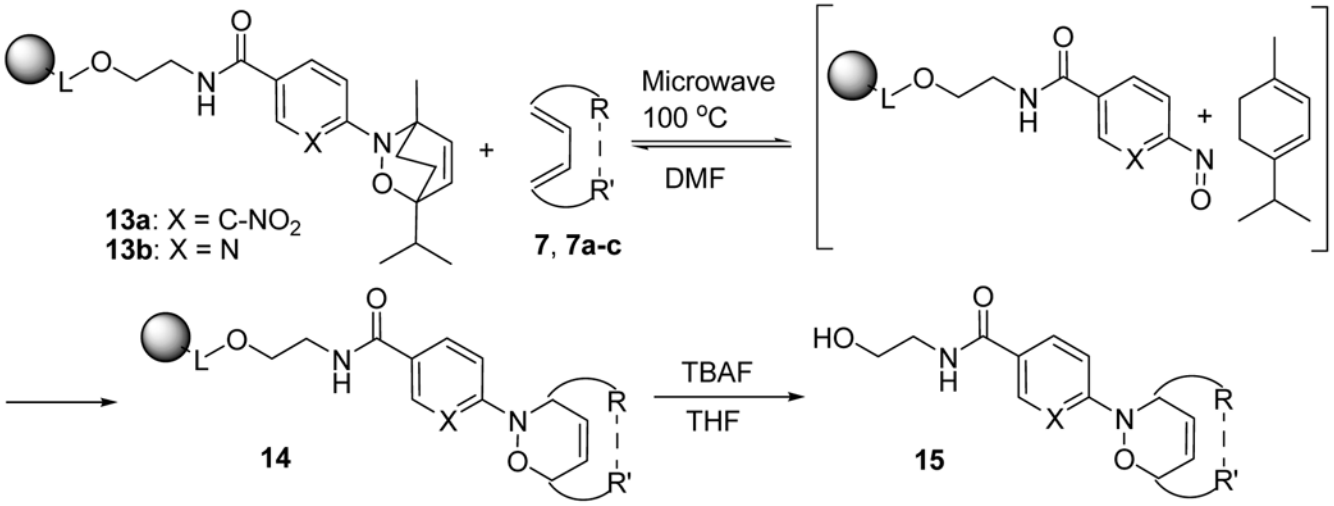
[b] Reaction was worked up at −20 °C.

[c] Isolated yields reported.

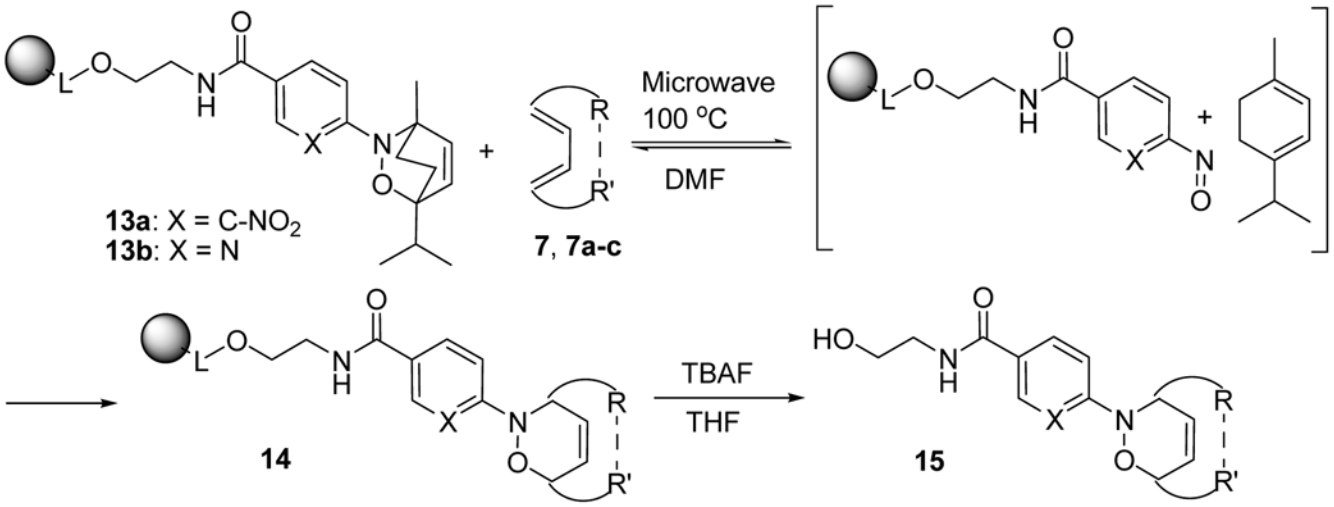
[d] Determined by Chiral HPLC.

