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Intermolecular Alkyl Radical Addition to the Carbon-Nitrogen Double Bond of Oxime Ethers and Hydrazones

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Abstract: Intermolecular carbon radical addition to the carbon-nitrogen double bond of oxime ethers and hydrazones was studied. The reaction of unactivated aldoxime ethers proceeded smoothly in the presence of $BF_3 \cdot OEt_2$ to give the alkylated products in high yields *via* the free radical-mediated carbon-carbon bond-forming process.

INTRODUCTION

Radical reactions have emerged as a valuable tool for organic chemists, providing many advantages over ionic chemistry.[1] Although the use of radical reactions in organic synthesis has continued to increase, intermolecular carbon radical additions to the carbon-nitrogen double bond of imine derivatives have received much less attention.[2-4] The nucleophilic addition to the carbon-nitrogen double bond constitutes an extremely useful method for preparing a variety of amines. Most synthetically useful reactions are restricted to the use of organometallic reagents.[5] However, the addition of organometallic reagents is frequently plagued by the enolization of the substrates with acidic α-hydrogens, poor electrophilicity of the imino group and the formation of reductive coupling products.[5] The mild addition of a strictly neutral species such as an uncharged free radical would provide a highly general solution to the fundamental problems that are associated with the strong basicity of organometallic reagents.[4] We report here in detail the first example of intermolecular carbon radical addition to the carbon-nitrogen double bond of aldoxime ethers, providing a new efficient carbon-carbon bond-forming method for the synthesis of a variety of amines.[6]

Among the different types of radical acceptors containing a C=N bond, the oxime ether and hydrazone are well known to be excellent radical acceptors because of the extra stabilization of the intermediate aminyl radical provided by the lone pair on the adjacent heteroatom.[7] However, the intermolecular carbon radical addition to oxime ethers and hydrazones has received much less attention compared to the intramolecular radical reaction. In the course of our investigations towards the intramolecular radical reaction of oxime ethers,[8] we became interested in the development of a general and practical method for the carbon-carbon bond-forming reactions

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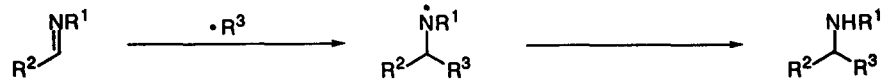
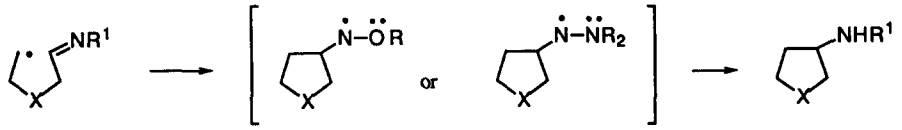
Intermolecular Reaction



Intramolecular Reaction



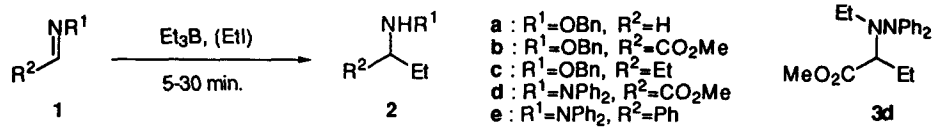
oxime ether : R^1=OR
hydrazone : R^1=NR_2

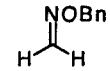
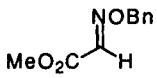
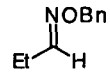
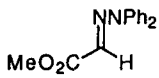
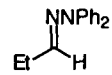
based on the intermolecular radical addition to imine derivatives. Hart's group reported the first studies on the intermolecular alkyl radical addition to the sterically less hindered formaldoxime ether.[2] Recently, the intermolecular radical-mediated acylation using α-sulfonyl oxime ether has been reported by the research group of Kim.[3] We have also recently reported the diastereofacial control in intermolecular radical additions to the sultam derivative of glyoxylic oxime ether.[4] These substrates are activated by the adjacent electron-withdrawing substituent. On the other hand, nothing has been known about the reactivity of unactivated substrates in the intermolecular radical reaction.

RESULTS AND DISCUSSION

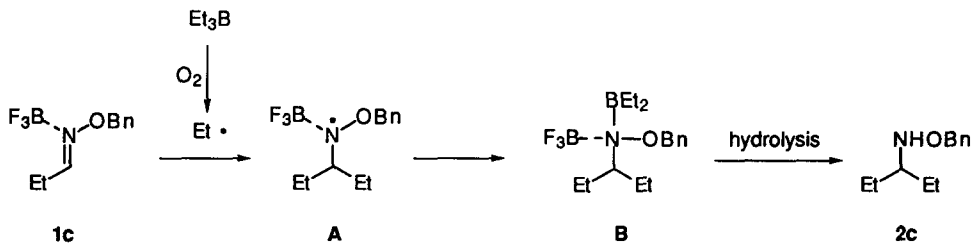
Since the intermolecular reactivity of aldoxime ethers and hydrazones is expected to be quite different from the intramolecular reactivity, we initially explored the intermolecular addition of an ethyl radical to different types of substrates **1a-e**. The reactions were run in dichloromethane at 25 °C by using Et_3B as a radical initiator and the results are summarized in Table 1. As expected, the addition of an ethyl radical, generated from Et_3B and O_2, to the sterically less hindered formaldoxime ether **1a**[2] proceeded smoothly to give an excellent yield of the ethylated product **2a** (Entry 1). High chemical yield was also observed even at -78 °C in the radical addition to glyoxylic oxime ether **1b** which is activated by an electron-withdrawing substituent (Entries 2 and 3). It is important to note that no reaction of aldoxime ether **1c** occurred under the same reaction conditions and 94% of the starting compound **1c** was recovered (Entry 3). These results suggest that the ethyl radical does add to glyoxylic oxime ether **1b** having lower LUMO energy, but does not add to the unactivated aldoxime ether **1c**. To enhance the reactivity of the oxime ether group of **1c** as a radical acceptor toward nucleophilic alkyl radicals, we examined the effect of Lewis acids which would lower the LUMO energy of the radical acceptor and decrease the electron density at the iminyl carbon atom.[9] Among several Lewis acids evaluated,[10] a twofold excess of $BF_3{\cdot}OEt_2$ was found to be most effective for the successful radical addition to the unactivated aldoxime ether **1c** which gave the ethylated products **2c** in 95% yield within 5 min (Entries 5-10). It should be noted that the aliphatic aldoxime ether having sensitive α-hydrogens reacted smoothly with an alkyl radical under these conditions to afford the adduct in high yields. In this reaction, more than a stoichiometric amount of $BF_3{\cdot}OEt_2$ was required because $BF_3{\cdot}OEt_2$ is trapped by the nitrogen atom of either the starting material or the product. Actually, reaction of aldoxime ether **1c** with ethyl radical did not proceed in the presence of a catalytic