Table 3

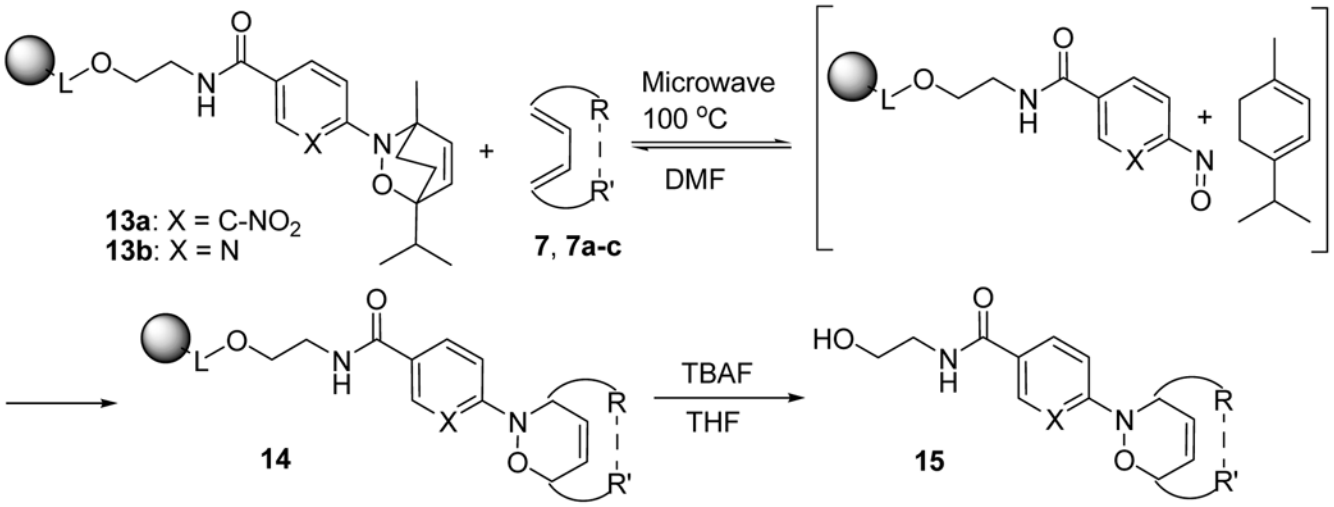
Retro HDA reaction of resin-bounded α-terpinene adducts with various dienes

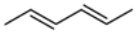
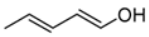