Table 1. Ethyl radical addition to imine derivatives **1**[a]



Entry	Imine derivative		Lewis acid[b]	Temp (°C)	Product	Yield (%)[c]
1		**1a**	none	25	**2a**	90
2		**1b**	none	25	**2b**	97
3		**1b**	none	-78	**2b**	95
4		**1c**	none	25	**2c**	n.r. (94)
5		**1c**	$BF_3{\cdot}OEt_2$	25	**2c**	95
6		**1c**	$BF_3{\cdot}OEt_2$	-78	**2c**	90
7		**1c**	TFA	25	**2c**	13 (83)
8		**1c**	Et_2AlCl	25	**2c**	14 (78)
9		**1c**	$Zn(OTf)_2$	25	**2c**	28 (70)
10		**1c**	$Yb(OTf)_3$	25	**2c**	17 (68)
11		**1d**	none	25	**2d** + **3d**	41 [**2d**] + 43 [**3d**]
12		**1e**	none	25	**2e**	n.r. (92)
13		**1e**	$BF_3{\cdot}OEt_2$	25	**2e**	n.r. (72)

[a]Reaction conditions: Under a nitrogen atmosphere, to a solution of imine derivative in CH_2Cl_2 were successively added EtOH (2.5 equiv), Lewis acid (2 equiv), ethyl iodide (5 equiv) and Et_3B (2.5 equiv, 1.0 M solution in hexane) at 25 °C. [b]2 equiv. of the Lewis acid was used. [c]Yields of isolated product; Yields in parentheses are for the recovered starting material.

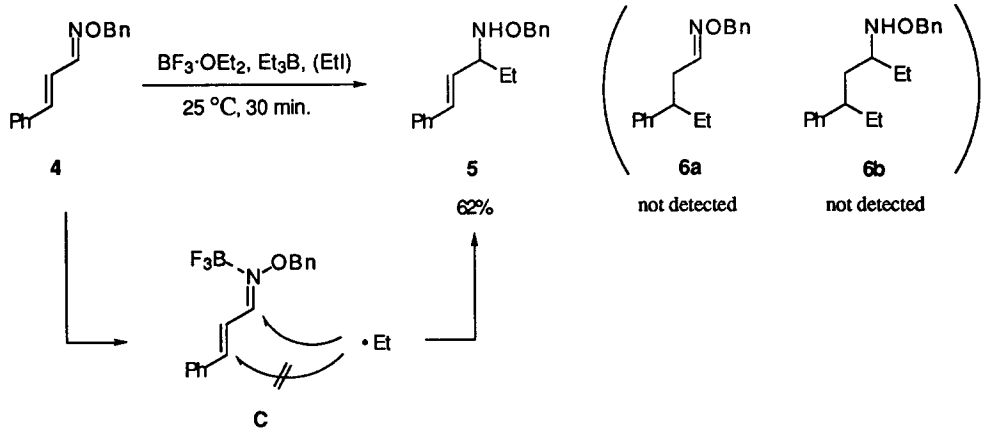


Scheme 1.

amount of $BF_3{\cdot}OEt_2$ but recovered the starting material **1c**. Additionally, it was also found that the ethyl radical addition using Et_3B (2.5 equiv.) proceeded in the absence of EtI. Based on these results, we propose the reaction mechanism as follows: The ethyl radical adds intermolecularly to the $BF_3{\cdot}OEt_2$-activated aldoxime ether **1c** to form the aminyl radical **A** which is then trapped by Et_3B to form the complex product **B** (Scheme 1). The desired ethylated product **2c** is obtained as a result of the hydrolysis of **B**. We have also investigated the

radical addition to hydrazones **1d** and **1e**. Under analogous conditions the reaction of glyoxylic hydrazone **1d** gave the desired *C*-ethylated product **2d** in 41% yield, even in the absence of a Lewis acid, along with the diethylated product **3d** (43%) which was formed as a result of the additional *N*-ethylation of the *C*-ethylated product **2d** (Entry 11). In the absence of Lewis acids, radical addition to the unactivated hydrazone **1e** did not take place but recovered completely the starting material (Entry 12). Hydrazone **1e**, by contrast with aldoxime ether **1c**, did not react with an ethyl radical even in the presence of $BF_3{\cdot}OEt_2$ (Entry 13). The unsuccessful reaction is presumably due to the formation of an insoluble complex from $BF_3{\cdot}OEt_2$ and the hydrazone **1c** which was observed by the spot with low Rf value on TLC. These observations suggest that $BF_3{\cdot}OEt_2$ is an effective Lewis acid for the activation of the carbon-nitrogen double bond of oxime ethers.

It is known that the carbon-carbon double bond of α,β-unsaturated carbonyl compounds is a good radical acceptor. The orientation of radical addition to α,β-unsaturated carbonyl compounds is influenced by steric factors and the addition takes place mainly at the β-carbon.[11] We next investigated the reaction site of α,β-unsaturated oxime ether **4** (Scheme 2). Only in the presence of $BF_3{\cdot}OEt_2$, a highly selective 1,2-addition proceeded to give **5** with no detection of 1,4-adducts **6a** and **6b**. It is noteworthy that in the present reactions the carbon-carbon double bond of α,β-unsaturated systems does not participate and remains intact. Thus, the oxime ether group activated by $BF_3{\cdot}OEt_2$ was found to be exclusively an excellent radical acceptor.

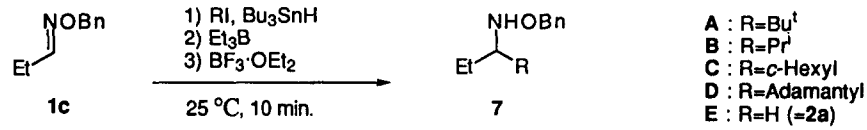


Scheme 2.

The radical addition to oxime ether **1c** was also studied using different radical precursors such as *tert*-butyl, isopropyl, cyclohexyl and adamantyl iodides as shown in Table 2. Treatment of oxime ether **1c** with alkyl iodides, Bu_3SnH and Et_3B followed by the addition of $BF_3{\cdot}OEt_2$ gave the desired *C*-alkylated products **7A-D** though a small amount of the ethylated product **2c** was formed as a result of the competitive addition of an ethyl radical generated from Et_3B. Not only secondary alkyl radicals but also bulky tertiary alkyl radicals worked well. In all cases, we have found that the addition of $BF_3{\cdot}OEt_2$ as a final reagent is crucial for the successful radical reaction. Actually, the addition of $BF_3{\cdot}OEt_2$ prior to those of alkyl iodide, Bu_3SnH and Et_3B underwent tributyltin hydride-mediated reduction to give significant amounts of the corresponding benzyloxyamines **7E** (=**2a**).[12] The radical alkylation reaction would proceed as follows: 1) The stannyl radical, generated from BEt_3 and Bu_3SnH, reacts with the secondary or tertiary alkyl iodide to give the alkyl radicals (R·). 2) The alkyl radical attacks intermolecularly the $BF_3{\cdot}OEt_2$-activated oxime ether **1c** to afford the intermediate aminyl radical **D**

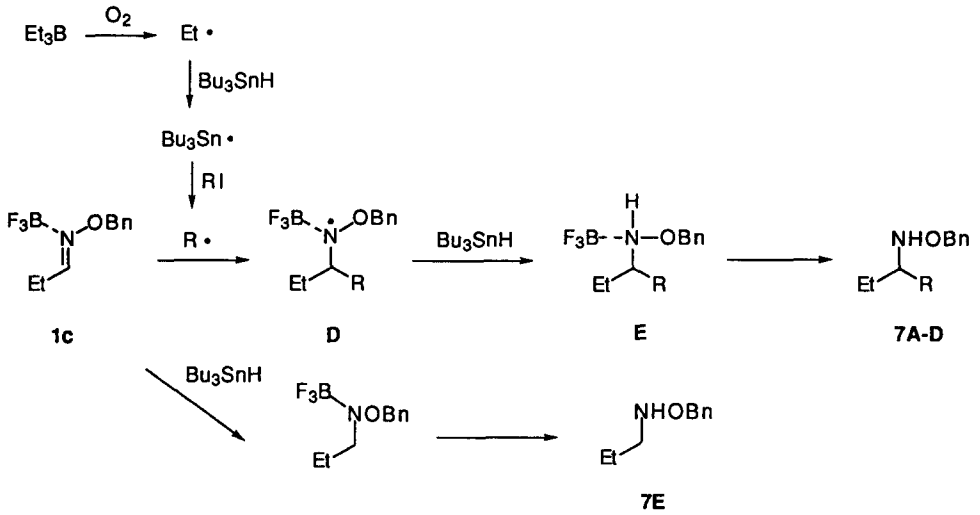
which was then reacted with Bu_3SnH (Scheme 3). When $BF_3{\cdot}OEt_2$ was initially added, the $BF_3{\cdot}OEt_2$-activated oxime ether would be preformed and successively reduced with Bu_3SnH to give **7E**.

Table 2. Alkyl radical addition to aldoxime ether **1c**[a]



Entry	R	Product	Yield (%)[b]
1	Bu^t	**7A**	98
2	Pr^i	**7B**	76
3	*c*-Hexyl	**7C**	58
4	Adamantyl	**7D**	41 (28)

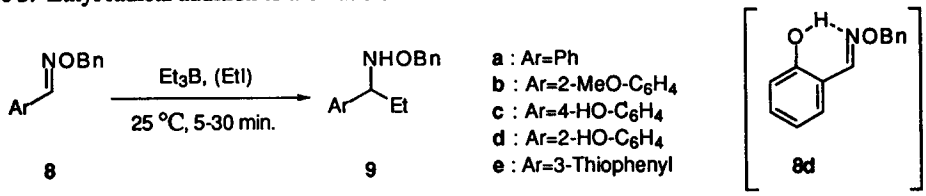
[a]Under the same reaction conditions, to a solution of oxime ether in CH_2Cl_2 were successively added Bu_3SnH (2.5 equiv), alkyl iodide (20 equiv), Et_3B (2.5 equiv, 1.0 M solution in hexane) and then $BF_3{\cdot}OEt$ (2 equiv) as a final reagent. [b]Yields of isolated product; Yields in parentheses are for the recovered starting material.



Scheme 3.

Several examples of the present radical addition to the aromatic oxime ethers **8a-e** bearing a variety of substituents are shown in Table 3. The reaction of simple benzaldoxime ether **8a** proceeded smoothly in the presence of $BF_3{\cdot}OEt_2$ to give the adduct **9a** in 98% yield (Entry 2). The benzaldoxime ether **8b** containing an electron-donating substituent, which was expected to be less reactive than **8a**, also produced an excellent yield of the ethylated products **9b** (Entry 4). The reaction of the oxime ether **8c** involving a 4-hydroxy group was also successful with no protection of the hydroxy group (Entry 6). Only a modest alkylation yield was observed in the reaction of intramolecularly hydrogen-bonded salicylaldehyde derivative **8d** with the recovery of