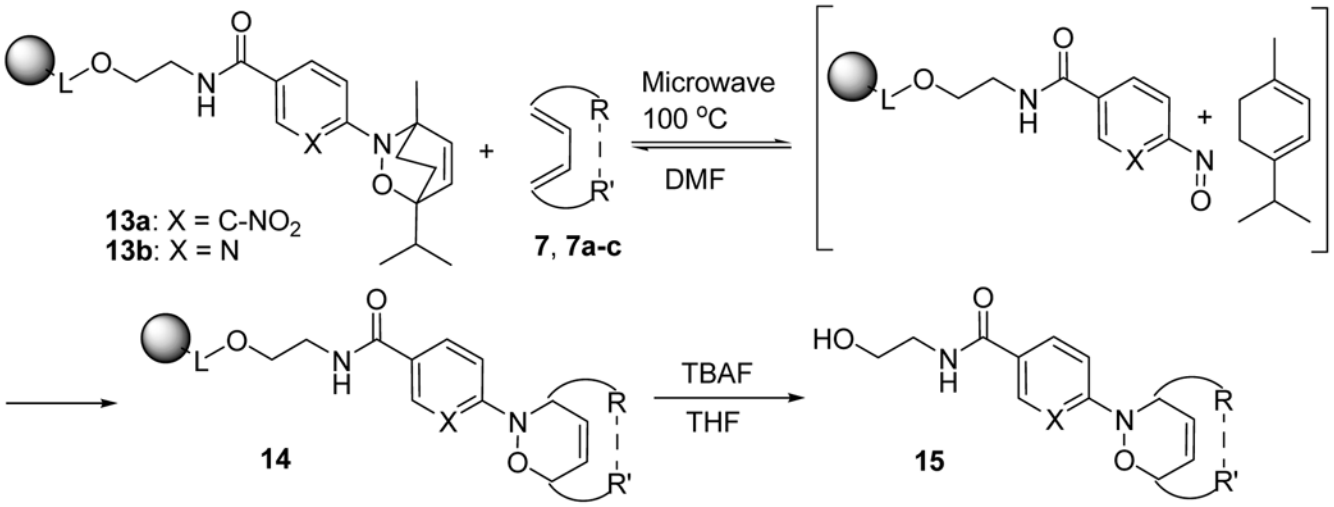
Entry	Adduct	Diene	15 (%)[a]
1	**13a**	**7** 	99



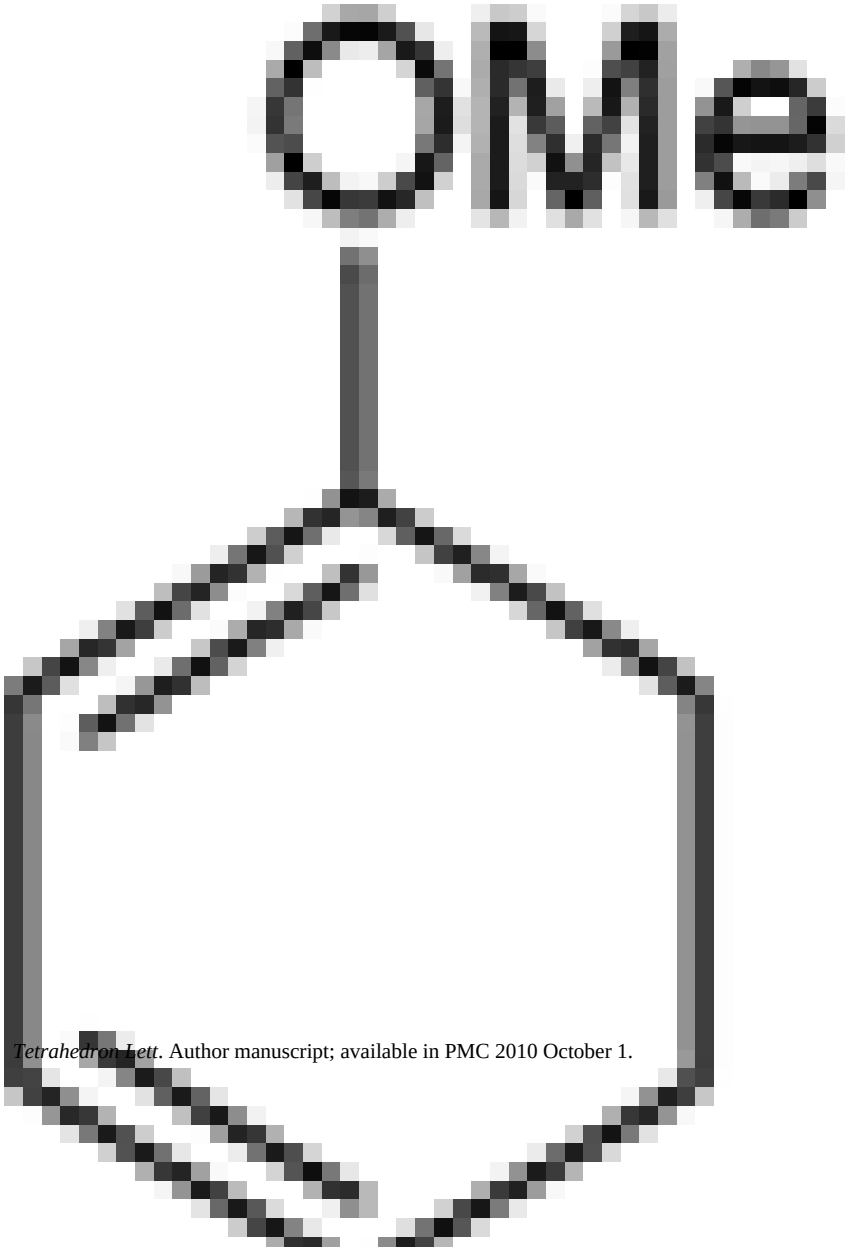
Entry	Adduct	Diene	15 (%)[a]
2	**13b**	**7**	81