Table 3. Ethyl radical addition to aromatic oxime ethers **8a-e**



8 9 8d

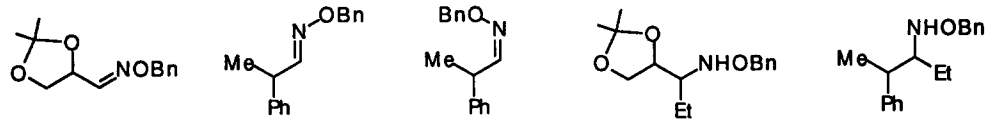
Entry	Substrate	Lewis acid[a]	Yield (%)[b]
1	**8a**	none	19 (73)
2	**8a**	$BF_3{\cdot}OEt_2$	98
3	**8b**	none	15 (72)
4	**8b**	$BF_3{\cdot}OEt_2$	93
5	**8c**	none	n.r.
6	**8c**	$BF_3{\cdot}OEt_2$	96
7	**8d**	none	5 (89)
8	**8d**	$BF_3{\cdot}OEt_2$	41 (38)
9	**8e**	none	n.r.
10	**8e**	$BF_3{\cdot}OEt_2$	57 (25)

[a]2 equiv. of the Lewis acid was used. [b]Yields of isolated product; Yields in parentheses are for the recovered starting material.

Table 4. Ethyl radical addition to oxime ethers **10** and **11**[a]

Entry	Oxime ether	Conditions[b]	Product	Yield (%)[c]
1	**10**	A	**12**	70 (1:1)
2	**10**	B	**12**	trace
3	**10**	C	**12**	55 (1:1)
4	***E*-11**	B	**13**	72 (13:1)
5	**Z-11**	B	**13**	55 (5:1)
6	***E*-11**	C	**13**	69 (17:1)

[a]2 equiv. of $BF_3{\cdot}OEt_2$ was used. [b]Condition A: in CH_2Cl_2, 25 °C; Condition B: in CH_2Cl_2, -78 °C; Condition C: in toluene, -78 °C. [c]Yields of isolated product; Ratios in parentheses are for diastereoselectivity based on ^1H NMR.



10 *E*-11 *Z*-11 12 13

the starting material in 38% yield (Entry 8). These observations suggest that aromatic oxime ethers are also effectively activated by $BF_3{\cdot}OEt_2$ although $BF_3{\cdot}OEt_2$ was less effective for the activation of the hydrogen-bonded carbon-nitrogen double bond. The reaction of the heterocyclic oxime ether **8e** derived from 3-thiophenecarboxaldehyde gave the ethylated product **9e** in 57% yield (Entry 10).

We then attempted the diastereoselective radical reaction using two types of aldoxime ethers **10** and **11**

(Table 4). In the reaction of an *E/Z* mixture of **10**, no 1,2-stereoinduction was observed even at lower temperature and a 1:1 mixture of ethylated product **12** was obtained (Entries 1-3). In the case of ***E*-11**, a 13:1 diastereomeric mixture of the desired ethylated product **13** was obtained when the radical reaction was carried out at -78 °C in dichloromethane (Entry 4). The stereoselectivity for **13** was shown to be dependent on the geometry of the oxime ether group. Thus, the use of **Z-11** as the starting material led to decreased diastereoselectivity to 5:1 (Entry 5). As an example of the solvent effect, a high degree of stereocontrol was achieved by the replacement of dichloromethane with toluene as a solvent (Entry 6).

This newly-found radical reaction has several advantages over the conventional organometallic reactions which require rigorous reaction conditions such as carefully dried reagents, solvents and apparatus. In agreement with the general advantages of the radical reactions over the anionic reaction, the present radical method would be useful because of the exceptional tolerance of functional groups such as aromatic, heterocycle, alcohol, acetal, ester and amide moieties.

CONCLUSION

We have developed the $BF_3 \cdot OEt_2$-mediated intermolecular alkyl radical addition to a wide range of aldoxime ethers such as aliphatic, aromatic, heterocyclic, and unsaturated congeners. The reaction using Et_3B as a radical initiator proceeded smoothly to afford the corresponding benzyloxyamines in high yields. The present method provides a useful route for the synthesis of a variety of amines.

EXPERIMENTAL SECTION

General. ^1H NMR spectra were measured using Varian Gemini-200 (200 MHz) instrument. ^{13}C NMR spectra were measured using Varian Gemini-200 (50 MHz). IR spectra were measured with a Perkin Elmer 1600 FTIR machine and mass spectra were taken by Hitachi M-4100 spectrometer. Mps were determined with a Kofler-type hot-stage apparatus and are uncorrected. For flash column chromatography, E. Merck Kieselgel 60 (230-400 mesh) was used. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). According to many examples[13] of the radical reactions using Et_3B, radical reactions were carried out under N_2 (99.99%) atmosphere using commercially available CH_2Cl_2 as solvent. Triethylborane proved to be an effective radical initiator in the presence of trace amounts of oxygen.[13b, c] Other roles of Et_3B, however, are not clear.

General procedure for the preparation of oxime ethers and hydrazones.

Method A: To a solution of aldehyde (10 mmol) in MeOH (50 ml) were added *O*-benzylhydroxylamine hydrochloride (10 mmol) and sodium acetate (20 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 1 h, the solvent was evaporated at reduced pressure. The resulting residue was diluted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated at reduced pressure.

Method B: To a solution of aldehyde (10 mmol) in pyridine (10 ml) was added *O*-benzylhydroxylamine hydrochloride (10 mmol) under a nitrogen atmosphere at room temperature. After the reaction mixture was heated at reflux for 1 h, the reaction mixture was diluted with Et_2O. The organic phase was washed with brine,

dried over $MgSO_4$ and concentrated at reduced pressure.

Methyl *E*-2-(Benzyloxyimino)ethanate (1b).[14]

Method A using methyl 2-hydroxy-2-methoxyacetate. Purification by flash column chromatography (hexane/AcOEt 4:1) afforded **1b** (91%) as a colorless oil. IR ($CHCl_3$) 2956, 1738, 1600, 1497, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.55 (1H, s), 7.4-7.3 (5H, m), 5.29 (2H, s), 3.83 (3H, s). HRMS: Calcd for $C_{10}H_{11}NO_3$ (M^+) : 193.0738, Found : 193.0749.

Propanal *O*-Benzyloxime (1c).[15]

Method B. Purification by flash column chromatography (hexane/AcOEt 20:1) afforded **1c** (99%) as a colorless oil and a 2:1 mixture of *E*/*Z*-oxime ether. IR ($CHCl_3$) 2938, 1606, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.46 (2/3H, t, *J*=5.9 Hz), 7.37-7.25 (5H, m), 6.66 (1/3H, t, *J*=5.4 Hz), 5.10 (2/3H, s), 5.05 (4/3H, s), 2.45-2.31 (2/3H, m), 2.28-2.14 (4/3H, m), 1.07 (2H, t, *J*=7.5 Hz), 1.06 (1H, t, *J*=7.7 Hz). HRMS: Calcd for $C_{10}H_{13}NO$ (M^+) : 163.0996, Found : 163.1003.

Methyl 2-(Diphenylaminoimino)ethanate (1d).

Method B. Purification by flash column chromatography (hexane/AcOEt 10:1) afforded **1d** (92%) as a white solid. IR ($CHCl_3$) 3018, 1700, 1591, 1552, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.46-7.15 (10H, m), 6.51 (1H, s), 3.80 (3H, s). SIMS: Calcd for $C_{15}H_{14}N_2O_2$ (M^+) : 254.1054, Found : 254.1035.

Benzaldehyde Diphenylhydrazone (1e).[16]

Method B. Purification by flash column chromatography (hexane/AcOEt 10:1) afforded **1e** (93%) as a white solid. IR ($CHCl_3$) 1590, 1563, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.62 (2H, dd, *J*=6.8, 1.0 Hz), 7.47-7.15 (14H, m). HRMS: Calcd for $C_{19}H_{16}N_2$ (M^+) : 272.1313, Found : 272.1318.

***trans*-3-Phenyl-2-propenal *O*-Benzyloxime (4).**[17]

Method B. Purification by flash column chromatography (hexane/AcOEt 2:1) afforded **4** (91%) as colorless crystals and a 3:1 mixture of *E*/*Z*-oxime ether. mp 85.0-88.5 °C (AcOEt/hexane). IR ($CHCl_3$) 1602, 1496, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.94 (3/4H, dd, *J*=7.7, 1.5 Hz), 7.5-7.19 (41/4H, m), 6.9-6.7 (2H, m), 5.19 (1/2H, s), 5.15 (3/2H, s). HRMS: Calcd for $C_{16}H_{15}NO$ (M^+) : 237.1153, Found : 237.1162. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.71; H, 6.37; N, 5.90, Found : C, 80.98; H, 6.37; N, 5.80.

Benzaldehyde *O*-Benzyloxime (8a).[18]

Method B. Purification by flash column chromatography (hexane/AcOEt 30:1) afforded **8a** (90%) as a colorless oil and a 5:1 mixture of *E*/*Z*-oxime ether. IR ($CHCl_3$) 3030, 1607, 1574, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.13 (5/6H, s), 7.62-7.52 (2H, m), 7.45-7.3 (8H, m), 7.23 (1/6H, s), 5.26 (1/3H, s), 5.21 (5/3H, s). HRMS: Calcd for $C_{14}H_{13}NO$ (M^+) : 211.0996, Found : 211.0995.

2-Methoxybenzaldehyde *O*-Benzyloxime (8b).

Method B. Purification by flash column chromatography (hexane/AcOEt 20:1) afforded ***E*-8b** (88%) and ***Z*-8b** (4%) as a colorless oil. ***E*-8b**: IR ($CHCl_3$) 2937, 1608, 1488, 1466 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.55 (1H, s), 7.79 (1H, dd, *J*=7.7, 1.8 Hz), 7.43-7.21 (6H, m), 6.96-6.84 (2H, m), 5.20 (2H, s), 3.80 (3H, s). HRMS: Calcd for $C_{15}H_{15}NO_2$ (M^+) : 241.1102, Found : 241.1119. ***Z*-8b**: IR ($CHCl_3$) 2942, 1600, 1482, 1465 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.32 (1H, dd, *J*=7.8, 1.8 Hz), 7.79 (1H, s), 7.40-7.29 (6H, m), 6.98-6.88 (2H, m), 5.23 (2H, s), 3.83 (3H, s). HRMS: Calcd for $C_{15}H_{15}NO_2$ (M^+) : 241.1102, Found : 241.1111.

4-Hydroxybenzaldehyde *O*-Benzyloxime (8c).

Method B. Purification by flash column chromatography (hexane/AcOEt 2:1) afforded **8c** (95%) as colorless crystals and a 7:1 mixture of *E*/*Z*-oxime ether. mp 98-98.5 °C (AcOEt/hexane). IR ($CHCl_3$) 3594, 1608,

1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.08 (7/8H, s), 7.81 (1/4H, d, *J*=8.5 Hz), 7.45-7.22 (57/8H, m), 6.75 (7/4H, d, *J*=8.6 Hz), 5.24 (1/4H, s), 5.18 (7/4H, s). HRMS: Calcd for $C_{14}H_{13}NO_2$ (M^+) : 227.0946, Found : 227.0963. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16, Found : C, 74.21; H, 5.84; N, 6.19.

2-Hydroxybenzaldehyde *O*-Benzyloxime (8d).[19]

Method A. Purification by flash column chromatography (hexane/AcOEt 15:1) afforded **8d** (49%) as colorless crystals. mp 62.5-63 °C (AcOEt/hexane). IR ($CHCl_3$) 3171, 1610, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.79 (1H, s), 8.20 (1H, s), 7.45-7.3 (5H, m), 7.25 (1H, br t, *J*=8.0 Hz), 7.13 (1H, dd, *J*=7.2, 1.3 Hz), 6.95 (1H, br d, *J*=8.0 Hz), 6.88 (1H, td, *J*=7.2, 1.0 Hz), 5.17 (2H, s). HRMS: Calcd for $C_{14}H_{13}NO_2$ (M^+) : 227.0946, Found : 227.0944. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16, Found : C, 74.12; H, 5.80; N, 6.18.