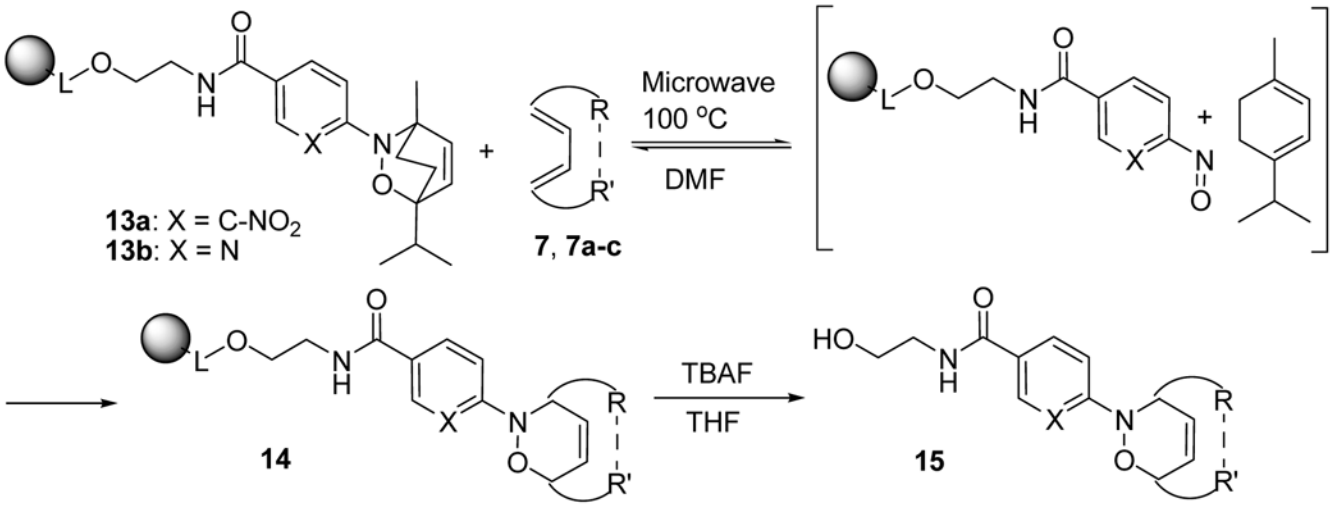


Entry	Adduct	Diene	15 (%)[a]
3	**13a**	**7a** 	99
4	**13a**	**7b** 	99 (6:4)