3-Thiophenecarboxaldehyde *O*-Benzyloxime (8e).

Method B. Purification by flash column chromatography (hexane/AcOEt 30:1) afforded *E*-**8e** (86%) and *Z*-**8e** (11%) as a colorless oil. *E*-**8e**: IR ($CHCl_3$) 2933, 1606, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.15 (1H, s), 7.43-7.22 (8H, m), 5.17 (2H, s). SIMS: Calcd for $C_{12}H_{11}NOS$ (M^+) : 217.0561, Found : 217.0559. *Z*-**8e**: IR ($CHCl_3$) 2932, 1618, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.05 (1H, dd, *J*=3.1, 1.1 Hz), 7.44-7.27 (7H, m), 7.23 (1H, dd, *J*=5.0, 3.0 Hz), 5.26 (2H, s). SIMS: Calcd for $C_{12}H_{11}NOS$ (M^+) : 217.0561, Found : 217.0573.

2,3-*O*-Isopropylidene-D-glyceraldehyde *O*-Benzyloxime (10).

Method B. Purification by flash column chromatography (hexane/AcOEt 4:1) afforded **10** (68%) as a colorless oil and a 2:1 mixture of *E*/*Z*-oxime ether. IR ($CHCl_3$) 2991, 1603, 1497, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40 (2/3H, d, *J*=7.0 Hz), 7.4-7.3 (5H, m), 6.94 (1/3H, d, *J*=4.1 Hz), 5.09 (2/3H, s), 5.08 (4/3H, s), 5.03 (1/3H, m), 4.63 (2/3H, br q, *J*=6.4 Hz), 4.31 (1/3H, dd, *J*=8.4, 7.2 Hz), 4.14 (2/3H, dd, *J*=8.6, 6.6 Hz), 3.86 (2/3H, dd, *J*=8.6, 6.4 Hz), 3.74 (1/3H, dd, *J*=8.4, 6.8 Hz), 1.42 (3H, s), 1.38 (2H, s), 1.37 (1H, s). HRMS: Calcd for $C_{13}H_{18}NO_3$ ($M+H^+$) : 236.1286, Found : 236.1287.

2-Phenylpropanal *O*-Benzyloxime (11).

Method B. Purification of the residue by flash column chromatography (hexane/AcOEt 30:1) afforded *E*-**11** (78%) and *Z*-**11** (5%) as a colorless oil. *E*-**11**: IR ($CHCl_3$) 1602, 1495, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.51 (1H, m), 7.38-7.13 (10H, m), 5.08 (2H, s), 3.64 (1H, m), 1.41 (3H, d, *J*=7.0 Hz). HRMS: Calcd for $C_{16}H_{17}NO$ (M^+) : 239.1309, Found : 239.1327. *Z*-**11**: IR ($CHCl_3$) 1601, 1495, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34-7.20 (10H, m), 6.77 (1H, d, *J*=7.3 Hz), 5.12 (2H, s), 4.40 (1H, m), 1.39 (3H, d, *J*=7.1 Hz). HRMS: Calcd for $C_{16}H_{17}NO$ (M^+) : 239.1309, Found : 239.1327.

General procedure for the ethyl radical addition.

To a solution of oxime ether or hydrazone (around 40 mg) in CH_2Cl_2 (4 ml) were added EtOH (2.5 eq), EtI (5 eq), Lewis acid (2 eq) and Et_3B (1.0 M in hexane, 2.5 eq) under a nitrogen atmosphere at 25 °C. After stirring at the same temperature for 5-30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Yields are shown in Tables 1, 3 and 4. As shown in Table 4, the reactions in entries 2, 4 and 5 were run in CH_2Cl_2 at -78 °C (condition B) and the reactions in entries 3 and 6 were run in toluene at -78 °C (condition C).

***O*-Benzyl-*N*-propylhydroxylamine (2a).**[20]

Purification of the residue by preparative TLC (hexane/AcOEt 20:1) afforded **2a** as a colorless oil. IR ($CHCl_3$)

3382, 2964, 1605, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.24 (5H, m), 4.70 (2H, s), 2.90 (2H, t, *J*=7.4 Hz), 1.54 (2H, m), 0.92 (3H, t, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 137.92, 128.22, 127.63, 76.05, 53.84, 20.40, 11.44. HRMS: Calcd for $C_{10}H_{15}NO$ (M^+) : 165.1153, Found : 165.1133.

Methyl 2-(Benzyloxyamino)butanate (2b).[21]

Purification of the residue by preparative TLC (hexane/AcOEt 30:1) afforded **2b** as a colorless oil. IR ($CHCl_3$) 3270, 2954, 1728, 1605, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.25 (5H, m), 4.69 (2H, s), 3.74 (3H, s), 3.53 (1H, br t, *J*=6.6 Hz), 1.53 (2H, m), 0.91 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 174.40, 137.64, 128.32, 128.13, 127.63, 75.95, 64.90, 51.70, 22.71, 10.28. HRMS: Calcd for $C_{12}H_{17}NO_3$ (M^+) : 223.1207, Found : 223.1227.

***O*-Benzyl-*N*-(3-pentyl)hydroxylamine (2c).**[22]

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **2c** as a colorless oil. IR ($CHCl_3$) 3500, 2965, 1602, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (5H, m), 4.70 (2H, s), 2.73 (1H, m), 1.6-1.35 (4H, m), 0.90 (6H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 138.04, 128.24, 127.61, 76.45, 63.07, 23.82, 9.95. HRMS: Calcd for $C_{12}H_{19}NO$ (M^+) : 193.1466, Found : 193.1481.

Methyl 2-(*N*,*N*-Diphenylhydrazino)butanate (2d) and Methyl 2-(*N'*-Ethyl-*N*,*N*-diphenyl hydrazino)butanate (3d).

Purification of the residue by preparative TLC (hexane/AcOEt 30:1) afforded **2d** and **3d** as a colorless oil. **2d**: IR ($CHCl_3$) 3025, 1733, 1589, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35-7.0 (10H, m), 3.59 (1H, m), 3.54 (3H, s), 1.76 (2H, m), 0.99 (3H, t, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 173.93, 147.83, 129.04, 122.65, 120.73, 62.51, 51.54, 24.19, 9.97. HRMS: Calcd for $C_{17}H_{20}N_2O_2$ (M^+) : 284.1524, Found : 284.1530. **3d**: IR ($CHCl_3$) 3009, 1732, 1589, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30-6.95 (10H, m), 3.60 (1H, dd, *J*=9.8, 8.7 Hz), 3.47 (3H, s), 3.07-2.79 (2H, m), 1.85-1.76 (2H, m), 1.11 (3H, t, *J*=7.0 Hz), 0.93 (3H, t, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 173.70, 128.75, 122.12, 69.40, 51.07, 44.12, 24.00, 12.82, 10.50. HRMS: Calcd for $C_{19}H_{24}N_2O_2$ (M^+) : 312.1837, Found : 312.1847.

***O*-Benzyl-*N*-(*E*-1-phenyl-1-penten-3-yl)hydroxylamine (5).**

Purification of the residue by preparative TLC (hexane/AcOEt 30:1) afforded **5** as a colorless oil. IR ($CHCl_3$) 3500, 2967, 1599, 1495, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.22 (10H, m), 6.55 (1H, d, *J*=15.9 Hz), 6.19 (1H, dd, *J*=15.9, 8.2 Hz), 4.72 (2H, s), 3.52 (1H, dt, *J*=8.2, 5.1 Hz), 1.82-1.42 (2H, m), 0.93 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 137.75, 136.95, 132.40, 129.96, 128.40, 128.35, 128.23, 127.67, 127.35, 126.27, 76.70, 65.38, 25.09, 10.18. HRMS: Calcd for $C_{18}H_{21}NO$ (M^+) : 267.1622, Found : 267.1636.

***O*-Benzyl-*N*-(1-phenylpropyl)hydroxylamine (9a).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **9a** as a colorless oil. IR ($CHCl_3$) 2967, 1604, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (10H, m), 4.63 (1H, d, *J*=11.3 Hz), 4.56 (1H, d, *J*=11.3 Hz), 3.90 (1H, dd, *J*=8.2, 5.4 Hz), 1.95-1.5 (2H, m), 0.80 (3H, t, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 128.62, 128.42, 128.00, 127.88, 127.53, 76.90, 67.64, 26.76, 10.69. HRMS: Calcd for $C_{16}H_{19}NO$ (M^+) : 241.1465, Found : 241.1468.

***O*-Benzyl-*N*-[1-(2-methoxyphenyl)propyl]hydroxylamine (9b).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1) afforded **9b** as a colorless oil. IR ($CHCl_3$) 3408, 2965, 1601, 1493, 1465 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.32-7.19 (7H, m), 6.98-6.85 (2H, m), 4.72 (1H, d, *J*=12.6 Hz), 4.64 (1H, d, *J*=12.6 Hz), 4.30 (1H, dd, *J*=8.1, 6.1 Hz), 3.80 (3H, s), 2.00-1.61 (2H, m), 0.83 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 157.44, 138.14, 129.42, 128.40, 128.29, 128.13, 127.95,

127.49, 120.38, 110.51, 76.21, 61.29, 55.21, 25.01, 10.69. HRMS: Calcd for $C_{17}H_{21}NO_2$ (M^+) : 271.1571, Found : 271.1577.

***O*-Benzyl-*N*-[1-(4-hydroxyphenyl)propyl]hydroxylamine (9c).**

Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **9c** as a colorless oil. IR ($CHCl_3$) 3595, 3356, 2968, 1614, 1497, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36-7.21 (5H, m), 7.16 (2H, d, *J*=6.6 Hz), 6.73 (2H, d, *J*=6.6 Hz), 4.66 (1H, d, *J*=11.3 Hz), 4.31 (1H, d, *J*=11.3 Hz), 3.84 (1H, dd, *J*=8.9, 5.4 Hz), 2.0-1.5 (2H, m), 0.78 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 155.02, 137.38, 132.87, 129.00, 128.39, 128.23, 127.73, 115.17, 76.49, 66.73, 26.18, 10.41. HRMS: Calcd for $C_{16}H_{19}NO_2$ (M^+) : 257.1414, Found : 257.1427.

***O*-Benzyl-*N*-[1-(2-hydroxyphenyl)propyl]hydroxylamine (9d).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **9d** as a colorless oil. IR ($CHCl_3$) 3573, 3224, 2937, 1619, 1492, 1462 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35-7.15 (6H, m), 7.04 (1H, dd, *J*=7.3, 1.5 Hz), 6.89-6.79 (2H, m), 4.70 (2H, s), 4.01 (1H, t, *J*=7.4 Hz), 1.74 (2H, m), 0.84 (3H, t, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 156.14, 136.62, 129.51, 128.68, 128.43, 128.11, 124.33, 119.35, 116.92, 76.45, 67.59, 24.35, 10.53. HRMS: Calcd for $C_{16}H_{19}NO_2$ (M^+) : 257.1414, Found : 257.1421.

***O*-Benzyl-*N*-[1-(3-thiophenyl)propyl]hydroxylamine (9e).**

Purification of the residue by preparative TLC (hexane/AcOEt 30:1) afforded **2c** as a colorless oil. IR ($CHCl_3$) 3419, 2966 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38-7.25 (6H, m), 7.16 (1H, dd, *J*=3.1, 1.3 Hz), 7.08 (1H, dd, *J*=4.9, 1.3 Hz), 4.65 (1H, d, *J*=11.4 Hz), 4.57 (1H, d, *J*=11.4 Hz), 4.03 (1H, dd, *J*=8.2, 5.5 Hz), 2.0-1.55 (2H, m), 0.84 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 142.59, 137.71, 128.35, 128.22, 127.65, 126.72, 125.25, 122.01, 76.66, 62.74, 26.18, 10.41. SIMS: Calcd for $C_{14}H_{17}NOS$ (M^+) : 247.1030, Found : 247.1007.