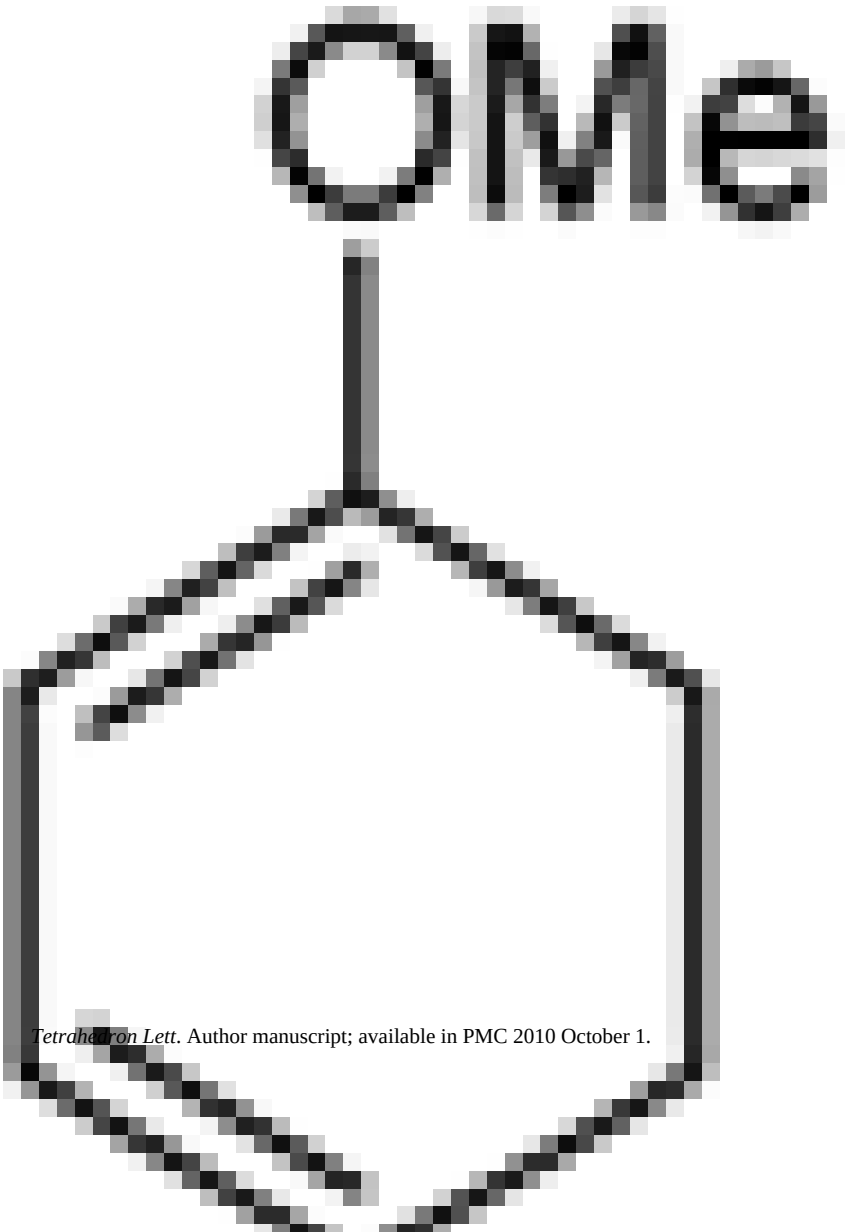


Entry	Adduct	Diene	15 (%)[a]
5	**13a**	**7c**	99 (> 9:1)





Entry	Adduct	Diene	15 (%)[a]
6	**13b**	**7c**	75 (6:4)



[a] Determined by LC/MS.