***O*-Benzyl-*N*-[1-(2,2-dimethyl-1,3-dioxolan-4-yl)propyl]hydroxylamine (12).**

Purification of the residue by preparative TLC (hexane/AcOEt 20:1, two repeats) afforded **12** as a colorless oil. IR ($CHCl_3$) 3520, 2967, 1604, 1496, 1462 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (5H, m), 4.69 (1H, s), 4.65 (1H, s), 4.48 (1H, m), 4.20-3.87 (2H, m), 2.73 (1H, m), 1.8-1.2 (2H, m), 1.04-0.9 (15/2H, m), 0.82 (3/2H, t, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 137.71, 137.60, 128.35, 128.24, 127.72, 127.71, 68.23, 67.91, 65.40, 65.07, 20.21, 19.94, 10.51, 7.55, 7.51. HRMS: Calcd for $C_{15}H_{23}NO_3$ (M^+) : 265.1676, Found : 265.1682.

***O*-Benzyl-*N*-(2-phenyl-3-pentyl)hydroxylamine (13).**

Purification of the residue by preparative TLC (hexane/AcOEt 40:1, two repeats) afforded **13** as a colorless oil. IR ($CHCl_3$) 3583, 1602, 1494, 1454 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.15 (10H, m), 4.71 (17/9H, s), 4.63 (1/9H, s), 3.15-2.75 (2H, m), 1.30 (51/18H, d, *J*=7.1 Hz), 1.24 (3/18H, d, *J*=7.1 Hz), 1.6-1.1 (2H, m), 0.94 (3/18H, t, *J*=7.1 Hz), 0.87 (51/18H, t, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 144.39, 138.11, 128.20, 128.198, 128.13, 127.85, 127.69, 127.57, 126.03, 76.19, 76.08, 67.16, 66.85, 40.37, 39.89, 21.66, 20.90, 17.65, 17.16, 10.79, 9.95. HRMS: Calcd for $C_{18}H_{23}NO$ (M^+) : 269.1779, Found : 269.1789.

General procedure for the alkyl radical addition.

To a solution of oxime ether **1c** (40 mg, 0.245 mmol) in CH_2Cl_2 (4 ml) were immediately added Bu_3SnH (0.16 ml, 0.61 mmol), RI (4.9 mmol) and Et_3B (1.0 M in hexane, 0.61 ml, 0.61 mmol) under a nitrogen atmosphere at 25 °C. After being stirred at the same temperature for 1-3 min, $BF_3 \cdot OEt_2$ (0.062 ml, 0.49 mmol) was added to the reaction mixture. After being stirred at the same temperature for 5-30 min, the reaction mixture was

diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Yields are shown in Table 2.

***O*-Benzyl-*N*-(2,2-dimethyl-3-pentyl)hydroxylamine (7A).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **7A** as a colorless oil. IR ($CHCl_3$) 3500, 2964, 1604, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.29 (5H, m), 4.69 (2H, s), 2.37 (1H, dd, *J*=9.1, 3.1 Hz), 1.64-1.48 (1H, m), 1.41-1.26 (1H, m), 1.01 (3H, t, *J*=7.5 Hz), 0.93 (9H, s). ^{13}C NMR ($CDCl_3$) δ 138.17, 128.21, 128.11, 127.48, 75.55, 71.29, 34.25, 27.31, 21.15, 12.68. SIMS: Calcd for $C_{14}H_{24}NO$ ($M+H^+$) : 222.1857, Found : 222.1862.

***O*-Benzyl-*N*-(2-methyl-3-pentyl)hydroxylamine (7B).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **7B** as a colorless oil. IR ($CHCl_3$) 3500, 2963, 1603, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45-7.25 (5H, m), 4.68 (2H, s), 2.57 (1H, m), 2.15-1.8 (1H, m), 1.6-1.4 (1H, m), 1.4-1.2 (1H, m), 0.921 (3H, t, *J*=7.4 Hz), 0.918 (3H, d, *J*=3.6 Hz), 0.88 (3H, d, *J*=3.6 Hz). ^{13}C NMR ($CDCl_3$) δ 138.07, 128.27, 128.20, 127.56, 76.19, 67.28, 28.37, 20.62, 18.83, 18.06, 10.93. HRMS: Calcd for $C_{13}H_{21}NO$ (M^+) : 207.1622, Found : 207.1598.

***O*-Benzyl-*N*-(1-cyclohexylpropyl)hydroxylamine (7C).**

Purification of the residue by preparative TLC (hexane/AcOEt 50:1, two repeats) afforded **7C** as a colorless oil. IR ($CHCl_3$) 3500, 2928, 1603, 1496, 1452 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36-7.25 (5H, m), 4.68 (2H, s), 2.56 (1H, m), 1.8-1.6 (6H, m), 1.50 (2H, m), 1.4-1.0 (6H, m), 0.91 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 128.28, 128.21, 127.56, 76.16, 66.75, 38.75, 29.36, 28.84, 26.62, 26.50, 21.11, 10.87. HRMS: Calcd for $C_{16}H_{25}NO$ (M^+) : 247.1935, Found : 247.1954.

***N*-(1-Adamantylpropyl)-*O*-Benzylhydroxylamine (7D).**

Purification of the residue by preparative TLC (hexane/AcOEt 80:1, two repeats) afforded **7D** as a colorless oil. IR ($CHCl_3$) 3500, 2907, 1602, 1490, 1453 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35-7.27 (5H, m), 4.68 (2H, s), 2.17 (1H, dd, *J*=9.2, 3.1 Hz), 1.96 (3H, br m), 1.75-1.54 (12H, m), 1.39-1.22 (2H, m), 1.00 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 138.24, 128.20, 128.09, 127.46, 75.48, 71.95, 39.36, 37.15, 36.22, 28.49, 19.54, 12.70. HRMS: Calcd for $C_{20}H_{29}NO$ (M^+) : 299.2248, Found : 299.2265.

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